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Xenobiotic, Bile Acid, and Cholesterol Transporters: Function and Regulation

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Abstract——**Transporters influence the disposition of chemicals within the body by participating in absorption, distribution, and elimination. Transporters of the solute carrier family (SLC) comprise a variety of proteins, including organic cation transporters (OCT) 1 to 3, organic cation/carnitine transporters (OCTN) 1 to 3, organic anion transporters (OAT) 1 to 7, various organic anion transporting polypeptide isoforms, sodium taurocholate cotransporting polypeptide, apical sodium-dependent bile acid transporter, peptide transporters (PEPT) 1 and 2, concentrative nucleoside transporters (CNT) 1 to 3, equilibrative nucleoside transporter (ENT) 1 to 3, and multidrug and toxin extrusion transporters (MATE) 1 and 2, which mediate the uptake (except MATEs) of organic anions and cations as well as peptides and nucleosides. Efflux transporters of the ATP-binding cassette superfamily, such as ATP-binding cassette transporter A1 (ABCA1), multidrug resistance proteins (MDR) 1 and 2, bile salt export pump, multidrug resistance-associated proteins (MRP) 1 to 9, breast cancer resistance protein, and ATP-binding cassette subfamily G members 5 and 8, are responsible for the unidirectional export of endogenous and exogenous substances. Other efflux transporters [ATPase copper-transporting β polypeptide (ATP7B) and ATPase class I type 8B member 1 (ATP8B1) as well as organic solute transporters (OST) α and β] also play major roles in the transport of some endogenous chemicals across biological membranes. This review article provides a comprehensive overview of these transporters (both rodent and human) with regard to tissue distribution, subcellular localization, and substrate preferences. Because uptake and efflux transporters are expressed in multiple cell types, the roles of transporters in a variety of tissues, including the liver, kidneys, intestine, brain, heart, placenta, mammary glands, immune cells, and testes are discussed. Attention is also placed upon a variety of regulatory factors that influence transporter expression and function, including transcriptional activation and post-translational modifications as well as subcellular trafficking. Sex differences, ontogeny, and pharmacological and toxicological regulation of transporters are also addressed. Transporters are important transmembrane proteins that mediate the cellular entry and exit of a wide range of substrates throughout the body and thereby play important roles in human physiology, pharmacology, pathology, and toxicology.**

I. Introduction

Pharmacokinetics is determined by the absorption, distribution, metabolism, and excretion of a chemical from the body. These processes dictate the circulating and cellular levels of endogenous and exogenous compounds and, in turn, their physiological and pharmacological activity. Movement of chemicals across lipid bilayers is necessary for their function and elimination. In some cases, simple diffusion is sufficient for chemicals to enter as well as to exit cells. In other instances, physical and chemical properties such as size, charge, and hydrophilicity necessitate assistance for chemicals to cross membranes.

Transporters are specialized proteins that span cell membrane bilayers and mediate translocation of chemicals into and out of cells using active and passive mechanisms. Active transport occurs when solutes are transported across biological membranes against a concentration gradient and/or an electrochemical potential. Because of counter forces, active transport requires energy. In primary active transport, substrates pass unidirectionally through transport pumps using energy generated from the hydrolysis of ATP. During this process, substrates bind on one surface, leading to a conformational change in the transporter protein that allows release on the other side of the membrane. Secondary active transport occurs when uphill transport of a chemical by a carrier protein is coupled to the transport of a cosubstrate (typically, an ion). Coupling of the transport to solutes across a membrane is called cotransport. Cotransport can occur in the same direction (symport) or in opposite directions (antiport). Antiport transport will often create an electrochemical gradient in and of itself that can be used for tertiary active transport.

There are endogenous and exogenous substances that are substrates for transporters. Transporters are expressed in many tissues within the body for the circulation of physiological chemicals and nutrients, elimination of metabolic waste, and detoxification and removal of environmental chemicals and drugs. Transporters in the intestines are important for the absorption of some substrates and excretion of other substrates. Transporters on the surface of hepatocytes enable entry of some chemicals into the liver. Subsequent distribution of some chemicals to other tissues also involves transporters. Finally, certain transporters such as those in the kidneys participate in the excretion of chemicals from the body.

The disposition of drugs and endogenous chemicals such as bile acids and cholesterol is most often associated with two superfamilies of transporters: the solute carrier (SLC[1]) and ATP-binding cassette transporters

[1] Abbreviations: ABC, ATP-binding cassette; ABCA1, ATP-binding cassette transporter A1; ABCG, ATP-binding cassette subfamily G; ABCG5/8, ATP-binding cassette subfamily G members 5 and 8;

(ABC) families. The SLC family is part of the major facilitator superfamily. The SLC transporters discussed in this review are typically considered to be uptake transporters, although there are examples of bidirectional transport. SLC transporters typically use secondary and tertiary active transport to move chemicals across biological membranes. The ABC are members of a superfamily of transporters and are found on extracellular and intracellular membranes. ABC transporters function as efflux pumps that remove chemicals from the cell or organelle using primary active transport. ABC transporters can exist as full and half transporters. In the case of half transporters, these proteins require homo- or heterodimerization for functional activity.

For a number of years, it has been difficult to dissect the biochemical and molecular events involved in transport without knowing the protein structure of transporters. An inability to determine the structure of many mammalian SLC and ABC transporters is due largely to difficulties associated with obtaining stable crystals of amphipathic membrane-associated proteins. Early attempts to determine the structure of one member of the ABCB subfamily, *Abcb1* or Mdr1, also known as P-glycoprotein (Pgp), yielded low- to medium-resolution electron microscopy structural information (Rosenberg et al., 1997, 2001, 2003). Theories regarding the steps of transport (including substrate extraction from the bilayer, ATP binding, ATP hydrolysis, and conformational changes) have been postulated based on the crystal structures of evolutionarily related transporters. Aller et al. (2009) have published the X-ray crystal protein structure of mouse *Abcb1* (Mdr1) with and without bound substrates. Although it has taken approximately 33 years from the first report of Pgp in drug-resistant cell lines (Juliano and Ling, 1976) to the elucidation of its protein structure by X-ray crystallography (Aller et al., 2009), a tremendous amount of information regarding this transporter has been obtained. Functional studies suggest that MDR1 is a "polyspecific" transporter that could accept compounds of varying sizes and structures with binding at multiple sites. The inward-facing crystal structure of Pgp confirmed distinct drug-binding sites in the internal cavity in which different and multiple substrates could associate. These findings will assist researchers in rational drug design and provide a better understanding of substrate cooperativity during transport.

This review article describes members of the SLC and ABC families (Table 1). Within the SLC family, a number of families [10, 15, 21 (*SLCO*), 22, 28, 29, and 47] will be discussed. With regard to ABC transporters, we will focus upon the A, B, C, and G subfamilies. Other efflux transporters that will be discussed include ATPase copper-transporting β polypeptide (ATP7B), ATPase class I type 8B member 1 (ATP8B1), and the organic solute transporters (OST). For each of these transporters, the tissue distribution, subcellular localization, and substrate preferences in humans and mice will be included. Transporter isoforms are denoted as rodent (lowercase) and/or human (uppercase). The function of uptake and efflux transporters in a variety of tissues will be highlighted. There are a variety of regulatory mechanisms that dictate transporter expression and function including post-translational processing and protein-protein interactions as well as sex, ontogeny, and pharmacological activation. Finally, the regulation of transporters during toxicological and pathological conditions of the liver will be discussed.

ABCP, ABC transporter highly expressed in placenta; AhR, aryl hydrocarbon receptor; ANIT, α-naphthylisothiocyanate; APAP, acetaminophen; ASBT, apical sodium-dependent bile acid transporter; ATP7B, ATPase copper-transporting β polypeptide; ATP8B1, ATPase class I type 8B member 1; BCRP, breast cancer resistance protein; BDL, bile-duct ligation; BQ-123, cyclo(D-Asp-Pro-D-Val-Leu-D-Trp); BSEP, bile salt export pump; CAR, constitutive androstane receptor; CNT, concentrative nucleoside transporter; ENT, equilibrative nucleoside transporter; FXR, farnesoid X receptor; Gly-Sar, glycylsarcosine; GF120918, elacridar; HEK, human embryonic kidney; HERG, human *ether-à-go-go*-related gene; HNF, hepatocyte nuclear factor; JNJ-7706621, 4-[5-amino-1-(2,6-difluorobenzoyl)-1*H*-[1,2,4]triazol-3-ylamino]-benzenesulfonamide; JVS, juvenile visceral steatosis; Keap1, Kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; MATE, multidrug and toxin extrusion transporter; MATE2-K, multidrug and toxin extrusion 2-K; MDCK, Madin-Darby canine kidney; MDR, multidrug resistance protein; MRP, multidrug resistance-associated protein; MXR, mitoxantrone resistance; NHERF, Na^+/H^+ exchanger regulatory factor; Nrf2, NFE2-related factor 2; NTCP, sodium taurocholate cotransporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; OCTN, organic cation/carnitine transporter; OST, organic solute transporter; PCN, pregnenolone-16α-carbonitrile; PDZ, postsynaptic density 95/disc-large/zona occludens; PDZK, PDZ kinase; PEPT, peptide transporter; PFDA, perfluorodecanoic acid; PFIC, progressive familial intrahepatic cholestasis; Pgp, P-glycoprotein; PHx, partial hepatectomy; PMEA, 9-(2-(phosphomethoxy)ethyl)-adenine, adefovir; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; RXRα, retinoid X receptor α; SLC, solute carrier; SNP, single-nucleotide polymorphism; SUMO, small ubiquitin-like modifier; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCPOBOP, 1,4-bis-[2-(3,5,dichloropyridyloxy)] benzene; TR−, transport-deficient; URAT, urate transporter; Wy14643, [[4-chloro-6-[(2,3-dimethylphenyl)amino]-2-pyrimidinyl]thio]-acetic acid.

II. Transporter Families: Tissue Distribution, Subcellular Localization, and Substrates

Tables and figures in this section provide important details for each transporter discussed. Table 1 lists the gene, mRNA, and protein information for human transporter isoforms. Figures 1 through 5 illustrate the distribution of transporter mRNA in a number of tissues from humans and mice. Tables 2, 4 to 6, 8, and 9 document subcellular localization of transporter isoforms, in particular tissues or cell types. Tables 3 and 7 list a number of identified substrates for rodent and/or human transporter isoforms. Figures 1 through 5 and Tables 1 through 9 should be cross-referenced with the text of this section.

TABLE 1

Human uptake and efflux transporter gene, mRNA, and protein nomenclature

The gene names and the chromosomal locations were obtained from Entrez Gene cytogenic band. The mRNA and splice variant information were obtained from NCBI Entrez Nucleotide. Protein names (including alternative names) were obtained from UniProt/Swiss-Prot and GeneCards.

Gene		mRNA		Protein	
Name	Locus	Accession No	Splice Variants	Name	Other Names
SLC Transporters					
SLCO1A2	12p12	NM_021094	Yes	OATP1A2	OATP, OATP-A
SLCO1B1	12p12	NM_006446		OATP1B1	OATP2, LST-1, OATP-C
SLCO1B3	12p12	NM_019844		OATP1B3	OATP8, LST-2
SLCO1C1	12p12	NM_001145946	Yes	OATP1C1	OATP-F
SLCO2A1	3q21	NM_005630	Yes	OATP2A1	PGT
SLCO2B1	11q13	NM_007256	Yes	OATP2B1	OATP-B
SLCO3A1	15q26	NM_013272	Yes	OATP3A1	OATP-D
SLCO4A1	20q13	NM_016354	Yes	OATP4A1	OATP-E
SLCO4C1	5q21	NM_180991		OATP4C1	OATP-H
SLCO5A1	8q13	NM_030958	Yes	OATP5A1	OATP-J
SLCO6A1	5q21	NM_173488		OATP6A1	OATP-I, GST
SLC22A1	6q26	NM_003057	Yes	OCT1	
SLC22A2	6q26	NM_003058	Yes	OCT2	
SLC22A3	6q26–27	NM_021977		OCT3	EMT, Orct3
SLC22A4	5q31.1	NM_003059		OCTN1	ET
SLC22A5	5q31	NM_003060		OCTN2	
SLC22A21	5q31	N.D.		OCTN3	
SLC22A6	11q13.1–2	NM_004790	Yes	OAT1	NKT
SLC22A7	6q21.1–2	NM_153320	Yes	OAT2	NLT
SLC22A8	11q11	NM_004254	Yes	OAT3	Roct
SLC22A11	11q13.1	NM_018484	Yes	OAT4	
SLC22A10/19	11q12.3	NM_001039752		OAT5	
SLC22A20	11q13.1	NM_001004326	Yes	OAT6	
SLC22A9	11q13.1	NM_080866		OAT7	hUST3
SLC22A12	11q13.1	NM_144585	Yes	URAT	RST
SLC10A1	14q24.1	NM_003049		NTCP	
SLC10A2	13q33	NM_000452		ASBT	IBAT, ISBT
SLC15A1	13q33-q34	NM_005073	Yes	PEPT1	HPEPT1
SLC15A2	3q13.33	NM_021082	Yes	PEPT2	
SLC28A1	15q25-q26	NM_004213	Yes	CNT1	hCNT1
SLC28A2	15q15	NM_004212		CNT2	SPNT, hCNT2
SLC28A3	9q22.2	NM_001532		CNT3	hCNT3
SLC29A1	6p21.2-p21.1	NM_001078177	Yes	ENT1	
SLC29A2	11q13	NM_022127	Yes	ENT2	DER12, HNP36
SLC29A3	10q22.1	NM_018344	Yes	ENT3	
SLC47A1	17p11.2	NM_018242	Yes	MATE1	
SLC47A2	17p11.2	NM_152908	Yes	MATE2-K	H+/cation antiporter
ABC Transporters					
ABCA1	9q31.1	NM_005502		ABCA1	
ABCB1	7q21.1	NM_000927		MDR1	Pgp
ABCB4	7q21.1	NM_000443	Yes	MDR3	PFIC3, PGY3
ABCB11	2q24	NM_003742		BSEP	SPGP, PFIC2
ABCC1	16p13.1	NM_004996	Yes	MRP1	MRP, GS-X
ABCC2	10q24	NM_000392		MRP2	cMOAT, DJS
ABCC3	17q22	NM_003786	Yes	MRP3	MOAT-D, cMOAT2
ABCC4	13q32	NM_005845	Yes	MRP4	MOAT-B
ABCC5	3q27	NM_005688	Yes	MRP5	MOAT-C, ABC11
ABCC6	16p13.1	NM_001171	Yes	MRP6	MOAT-E, PXE, ARA
ABCC10	6p21.1	NM_033450	Yes	MRP7	
ABCC11	16q12.1	NM_032583	Yes	MRP8	
ABCC12	16q12.1	NM_033226	Yes	MRP9	
ABCG2	4q22	NM_004827	Yes	BCRP	MXR
ABCG5	2p21	NM_022436		ABCG5	Sterolin-1
ABCG8	2p21	NM_022437		ABCG8	Sterolin-2
ATP7B	13q14.3	NM_000053	Yes	ATP7B	WD
ATP8B1	18q21-q22	NM_005603		ATP8B1	PFIC1, FIC1, BRIC
OSTα	3q29	NM_152672		OSTα	
OSTβ	15q22.31	NM_178859		OSTβ	

ET, ergothioneine transporter; NKT, novel kidney transporter; NLT, novel liver transporter; Roct, reduced in osteosclerosis transporter; IBAT/ISBT, ileal sodium-dependent bile acid cotransporter; RST, renal-specific transporter; SPNT, sodium-dependent purine nucleoside transporter.

A. Solute Carrier Transporters

1. Organic Anion Transporting Polypeptides. Oatps/OATPs are members of the *SLCO* family (Table 1) and are responsible for the uptake of a wide range of substrates. Rat Oatp1a1 was the first member of the OATP family identified (Jacquemin et al., 1994) followed by rat Oatp2a1 (Kanai et al., 1995). OATP1A2 was the first human OATP to be cloned (Kullak-Ublick et al., 1995). The rapid and independent classification of multiple Oatp/OATP isoforms led to confusion regarding protein nomenclature. New nomenclature and classification of OATP isoforms according to evolutionary relationships

and amino acid sequence identity were established in 2004 and approved by the HUGO Gene Nomenclature Committee (Hagenbuch and Meier, 2004). Oatps/OATPs with more than 40% amino acid sequence identity are members of the same family (OATP1, OATP2, OATP3…). Designation of isoforms to a particular subfamily (OATP1A, -1B, and -1C) requires more than 60% amino acid sequence identity. More than 15 rodent and 10 human isoforms have been described (Hagenbuch and Meier, 2004; Hagenbuch and Gui, 2008). In addition, an Oatp ortholog (Oatp1d1) was identified in skate liver and has been proposed to be an evolutionarily ancient precursor of mammalian OATP1B1/OATP1B3/Oatp1b2 responsible for uptake of cyclic peptides (Meier-Abt et al., 2007).

OATPs are integral membrane proteins predicted to contain 12 transmembrane helices with amino and carboxyl termini oriented to the cytoplasmic face (Noe et al., 1997; Hagenbuch et al., 2000; Mikkaichi et al., 2004). A large extracellular domain is thought to be located between transmembrane domains 9 and 10, with *N*-glycosylation sites present in extracellular loops 2 and 5 (Hagenbuch and Meier, 2003).

Expression of mouse Oatp isoforms varies among tissues (Fig. 1). Oatp1a1, -1a4, -1b2, and -2b1 are expressed in liver, whereas Oatp1a6, -3a1, and -4c1 are expressed in kidneys (Choudhuri et al., 2001; Cheng et al., 2005a). Levels of Oatp1a4 and -1c1 mRNA are high in the brain (Cheng et al., 2005a). Oatp1a5, -6b1, -6c1, and -6d1 mRNA are predominantly expressed in mouse testes. Within the testes, rat Oatp6b1 and -6c1 are expressed in Sertoli cells, spermatogonia, and Leydig cells (Suzuki et al., 2003). Oatp2a1, -4a1, and -5a1 are highest in the placenta (Cheng et al., 2005a).

The tissue distribution of the various OATP isoforms in humans also ranges from a single tissue to ubiquitous expression. For example, human OATP1B1 and OATP1B3 are primarily expressed in liver (Fig. 1) (Abe et al., 1999; Hsiang et al., 1999; König et al., 2000a,b). In contrast, OATP1C1, OATP2A1, OATP2B1, OATP3A1, and OATP4A1 mRNA can be detected in multiple tissues (Fig. 1) (Tamai et al., 2000a; Kullak-Ublick et al., 2001; Pizzagalli et al., 2002; Grube et al., 2006a).

There are similarities and differences in the tissue distribution of Oatp/OATP transporters between mice and humans (Fig. 1). For example, mouse Oatp1c1 and human OATP1C1 are highly expressed in brain (Pizzagalli et al., 2002; Cheng et al., 2005a). Likewise, both rat and mouse Oatp1a4 are most abundant in brain and liver (Noe et al., 1997; Cheng et al., 2005a). In contrast, Oatp4a1 is specifically expressed in mouse placenta, yet OATP4A1 is widely expressed in multiple human tissues (Tamai et al., 2000a; Cheng et al., 2005a). Therefore, differences in the tissue distribution of some Oatp/OATP isoforms are important when extrapolating from rodents to humans.

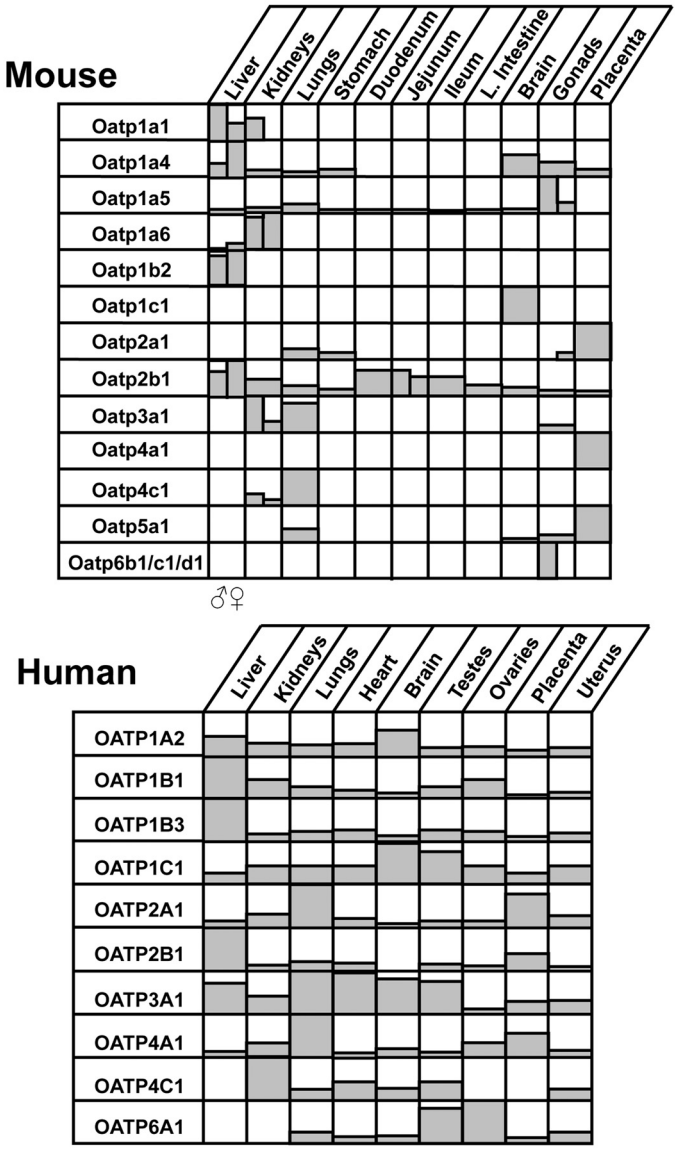

FIG. 1. Tissue distribution of Oatp mRNA in mice and humans. Top, relative mRNA levels of transporters in mouse liver, kidneys, lung, stomach, duodenum, jejunum, ileum, large intestine, brain, gonads (testes and ovaries), and placenta are shown. Male (♂) mRNA is shown on the left, whereas female (♀) mRNA is shown on the right side of each box. References for mouse mRNA expression are included (Cheng et al., 2005a). Bottom, relative mRNA levels of transporters in human liver, kidneys, lung, heart, brain, testes, ovaries, placenta, and uterus are shown. Data for humans were obtained from GNF SymAtlas (http://symatlas.gnf.org/; now located at http://biogps.gnf.org). The GNF1H/MAS5 data set was accessed during September 2008.

Cellular localization of Oatp/OATP isoforms can be apical or basolateral depending on the tissue and cell type (Table 2). In liver, Oatp/OATP isoforms are typically on the basolateral (also called sinusoidal) membrane of hepatocytes (Oatp1a1, -1a4, -1b2 and OATP1B1, -1B3, -2B1), although human OATP1A2 is localized to the apical surface of cholangiocytes (Bergwerk et al., 1996; Kakyo et al., 1999; Reichel et al., 1999; König et al., 2000a,b; Cattori et al., 2001; Lee et al., 2005a; Grube et al., 2006a). Within the liver, human OATP1B3 and rat Oatp1a4 are mostly confined to cen-

TABLE 2
Subcellular localization of uptake OATP/Oatp transporters in various species

For each transporter, the apical or basolateral localization in a particular tissue and/or species is provided. Species included rat (R), mouse (M), human (H), and bovine (B). Detailed information regarding particular cellular populations or regions of the tissue are provided for some transporter isoforms.

Cellular Localization	Tissue	Species	Cell Types	References
Oatp1a1				
Basolateral	Liver	R	Hepatocytes	Eckhardt et al., 1999
Apical	Kidney	R	Proximal tubule cells	Bergwerk et al., 1996
Apical	Choroid plexus	R	Epithelial cells	Angeletti et al., 1997
Oatp1a4				
Basolateral	Liver	R	Hepatocytes (midzonal to centrilobular)	Kakyo et al., 1999; Reichel et al., 1999
Basolateral	Choroid plexus	R	Epithelial cells	Gao et al., 1999
Basolateral	Brain	R	Capillary endothelial cells	Roberts et al., 2008
Apical	Eye	R	Retinal pigment epithelium	Gao et al., 2002; Ito et al., 2002
Oatp1a5				
Apical	Choroid plexus	M	Epithelial cells	Ohtsuki et al., 2004b
Apical	Brain	M	Capillary endothelial cells	Ohtsuki et al., 2004b
Apical	Jejunum	R	Enterocytes	Walters et al., 2000
N.D.	Eye	R	Nerve fiber, ganglion cells	Ito et al., 2002
Oatp1b2				
Basolateral	Liver	R	Hepatocytes	Cattori et al., 2001
Oatp2a1				
N.D.	Kidney	R	Glomeruli, endothelial cells, collecting ducts	Bao et al., 2002
Oatp2b1				
Basolateral	Brain	R	Capillary endothelial cells	Roberts et al., 2008
Apical	Choroid Plexus	R	Epithelial cells	Roberts et al., 2008
Oatp3a1				
N.D.	Heart	R	Aorta endothelial cells	Adachi et al., 2003
N.D.	Lung	R	Alveolar epithelial cells	Adachi et al., 2003
N.D.	Trachea	R	Mucosal epithelium	Adachi et al., 2003
N.D.	Testes	R	Spermatozoa tails	Adachi et al., 2003
N.D.	Ovary	R	Oocytes and smooth muscle cells	Adachi et al., 2003
N.D.	Uterus	R	Glandula uterine epithelium, smooth muscle cells of myometrium, surface epithelium of endometrium	Adachi et al., 2003
N.D.	Kidney	R	Distal tubules and collecting ducts	Adachi et al., 2003
Oatp4a1				
N.D.	Eye	R	Corneal epithelium, ciliary body, iris, retina	Ito et al., 2003
Oatp4c1				
Basolateral	Kidney	R	Proximal tubule cells	Mikkaichi et al., 2004
OATP1A2				
Apical	Liver	H	Cholangiocytes	Lee et al., 2005a
Apical	Small Intestine	H	Enterocytes at the villus tip	Glaeser et al., 2007
Apical	Kidney	H	Distal tubules	Lee et al., 2005a
N.D.	Brain	H	Capillary endothelial cells	Lee et al., 2005a
OATP1B1				
Basolateral	Liver	H	Hepatocytes	Cui et al., 2003
OATP1B3				
Basolateral	Liver	H	Hepatocytes (centrilobular)	Cui et al., 2003
OATP1C1				
N.D.	Testes	H	Leydig cells	Pizzagalli et al., 2002
OATP2B1				
Basolateral	Liver	H	Hepatocytes	Grube et al., 2006a
Basolateral	Placenta	H	Syncytiotrophoblasts	St-Pierre et al., 2002; Grube et al., 2007
Apical	Small Intestine	H	Enterocytes	Kobayashi et al., 2003
N.D.	Heart	H	Vascular endothelium	Grube et al., 2006a
OATP4A1				
Apical	Placenta	H	Syncytiotrophoblasts	Sato et al., 2003

N.D., not determined.

trilobular hepatocytes, whereas human OATP1B1 is expressed uniformly throughout the lobule (Kakyo et al., 1999; Reichel et al., 1999; Ho et al., 2006b). Likewise, Oatps/OATPs are detected on both the apical and basolateral surfaces of the kidneys (apical OATP1A2 and Oatp1a1; basolateral Oatp4c1) and placenta (apical OATP4A1; basolateral OATP2B1) (Table 2) (Bergwerk et al., 1996; St-Pierre et al., 2002; Sato et al., 2003; Mikkaichi et al., 2004; Lee et al., 2005a; Grube et al., 2007).

Oatp/OATPs transport solutes with diverse characteristics. In general, Oatp/OATP substrates contain steroidal or peptide structural backbones and/or are anionic or cationic chemicals. Classes of pharmaceuticals transported by Oatp/OATPs include HMG-CoA reductase inhibitors (statins), angiotensin-converting enzyme inhibitors, angiotensin receptor II antagonists, and cardiac glycosides (Table 3). A number of endogenous chemicals, including thyroxine, steroid conjugates, bile acids, bilirubin, and prostaglandins are also substrates of Oatp/

TABLE 3
Substrates for SLC transporters

Substrates of the various transporter isoforms were identified using in vitro transport studies of human or rodent isoforms or from in vivo studies using knockout mice or mutant rats. A number of substrates are provided. Not all substrates are included in this list.

OATP1A2	Sulfobromophthalein, BQ-123, cholic acid, dehydroepiandrosterone sulfate, deltophorin II, DPDPE, estrone-3-sulfate, fexofenadine, glycocholate, levofloxacin, methotrexate, microcystin-LR, ouabain, prostaglandin E_2, rosuvastatin, saquinavir, taurocholate, thyroxine, triiodothyronine
OATP1B1	Benzylpenicillin, bilirubin and its conjugates, bosentan, BQ-123, bromosulfophthalein, caspofungin, cerivastatin, cholic acid, dehydroepiandrosterone sulfate, DPDPE, estradiol 17β-glucuronide, estrone-3-sulfate, fluvastatin, glycocholate, irinotecan (SN38 metabolite), leukotriene C_4, microcystin-LR, olmesartan, phalloidin, pravastatin, prostaglandin E_2, rifampicin, rifampin, rosuvastatin, taurocholate, thromboxane B_2, thyroxine, triiodothyronine, troglitazone sulfate, valsartan
OATP1B3	Bilirubin conjugates, bosentan, sulfobromophthalein, BQ-123, cholecystokinin-8, dehydroepiandrosterone sulfate, deltorphin II, digoxin, DPDPE, docetaxel, estradiol 17β-glucuronide, fexofenadine, fluvastatin, glycocholate, irinotecan (SN38 metabolite), leukotriene C_4, microcystin-LR, olmesartan, ouabain, paclitaxel, phalloidin, rifampicin, rifampin, rosuvastatin, taurocholate, telmisartan, thyroxine, triiodothyronine, valsartan
OCT1	Acetylcholine, acyclovir, cimetidine, choline, dopamine, famotidine, ganciclovir, lamivudine, metformin, *N*-methylnicotinamide, 1-methyl-4-phenylpyridinium, quinine, ranitidine, serotonin, spermine, spermidine, tetraethylammonium, zalcitabine
OCT2	Acetylcholine, amantadine, cimetidine, cisplatin, choline, dopamine, epinephrine, histamine, lamivudine, memantine, metformin, 1-methyl-4-phenylpyridinium, *N*-methylnicotinamide, norepinephrine, paraquat, prostaglandin E_2, prostaglandin F_2, quinine, ranitidine, serotonin, tetraethylammonium, zalcitabine
OCT3	Atropine, dopamine, epinephrine, etilefrine, guanidine, histamine, 1-methyl-4-phenylpyridinium, tetraethylammonium
OCTN1	L-Carnitine, ergothioneine, pyrilamine, quinidine, quinine, tetraethylammonium, verapamil
OCTN2	L-Carnitine, cephaloridine, mildronate, pyrilamine, quinidine, spironolactone, tetraethylammonium, valproic acid, verapamil
OAT1	Acetylsalicylate, acyclovir, adefovir, *p*-aminohippurate, cephaloridine, cidofovir, cimetidine, cyclic AMP and GMP, didanosine, edaravone sulfate, furosemide, ganciclovir, indoxyl sulfate, indomethacin, α-ketoglutarate, lamivudine, methotrexate, ochratoxin A, penicillin G, prostaglandins E_2 and $F_2\alpha$, salicylate, stavudine, tetracycline, trifluridine, urate, zidovudine, zalcitabine
OAT2	*p*-Aminohippurate, acetylsalicylate, allopurinol, bumetanide, cyclic AMP, dehydroepiandrosterone sulfate, estrone-3-sulfate, 5-fluorouracil, glutarate, α-ketoglutarate, methotrexate, paclitaxel, prostaglandins E_2 and $F_2\alpha$, ochratoxin A, salicylate, tetracycline, valproic acid, zidovudine
OAT3	Allopurinol, *p*-aminohippurate, benzylpenicillin, L-carnitine, cefazolin, cephaloridine, cholic acid, cimetidine, cortisol, dehydroepiandrosterone sulfate, edaravone sulfate, estrone-3-sulfate, famotidine, 5-fluorouracil, glutarate, glutathione, glycocholate, indoxyl sulfate, methotrexate, 6-mercaptopurine, ochratoxin A, pravastatin, prostaglandins E_2 and $F_2\alpha$, rosuvastatin, taurocholate, tetracycline, urate, valacyclovir, zidovudine
OAT4	*p*-Aminohippurate, dehydroepiandrosterone sulfate, estrone-3-sulfate, glutarate, indoxyl sulfate, ochratoxin A, tetracycline, zidovudine
PEPT1	5-Aminolevulinic acid, bestatin, cefadroxil, ceftibuten, cefixime, cephradine, cephalexin, glycylsarcosine
PEPT2	5-Aminolevulinic acid, bestatin, cefadroxil, glycylsarcosine, *l*-kyotorphin
CNT1	Adenosine, cladribine, cytarabine, fialuridine, 5-fluorouridine, gemcitabine, stavudine, thymidine, uridine, zalcitabine, zidovudine
CNT2	Adenosine, cladribine, clofarabine, cytidine, didanosine, fialuridine, 5-fluorouridine, formycin B, inosine, guanosine, ribavirin, tiazofurin, uridine
CNT3	Adenosine, benzamide riboside, cladribine, clofarabine, cytarabine, cytidine, didanosine, fludarabine, 5-fluorouridine, gemcitabine, guanosine, inosine, 6-mercaptopurine, ribavirin, uridine, 6-thioguanine, tiazofurin, thymidine, zalcitabine, zebularine, zidovudine
ENT1	Adenosine, cladribine, clofarabine, cytidine, fialuridine, gemcitabine, guanosine, ribavirin, thymidine, tiazofurin, uridine
ENT2	Adenine, adenosine, clofarabine, cytidine, fialuridine, gemcitabine, guanine, guanosine, hypoxanthine, inosine, thymidine, tiazofurin, uridine
ENT3	Adenine, adenosine, cladribine, fludarabine, guanosine, inosine, thymidine, uridine, zebularine, zidovudine
MATE1	Acyclovir, cephalexin, cephradine, cimetidine, creatinine, estrone sulfate, ganciclovir, guanidine, 1-methyl-4-phenylpyridinium, metformin, oxaliplatin, paraquat, procainamide, tenofovir, tetraethylammonium, thiamine, topotecan
MATE2-K	Acyclovir, cimetidine, creatinine, estrone sulfate, ganciclovir, guanidine, metformin, 1-methyl-4-phenylpyridinium, N^1-methylnicotinamide, oxaliplatin, procainamide, tetraethylammonium, thiamine, topotecan

OATPs. It has long been recognized that chemicals secreted into bile are structurally larger than those excreted by the kidneys and may be due to selective extraction of bulky chemicals from the circulation by hepatic Oatp/OATPs. More recent evidence points to the influence of pH in the transport kinetics of Oatp/OATPs (Leuthold et al., 2009). Using Oatp/OATP-expressing oocytes and cultured cells, it was demonstrated that the transport activity of number of isoforms (with the exception of OATP1C1) is enhanced by low extracellular pH and that this flux is countered by bicarbonate efflux (Leuthold et al., 2009).

Although OATPs are typically considered uptake transporters, there are examples of bidirectional transport for various isoforms (Li et al., 2000; Mahagita et al., 2007). Transport of taurocholate and leukotriene C_4 by rat Oatp1a1 in oocytes is *cis* inhibited and *trans* stimulated by glutathione, suggesting that glutathione efflux provides a driving force for uptake (Li et al., 1998). Additional research demonstrates that Oatp1a4-mediated transport of taurocholate is bidirectional and stimulated by glutathione and its conjugates (Li et al., 2000). More recent research demonstrates that human OATP1B1 and -1B3 are similarly bidirectional facilitated diffusion transporters, but that glutathione is not a substrate or activator of their transport activity (Mahagita et al., 2007).

Human OATP1A2 transports and is inhibited by a large number of endogenous compounds as well as pharmaceuticals in in vitro systems (Table 3). Because of the

promiscuity of this transporter, a number of drug-drug interactions have been proposed for OATP1A2. OATP1A2-mediated transport of fexofenadine is inhibited by antivirals, antifungals, antibiotics, and anticholesterol drugs (Cvetkovic et al., 1999). OATP1A2 can also transport the fluoroquinolone antibiotic levofloxacin and is inhibited by other quinolones (Maeda et al., 2007b). In addition to pharmaceutical inhibition, dietary constituents may also modulate drug transport by inhibiting OATP1A2 function. The grapefruit flavonoid naringin inhibits OATP1A2 uptake of fexofenadine in vitro, and thus grapefruit juice alters clinical fexofenadine pharmacokinetics (Dresser et al., 2002; Bailey et al., 2007; Glaeser et al., 2007). These data suggest that naringin probably interferes with the intestinal OATP1A2-mediated absorption of oral fexofenadine (Glaeser et al., 2007). Similar reports demonstrate in vitro inhibition of OATP2B1 transport by grapefruit and orange juices as well as other herbal extracts (Satoh et al., 2005; Fuchikami et al., 2006).

Rodent Oatp1a1 and -1a4 share similar substrates with OATP1A2, including unconjugated and conjugated bile acids, bromosulfophthalein, sulfated steroids, thyroid hormones, ouabain, β-lactam antibiotics, and fexofenadine (Cvetkovic et al., 1999; Reichel et al., 1999; Hagenbuch et al., 2000; Meng et al., 2002; van Montfoort et al., 2002; Nakakariya et al., 2008). Rat Oatp1a1 and Oatp1a4 can transport opioid peptides [D-Pen^2,D-Pen^5]-enkephalin and deltorphin II (Oatp1a1 only), which may be important in their transport across the blood-brain and blood-cerebrospinal fluid barriers (Kakyo et al., 1999; Gao et al., 2000). There are notable differences in transport by mouse and rat Oatp1a4; digoxin is a high-affinity substrate for rat Oatp1a4 but a low-affinity substrate for mouse Oatp1a4 (Noe et al., 1997; van Montfoort et al., 2002). Likewise, bromosulfophthalein is transported by mouse Oatp1a4 but not by the rat isoform (van Montfoort et al., 2002).

OATP1B1 and -1B3 are the primary OATP1B isoforms in human livers. Oatp1b2 is the rodent ortholog of OATP1B1 and -1B3. Because of the prominent expression of these transporters on the basolateral membrane of hepatocytes, they represent a critical mechanism for chemical uptake into liver. OATP1B1 and -1B3 exhibit overlapping and specific substrates (Table 3). Human OATP1B1 transports various statin drugs as well as thyroxine, taurocholate, and dehydroepiandrosterone sulfate (Hsiang et al., 1999). Both OATP1B1 and -1B3 can transport conjugated bilirubin; however, 1B1 appears to be more important for unconjugated bilirubin uptake (Cui et al., 2001). Using overexpressing oocytes, Oatp1b2 and OATP1B3 transport cholecystokinin, a gastrointestinal peptide that is released postprandially and stimulates gallbladder contraction, release of pancreatic enzymes, and intestinal motility (Ismair et al., 2001).

More recently, attention has been brought to the uptake mechanisms for hepatotoxic drugs, including bosentan and troglitazone. Bosentan and its active metabolite are substrates of OATP1B1 and -1B3 (Treiber et al., 2007). Likewise, OATP1B1 can transport and be inhibited by troglitazone sulfate (Nozawa et al., 2004b). It is hypothesized that inhibition of OATP1B1 by troglitazone sulfate may be a novel mechanism underlying idiosyncratic hepatotoxicity associated with this pharmaceutical (Nozawa et al., 2004b).

Clinical drug interactions may also occur at the level of OATP transporters. OATP1B1 transports pravastatin (Nakai et al., 2001). OATP1B1 transport is inhibited by fibric acid derivatives and may contribute to known drug-drug interactions, such as gemfibrozil-cerivastatin (Shitara et al., 2004; Yamazaki et al., 2005) and rifampin-atorvastatin (Lau et al., 2007). In contrast, rosuvastatin can be transported by a number of OATP isoforms, including OATP1B1, -1B3, -2B1, and -1A2 as well as rat Oatp1a1, -1a4, -1a5, and -1b2, probably reducing the chance of drug-drug interactions (Ho et al., 2006b). OATP1B1 also transports the active metabolite of the anticancer drug irinotecan (Nozawa et al., 2005). OATP1B1 and -1B3 transport the angiotensin-II blocker olmesartan (Nakagomi-Hagihara et al., 2006). Further work is necessary to better characterize clinical-relevant drug-drug interactions of these and other OATP1B1 and -1B3 substrates.

OATP1B1, -1B3, and rat Oatp1b2 participate in the uptake of rifampin (Tirona et al., 2003). Overexpression of OATP1B1 not only enhances rifampin transport but also its function as evidenced by enhancement of rifampin-stimulated pregnane X receptor gene transactivation (Tirona et al., 2003). Rifampicin can inhibit OATP1B1 and -1B3 transport (and be transported by them), whereas rifamycin SV can also inhibit OATP1A2 and -2B1 (Vavricka et al., 2002).

OATP2B1 is expressed in human placenta and, along with the breast cancer resistance protein, (BCRP; ABCG2) is probably responsible for transepithelial transport of sulfated steroids from the fetus to the mother during pregnancy (St-Pierre et al., 2002; Grube et al., 2007). Likewise, OATP2B1 is also expressed in ductal epithelial cells of the mammary gland (Pizzagalli et al., 2003). OATP2B1 prefers sulfate conjugates (estrone sulfate) rather than glucuronide conjugates (i.e., estradiol-17β-glucuronide) (Tamai et al., 2001b; Nozawa et al., 2004a). OATP2B1 can also transport dehydroepiandrosterone sulfate, the antihistamine fexofenadine, and the antidiabetic drug glibenclamide (Nozawa et al., 2004a; Satoh et al., 2005).

2. Organic Cation Transporters. OCTs are polyspecific cationic transporters of the *SLC22* family (*SLC22A1–3*) (Table 1). In 1994, Oct1 was the first member of the organic cation transporter family cloned from a rat kidney cDNA library (Gründemann et al., 1994). Human and mouse orthologs were soon cloned thereaf-

ter (Schweifer and Barlow, 1996; Gorboulev et al., 1997; Zhang et al., 1997). Subsequently, Oct2 and Oct3, two organic cation transporters with high homology to Oct1, were cloned and characterized in humans, rats, mice, and rabbits (Okuda et al., 1996; Gorboulev et al., 1997; Zhang et al., 1997; Kekuda et al., 1998; Urakami et al., 1998; Karbach et al., 2000). Oct3 is also called the extraneuronal monoamine transporter and participates in the uptake of extraneuronal monoamines in peripheral tissues and glia cells (also known as the uptake-2 system) (Gründemann et al., 1998; Wu et al., 1998). The membrane topology of OCT isoforms is predicted to be similar with 12 α-helical transmembrane domains with intracellular amino and carboxy termini (Burckhardt and Wolff, 2000). An extracellular loop between transmembrane domains 1 and 2 contains potential *N*-glycosylation sites (Burckhardt and Wolff, 2000). A large intracellular loop resides between transmembrane domains 6 and 7 and possesses predicted phosphorylation sites.

In mice, Oct1 mRNA expression is highest in kidneys and liver (Fig. 2) (Alnouti et al., 2006). Human OCT1 is primarily expressed in liver and to a lesser extent in other organs (Fig. 2) (Gorboulev et al., 1997; Zhang et al., 1997). Oct1/OCT1 proteins are localized to the basolateral membrane of centrilobular hepatocytes, proximal tubule cells, Sertoli cells, enterocytes, and in serotoninergic neurons of the small intestine (Table 4) (Meyer-Wentrup et al., 1998; Karbach et al., 2000; Muller et al., 2005; Maeda et al., 2007a). Prominent expression of OCT1 on the sinusoidal membrane of hepatocytes suggests that this transporter mediates the first step in hepatic excretion of cationic drugs.

Rodent Oct2 and human OCT2 mRNA are highest within the kidneys (Fig. 2) (Gorboulev et al., 1997; Slitt et al., 2002; Alnouti et al., 2006). Within renal proximal tubule cells, Oct2/OCT2 proteins are present on the basolateral membrane, which makes this transporter a key entry site for renally excreted cationic drugs (Table 4) (Karbach et al., 2000; Motohashi et al., 2002). Neurons of the human central nervous system have detectable OCT2 protein (Busch et al., 1998). Similar to Oct1, apical expression of Oct2 protein is seen in bovine olfactory mucosa and ciliated epithelial cells of rodent and human lungs (Lips et al., 2005; Kummer et al., 2006; Chemuturi and Donovan, 2007) (Table 4).

The tissue distribution of mouse Oct3 and human OCT3 is broader than Oct1/OCT1 and Oct2/OCT2. Oct3/OCT3 are expressed in many tissues with high levels in placenta, ovaries, and uterus (Fig. 2) (Kekuda et al., 1998; Wu et al., 1998, 2000b; Verhaagh et al., 1999; Slitt et al., 2002; Alnouti et al., 2006). Subcellular localization patterns for human OCT3 are cell-type specific. OCT3 protein is observed on basolateral (trophoblasts, renal tubule cells) and apical (enterocytes, Sertoli cells, ciliated lung epithelia) membranes (Table 4) (Lips et al., 2005; Muller et al., 2005; Sata et al., 2005; Kummer et al., 2006; Maeda et al., 2007a; Glube and Langguth, 2008) as well as in numerous regions of the rat brain (Vialou et al., 2004).

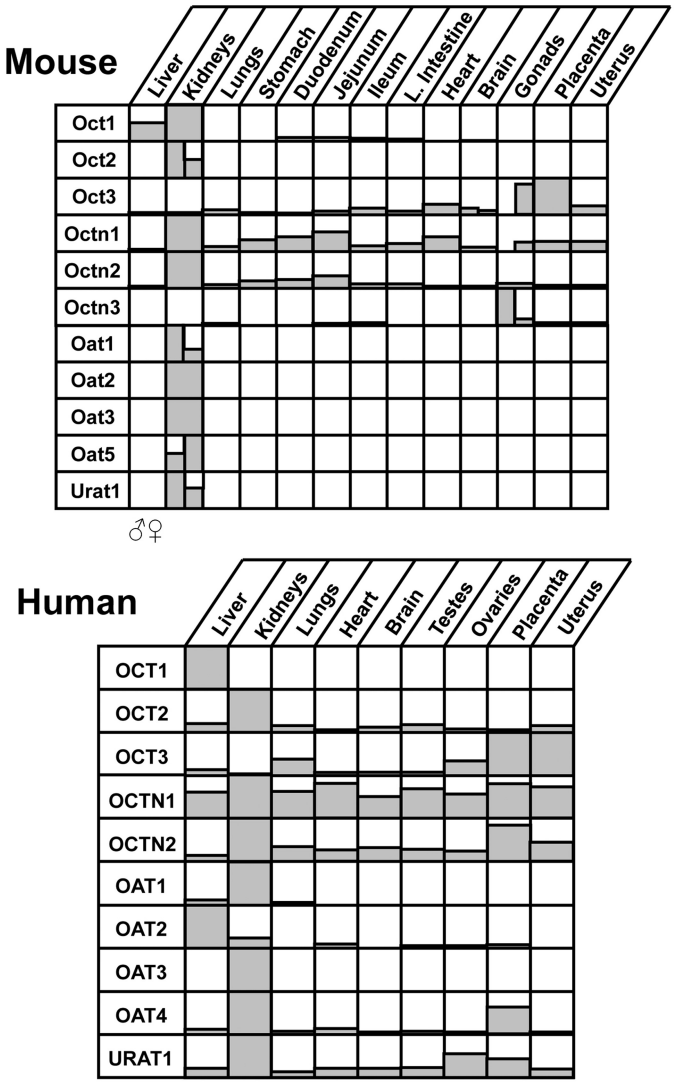

FIG. 2. Tissue distribution of Oct, Octn, Oat, and Urat mRNA in mice and humans. Top, relative mRNA levels of transporters in mouse liver, kidneys, lung, stomach, duodenum, jejunum, ileum, large intestine, heart, brain, gonads (testes and ovaries), placenta, and uterus are shown. Male (♂) mRNA is shown on the left whereas female (♀) mRNA is shown on the right side of each box. References for mouse mRNA expression are included (Buist and Klaassen, 2004; Alnouti et al., 2006). Bottom, relative mRNA levels of transporters in human liver, kidneys, lung, heart, brain, testes, ovaries, placenta, and uterus are shown. Data for humans were obtained from GNF SymAtlas (http://symatlas.gnf.org/; now located at http://biogps.gnf.org). The GNF1H/MAS5 data set was accessed during September 2008.

Oct/OCT transporters mediate the uptake of organic cations that are positively charged at physiological pH. OCTs are classified as uniporters and enhance cellular entry of chemicals by facilitated diffusion. OCT-mediated transport is electrogenic and independent from sodium (Koepsell and Endou, 2004). The primary driving force that determines the direction of translocation is the electrochemical gradient of the transported organic cation, typically an inside-negative membrane potential.

Substrates of Oct/OCT transporters have relatively low molecular weights and are hydrophilic organic cat-

TABLE 4

Subcellular localization of uptake Oct, Octn, Oat, and Urat transporters in various species

For each transporter, the apical or basolateral localization in a particular tissue and/or species is provided. Species included rat (R), mouse (M), human (H), and bovine (B). Detailed information regarding particular cellular populations or regions of the tissue are provided for some transporter isoforms.

Cellular Localization	Tissue	Species	Cell Types	References
Oct1				
Basolateral	Liver	R	Hepatocytes (centrilobular)	Meyer-Wentrup et al., 1998
Basolateral	Kidney	R	Proximal tubule cells (S1/S2)	Karbach et al., 2000
Basolateral	Jejunum	H	Enterocytes	Muller et al., 2005
Basolateral	Testes	R	Sertoli cells	Maeda et al., 2007a
Apical	Lung	R, H	Ciliated epithelial cells	Lips et al., 2005
Oct2				
Basolateral	Kidney	R, H	Proximal tubule cells (S2/S3)	Karbach et al., 2000; Motohashi et al., 2002
Apical	Lung	R, H	Ciliated epithelial cells	Lips et al., 2005
Apical	Choroid plexus	R	Epithelial cells	Sweet et al., 2001
Apical	Olfactory mucosa	B	Epithelial cells	Chemuturi and Donovan, 2007
Oct3				
Basolateral	Kidney	H	Proximal tubule cell line	Glube and Langguth, 2008
Basolateral	Placenta	H	Syncytiotrophoblasts	Sata et al., 2005
Apical	Jejunum	H	Enterocytes	Muller et al., 2005
Apical	Testes	R	Sertoli cells	Maeda et al., 2007a
Apical	Lung	R, H	Ciliated epithelial cells	Lips et al., 2005
Octn1				
Apical	Kidney	M	Proximal tubule cells	Tamai et al., 2004
Apical	Eye	H	Corneal-limbal and conjunctival epithelium	Garrett et al., 2008
N.D.	Heart	M	Endothelial cells in blood vessels	Iwata et al., 2008
Octn2				
Apical	Kidney	M, R, H	Proximal tubule cells	Tamai et al., 2001a; Masuda et al., 2006
Apical	Placenta	H	Syncytiotrophoblasts	Lahjouji et al., 2004; Grube et al., 2005
Apical	Small intestine	R	Enterocytes	Duran et al., 2005
Apical	Eye	H	Corneal-limbal and conjunctival epithelium	Garrett et al., 2008
Apical	Epididymis	M	Principal cells, spermatozoa	Yakushiji et al., 2006; Kobayashi et al., 2007
Basolateral	Epididymis	R	Epithelia of distal caput and corpus	Rodriguez et al., 2002
Basolateral	Testes	R	Sertoli cells	Kobayashi et al., 2005a
Basolateral	Brain	R	Capillary endothelial cells	Miecz et al., 2008
N.D.	Brain	M, R	Olfactory bulb and nerve, cortex, cerebellum, spinal cord, hippocampus, hypothalamus, choroid plexus, astrocytes	Inazu et al., 2006; Lamhonwah et al., 2008
N.D.	Pancreas	M	α Cells	Kai et al., 2005
N.D.	Heart	M, H	Cardiac muscle cells, endothelial cells	Grube et al., 2006b; Iwata et al., 2008
Octn3				
Basolateral	Small intestine	R	Enterocytes	Duran et al., 2005
N.D.	Epididymis	M	Spermatozoa	Kobayashi et al., 2007
N.D.	Brain	M	Olfactory bulb and nerve, cortex, cerebellum, grey matter, hippocampus, hypothalamus, choroid plexus	Lamhonwah et al., 2008
Oat1				
Basolateral	Kidney	M, R, H	Proximal tubule cells	Hosoyamada et al., 1999; Tojo et al., 1999; Eraly et al., 2006
Basolateral	Choroid plexus	M	Ependymal cells	Bahn et al., 2005
N.D.	Muscle	H	Skeletal muscle cells	Takeda et al., 2004
N.D.	Adrenal gland	R	Outer zona fasciculate	Beery et al., 2003
Oat2				
Basolateral	Liver	R	Hepatocytes	Simonson et al., 1994
Basolateral	Kidney	H	Proximal tubule cells	Enomoto et al., 2002b
Apical	Kidney	M, R	Proximal tubule cells	Kojima et al., 2002; Ljubojevic et al., 2007
Oat3				
Basolateral	Kidney	M, R, H	Proximal tubule cells	Cha et al., 2001; Kojima et al., 2002; Bahn et al., 2005
Basolateral	Eye	R	Retinal vascular endothelial cells	Hosoya et al., 2008
Basolateral	Brain	R	Capillary endothelial cells	Kikuchi et al., 2003; Roberts et al., 2008
Apical	Choroid plexus	M	Epithelial cells	Sweet et al., 2002; Sykes et al., 2004
N.D.	Muscle	H	Skeletal muscle cells	Takeda et al., 2004
Oat4				
Apical	Kidney	H	Proximal tubule cells	Babu et al., 2002a; Ekaratanawong et al., 2004
Basolateral	Placenta	H	Syncytiotrophoblasts	Ugele et al., 2008
Oat5				
Apical	Kidney	R	Proximal tubule cells	Anzai et al., 2005
Oat6				
N.D.	Olfactory mucosa	M	Olfactory cells	Monte et al., 2004
Oat7				
Basolateral	Liver	H	Hepatocytes	Shin et al., 2007
Urat1				
Apical	Kidney	M, H	Proximal tubule cells	Enomoto et al., 2002a; Hosoyamada et al., 2004

N.D., not determined.

ions with widely diverse molecular structures (Table 3). There is extensive overlap of substrate and inhibitor specificities among OCT1–3 from different species. Oct1/OCT1 orthologs from four species (rat, mouse, rabbit, and human) all transport tetraethylammonium. However, there are some differences in affinity and transport rates. In contrast to rabbit and human, rat and mouse Oct1 do not transport larger structural analogs (i.e., tetrapropylammonium and tetrabutylammonium) (Dresser et al., 2000).

Model compounds for Oct/OCT-mediated transport include tetraethylammonium, the neurotoxin 1-methyl-4-phenylpyridinium, and N^1-methyl-nicotinamide (Busch et al., 1996b; Gorboulev et al., 1997; Zhang et al., 1997; Kekuda et al., 1998; Urakami et al., 1998; Wu et al., 2000b). Pharmaceuticals have also been identified as Oct/OCT substrates and consist of the antidiabetic drug metformin (Kimura et al., 2005), the antiviral drugs acyclovir and zalcitabine (Takeda et al., 2002; Jung et al., 2008), the antineoplastic agent cisplatin (Ciarimboli et al., 2005b; Yokoo et al., 2007), the *N*-methyl-D-aspartate-receptor antagonist memantine (Busch et al., 1998), and the histamine H_2-receptor antagonist ranitidine (Bourdet et al., 2005). Biogenic amine neurotransmitters including dopamine, epinephrine, norepinephrine, and histamine are also transported by OCTs (especially OCT3 as the extraneuronal monoamine transporter) (Busch et al., 1996a, 1998; Amphoux et al., 2006). Substrates of the various isoforms are shown in Table 3.

3. Organic Cation/Carnitine Transporters. Like OCT transporters, OCTNs are members of the *SLC22* family. Although they can transport cationic chemicals, OCTNs are most notably known for their ability to influx carnitine (Table 4). OCTN1 was cloned from a human fetal liver cDNA library in 1997, and rat and mouse isoforms were subsequently isolated (Tamai et al., 1997, 2000b; Wu et al., 2000a). OCTN2 was cloned from a human kidney cDNA library (Tamai et al., 1998). Whereas OCTN1 protein is predicted to contain 11 transmembrane domains and one-nucleotide binding domain (Tamai et al., 1997), OCTN2 probably has 12 transmembrane domains (Tamai et al., 1998). Octn3 was first found in mice, and although OCTN3 protein has been detected in a human cell line, the human gene has not been described (Tamai et al., 2000b; Lamhonwah et al., 2003).

Mouse and rat Octn1 are most prominently expressed in kidneys, with detectable mRNA in small intestine, stomach, heart, etc. (Fig. 2) (Tamai et al., 2000b; Slitt et al., 2002; Alnouti et al., 2006). In situ hybridization localizes Octn1 transcript to rat brain, kidney (cortex and medulla), heart (myocardium and valves), and placenta (labyrinth zone) (Wu et al., 2000a). Human OCTN1 is expressed in kidneys, skeletal muscle, placenta, prostate, heart, fetal liver, eyes, and lungs (Fig. 2) (Tamai et al., 1997; Garrett et al., 2008). There is also prominent expression of human OCTN1 in spleen, bone marrow, and whole blood, with particularly high levels in $CD14^+$ cells (Tokuhiro et al., 2003). Likewise, immunohistochemical findings demonstrate Octn1 in different regions of the mouse brain and on the apical membrane of mouse proximal tubule cells (Table 4) (Tamai et al., 2004; Lamhonwah et al., 2008). Although OCTN1 is typically localized to the plasma membrane, intracellular localization in mitochondria has been reported and may be responsible for carnitine accumulation in this organelle (Lamhonwah and Tein, 2006).

Mouse and rat Octn2 mRNA are primarily expressed in kidneys (Fig. 2) (Kido et al., 2001; Rodríguez et al., 2002; Slitt et al., 2002; Alnouti et al., 2006). Messenger RNA and/or protein staining also localize Octn2 to heart (myocardium, valves, and arterioles), epididymis, pancreas (α-cells), and brain (cortex, hippocampus, choroid plexus, cerebellum) (Table 4) (Wu et al., 1999; Rodríguez et al., 2002; Kai et al., 2005; Lamhonwah et al., 2008). Human OCTN2 is most notably detected in kidneys and placenta and to a lesser degree in other tissues (Fig. 2) (Tamai et al., 1998; Tokuhiro et al., 2003; Lahjouji et al., 2004; Garrett et al., 2008). Octn2 and OCTN2 proteins are present on the brush border membrane vesicles from kidneys (Tamai et al., 2001a), placental syncytiotrophoblasts (Grube et al., 2005), and small intestine enterocytes (Durán et al., 2005), as well as the basolateral surface of epididymal cells (Rodríguez et al., 2002) (Table 4).

Mouse testes and epididymal spermatozoa (middle piece of sperm tail) express the highest levels of Octn3 mRNA and/or protein (Fig. 2) (Tamai et al., 2000b; Alnouti et al., 2006; Kobayashi et al., 2007). Octn3 is also detected in mouse ovaries (Alnouti et al., 2006), along the basolateral membrane of rat enterocytes (Durán et al., 2005), and within multiple mouse brain regions (Lamhonwah et al., 2008). Although Octn3 and OCTN3 proteins are found on the plasma membrane of various cell types, localization of these proteins to the peroxisome has also been reported and may be important in supplying carnitine for peroxisomal lipid metabolism (Lamhonwah et al., 2005).

As implied by their name, Octn/OCTN proteins transport carnitine (Table 3). During the generation of metabolic energy, carnitine is required for the transport of fatty acids from the cytosol into the mitochondria during the breakdown of lipids. Carnitine transports long-chain acyl groups generated from fatty acids into the mitochondrial matrix, where they can be broken down through β-oxidation. Octn1/OCTN1 is an organic cation uniporter or H^+/organic cation antiporter that can transport in both directions. Octn2/OCTN2 can act as organic cation uniporters or sodium-carnitine cotransporters (Tamai et al., 1998). Mouse Octn3 is the most selective transporter for carnitine, whereas Octn1 is the least (Tamai et al., 2000b). Mouse Octn1 and Octn2 transport carnitine in a sodium-dependent manner, and

Octn3 transports carnitine in a sodium-independent manner (Tamai et al., 2000b).

Octn1/OCTN1 and Octn2/OCTN2 also transport organic cations (Table 3). Both OCTN1 and OCTN2 transport tetraethylammonium, verapamil, quinidine, ergothioneine, and pyrilamine (Tamai et al., 1997; Ohashi et al., 1999; Yabuuchi et al., 1999; Ganapathy et al., 2000; Grube et al., 2006b). OCTN2 also transports the antiseizure drug valproic acid, the antibiotic cephaloridine, and the diuretic spironolactone (Ohashi et al., 1999; Ganapathy et al., 2000; Grube et al., 2006b). In contrast to Octn1 and Octn2, Octn3 has little or no affinity for organic cation model compounds (i.e., tetraethylammonium) and seems to function only as a carnitine transporter (Tamai et al., 2000b).

4. Organic Anion Transporters. OATs are members of the solute carrier family *SLC22A* along with OCTs and OCTNs (Table 1). OAT transporters have 12 predicted transmembrane domains arranged in two sets of six helical domains (Simonson et al., 1994; Hosoyamada et al., 1999; Race et al., 1999; Cha et al., 2000). OATs are thought to have two large loop structures between transmembrane domains 1 and 2 and domains 6 and 7 (Hosoyamada et al., 1999). The first loop is extracellular and contains glycosylation sites (Hosoyamada et al., 1999). Glycosylation at multiple sites often results in a range of molecular weights reported for OAT transporters. The second loop occurs intracellularly and contains phosphorylation sites (Hosoyamada et al., 1999). Based on hydropathy analysis, OAT1–3 probably contain cytoplasmic amino and carboxyl termini (Simonson et al., 1994; Hosoyamada et al., 1999). Individual OAT transporters are often linked as phylogenic pairs based upon closely related sequence alignment: OAT1 and OAT3; OAT4 and the urate transporter 1 (URAT1). For example, both OAT4 and URAT1 are found sequentially on chromosome 11q13.1.

Oat1 was first cloned from a rat kidney cDNA library in 1997 (Sekine et al., 1997; Sweet et al., 1997). During the same period, mouse Oat1 was cloned and called the novel kidney transporter (Lopez-Nieto et al., 1997). Human OAT1 was subsequently identified (Reid et al., 1998; Hosoyamada et al., 1999; Race et al., 1999). Rodent Oat1 and human OAT1 mRNA are highest in kidneys (Fig. 2) (Hosoyamada et al., 1999; Buist and Klaassen, 2004), and their proteins are abundantly expressed on the basolateral membranes of renal proximal tubules (Hosoyamada et al., 1999; Tojo et al., 1999). Specifically, OAT1 is strongly expressed on the basolateral membrane of proximal tubules in the S2 segment (Table 4) (Ljubojevic et al., 2004).

Oat2 was first identified in 1994 using a rat liver cDNA library and named the "novel liver-specific transporter" (Simonson et al., 1994). Oat2 was later recloned and renamed (Sekine et al., 1998; Sun et al., 2001b; Kobayashi et al., 2002b). Oat2/OAT2 show species differences in tissue distribution. Mouse Oat2 is found almost exclusively in kidneys (Fig. 2) (Kobayashi et al., 2002b; Buist and Klaassen, 2004). In contrast, rat Oat2 and human OAT2 are expressed primarily in liver with lower levels in kidneys (Fig. 2) (Sekine et al., 1998; Sun et al., 2001b). Furthermore, localization of Oat2/OAT2 proteins in kidney is species-dependent. Rodent Oat2 protein is expressed on the apical membrane of S3 proximal tubules (Table 4) (Kojima et al., 2002; Ljubojević et al., 2007), whereas human OAT2 protein is basolateral (Enomoto et al., 2002b). It is noteworthy that in liver, rat Oat2 protein traffics to the basolateral membrane of hepatocytes (Simonson et al., 1994).

Rat and mouse Oat3 and human OAT3 were identified simultaneously in 1999 (Brady et al., 1999; Kusuhara et al., 1999; Race et al., 1999). Mouse Oat3 was isolated from an animal model of osteosclerosis and termed reduced in osteosclerosis transporter (Brady et al., 1999). Expression of Oat3/OAT3 in mice and humans is confined primarily to the kidneys, where it is localized to the basolateral membrane of proximal tubule cells (Fig. 2, Table 4) (Cha et al., 2001; Kojima et al., 2002; Buist and Klaassen, 2004). Within the kidneys, rat Oat3 is observed in proximal tubule S1 and S2 segments as well as thick ascending limb, distal tubules, and collecting ducts (Ljubojevic et al., 2004). In brain, Oat3 mRNA is expressed in choroid plexus in rats (Choudhuri et al., 2003), and Oat3 protein localizes to the basolateral membrane of brain capillary endothelial cells in rodents (Kikuchi et al., 2003; Ohtsuki et al., 2004a). Mouse Oat3 protein is also expressed on the apical membrane of choroid plexus epithelial cells (Sweet et al., 2002) as well as in developing bone (Brady et al., 1999).

In 2000, OAT4 was identified and functionally characterized (Cha et al., 2000). OAT4 mRNA is expressed largely in kidneys and placenta (Fig. 2) (Cha et al., 2000). Within the kidneys, OAT4 is found on the apical membrane of renal proximal tubule cells (Table 4) (Babu et al., 2002a; Ekaratanawong et al., 2004). In contrast, OAT4 protein is expressed on the basolateral membrane of placental syncytiotrophoblasts (Ugele et al., 2008). No mouse or rat Oat4 ortholog has been identified.

Much less is known about OAT5–7. OAT5 was first identified in humans in 2001 (Sun et al., 2001b) and subsequently in mice (Youngblood and Sweet, 2004) and rats (Anzai et al., 2005). Mouse and rat Oat5 are primarily expressed in kidneys and localize to the apical membrane of proximal tubules in the outer medullary and juxtamedullary cortex in the S2 and S3 segments (Table 4) (Youngblood and Sweet, 2004; Anzai et al., 2005; Kwak et al., 2005). Oat6 has been described only in mice and is uniquely localized to the olfactory mucosa (Monte et al., 2004). OAT7 is the most recently described OAT and was cloned from a human liver cDNA library (Shin et al., 2007). OAT7 protein is localized to the basolateral membrane of human hepatocytes (Shin et al., 2007).

Like Oats, Urat1 is a member of the *SLC22A* family. The Urat1 transporter was first cloned from a mouse kidney cDNA library and named renal-specific transporter (Table 1) (Mori et al., 1997). The human URAT1 ortholog was later identified (Enomoto et al., 2002a). Urat1/URAT1 transporters are expressed predominantly in the kidneys along the apical border (Fig. 2, Table 4) (Enomoto et al., 2002a; Hosoyamada et al., 2004). Mouse Urat1 protein is also detected in brain capillaries and along the choroid plexus (Imaoka et al., 2004).

The function of Oat/OATs as organic anion exchangers (antiporters) is enabled by sodium and dicarboxylate gradients generated by the sodium-dicarboxylate cotransporter and the sodium-potassium ATPase. In the cases of OAT1 and -3, uptake of substrates across the basolateral membrane is coupled to an outwardly directed concentration gradient of dicarboxylates (i.e., α-ketoglutarate and glutarate) (Wolff et al., 1992; Sekine et al., 1997; Sweet et al., 1997; Bakhiya et al., 2003; Koepsell and Endou, 2004). The concentration gradient of the dicarboxylate provides the driving force for entry of organic anions against an opposing force (inside-negative membrane potential). Because the concentration gradient of the dicarboxylate is maintained by a sodium-potassium-ATPase pump, this mechanism of transport is typically referred to as tertiary transport (Srimaroeng et al., 2008). Coexpression of mouse Oat3 and a sodium-dicarboxylate transporter stimulates Oat3-mediated transport (Ohtsuki et al., 2004a). Rat Oat2 is not thought to be an organic anion-dicarboxylate exchanger (Sekine et al., 1998).

Oat1/OAT1 and Oat3/OAT3 display wide substrate selectivity including endogenous substrates (cyclic nucleotides, urate, indoxyl sulfate) and pharmaceuticals (antibiotics, nonsteroidal anti-inflammatory drugs, diuretics, anticancer drugs, uricosuric agents) (Table 3) (Sekine et al., 1997; Sweet et al., 1997; Apiwattanakul et al., 1999; Enomoto et al., 2003). *p*-Aminohippurate and estrone sulfate are the prototypical substrates of OAT1 and OAT3, respectively. Oat1/OAT1 transport antibiotics (penicillin G, cephaloridine, tetracycline) and antivirals (such as cidofovir, adefovir, zidovudine, acyclovir, etc.) (Cihlar et al., 1999; Jariyawat et al., 1999; Wada et al., 2000; Babu et al., 2002b). Mercapturic acids are *N*-acetyl-L-cysteine *S*-conjugates that are transported by Oat1 and thus eliminated by the kidneys. For example, rat Oat1 can transport *S*-(2,4-dinitrophenyl)-*N*-acetyl-L-cysteine (Pombrio et al., 2001). Oat1/OAT1 also transports the chelator 2,3-dimercapto-1-propanesulfonic acid and the mercury thiol conjugates of *N*-acetylcysteine, homocysteine, and cysteine, probably representing a mechanism for clearance of the environmental neurotoxin methyl mercury (Islinger et al., 2001; Pombrio et al., 2001; Koh et al., 2002; Zalups and Ahmad, 2005a,c).

Oat2/OAT2 mediates the sodium-independent uptake of not only *p*-aminohippurate but also endogenous (prostaglandins, glutarate) and other exogenous (methotrexate, valproic acid, allopurinol) chemicals (Sun et al., 2001b; Kobayashi et al., 2002b). Species-specific transport of salicylate has been noted: it is transported by rat Oat2, but not by mouse Oat2 (Sekine et al., 1998; Kobayashi et al., 2002b). OAT4 mediates sodium-independent transport of sulfate conjugates (estrone sulfate, indoxyl sulfate, dehydroepiandrosterone sulfate) (Cha et al., 2000; Babu et al., 2002a; Enomoto et al., 2003; Zhou et al., 2006). In general, Oat/OAT5–7 transport dehydroepiandrosterone sulfate and estrone sulfate (Anzai et al., 2005; Schnabolk et al., 2006; Shin et al., 2007). The mycotoxin ochratoxin A is also a substrate for mouse Oat5 (Youngblood and Sweet, 2004). Finally, human OAT7 transports butyrate (Shin et al., 2007).

Urat1/URAT1 seem to be urate-organic anion exchangers (Enomoto et al., 2002a) and are responsible for urate reabsorption in exchange for anions (Hosoyamada et al., 2004). Other organic anions transported by mouse Urat1 include ochratoxin, dehydroepiandrosterone sulfate, and benzylpenicillin (Imaoka et al., 2004).

5. Peptide Transporters. PEPT1 and PEPT2 are members of the solute carrier family (*SLC15A*) that transports di- and tripeptides into cells (Table 1). Pept/PEPT1 and -2 were first identified as key peptide carriers in the small intestine and kidneys, respectively (Fei et al., 1994; Liu et al., 1995). PEPT transporters are predicted to have 12-α-helical transmembrane domains with a large extracellular loop between domains 9 and 10 and intracellular carboxyl and amino termini (Fei et al., 1994).

The tissue distribution of Pept/PEPT1 and -2 in mice and humans is shown in Fig. 3 (Saito et al., 1995; Rubio-Aliaga et al., 2000; Herrera-Ruiz et al., 2001; Lu and Klaassen, 2006). Pept/PEPT1 is most prominently expressed in the small intestine of rodents and humans, where it localizes to the apical membrane of enterocytes (Fig. 3, Table 5) (Fei et al., 1994; Ogihara et al., 1999; Shen et al., 1999; Terada et al., 2005; Lu and Klaassen, 2006). Both peptide transporters are detected in the kidneys with Pept1 along the brush border membrane of S1 proximal tubules in the rat and Pept2 expressed in the S2 and S3 segments (Shen et al., 1999). It is noteworthy that Pept1 mRNA is detected in rat but not mouse kidneys (Lu and Klaassen, 2006). In addition to plasma membrane localization, Pept1 is also found in lysosomes (Bockman et al., 1997; Zhou et al., 2000; Sun et al., 2001a). PEPT1 mRNA is also detected in human kidneys, lungs, colon, pancreas, and liver (Liang et al., 1995; Zhang et al., 2004a).

Pept2 mRNA is expressed primarily in mouse kidneys (Fig. 3) (Lu and Klaassen, 2006). Pept2 mRNA is expressed in specific cell types of the brain, including astrocytes, subependymal cells, and ependymal cells, and Pept2 protein is detected along the apical membrane of epithelial cells of the choroid plexus (Table 5) (Berger and Hediger, 1999; Shu et al., 2002). Pept2/PEPT2

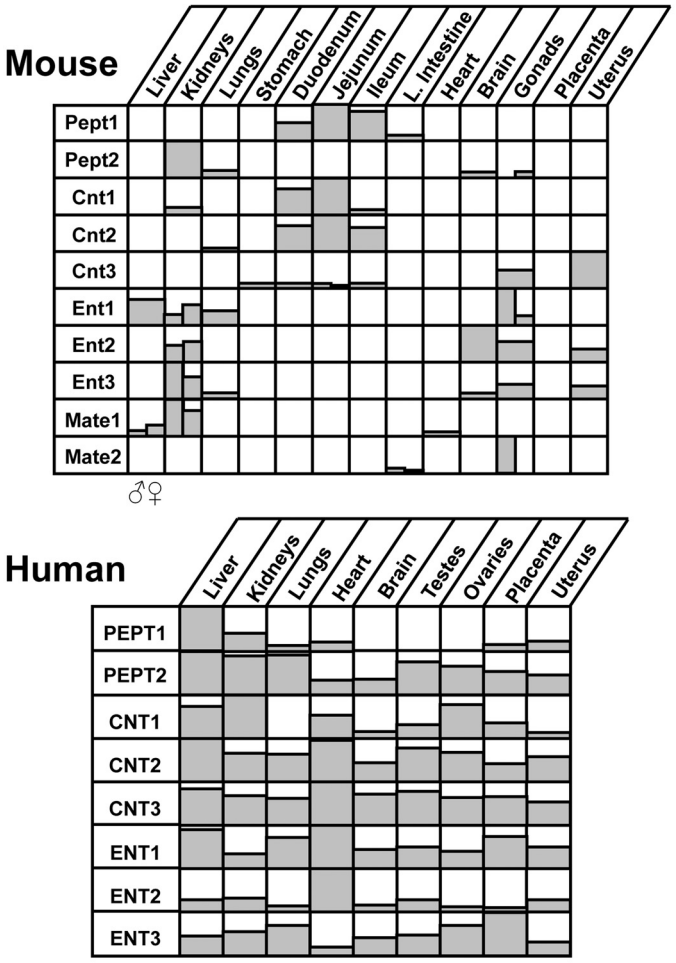

FIG. 3. Tissue distribution of Pept, Cnt, Ent, and Mate mRNA in mice and humans. Top, relative mRNA levels of transporters in mouse liver, kidneys, lung, stomach, duodenum, jejunum, ileum, large intestine, heart, brain, gonads (testes and ovaries), placenta, and uterus are shown. Male (♂) mRNA is shown on the left whereas female (♀) mRNA is shown on the right side of each box. References for mouse mRNA expression are included (Lu et al., 2004; Lu and Klaassen, 2006; Lickteig et al., 2008). Bottom, relative mRNA levels of transporters in human liver, kidneys, lung, heart, brain, testes, ovaries, placenta, and uterus are shown. Data for humans were obtained from GNF SymAtlas (http://symatlas.gnf.org/; now located at http://biogps.gnf.org). The GNF1H/MAS5 data set was accessed during September 2008.

mRNA and/or protein are also expressed in the enteric nervous system, colon, liver, pancreas, lungs, nasal mucosa, and mammary glands (Groneberg et al., 2001, 2002; Zhang et al., 2004a; Bahadduri et al., 2005; Ruhl et al., 2005; Lu and Klaassen, 2006; Quarcoo et al., 2009).

Pept/PEPT1 and -2 have broad substrate and inhibitor specificity, including di- and tripeptides but not amino acids or tetrapeptides (Table 3) (Daniel and Herget, 1997; Terada et al., 2000; Daniel and Kottra, 2004). Peptide transport by PEPT1 and -2 is coupled with the inward translocation of protons leading to electrogenic transport. Key structural features of PEPT1 and -2 substrates have been described elsewhere (Rubio-Aliaga and Daniel, 2008). Glycylsarcosine (Gly-Sar) is a prototypical substrate for Pept/PEPT1 and -2 transport (Liang et al., 1995; Liu et al., 1995). A number of pharmaceuticals are substrates of Pept/PEPTs, including β-lactam antibiotics (cefadroxil, cefixime, ceftibuten), the photosensitizing agent 5-aminolevulinic acid, and the investigational anticancer drug bestatin (Saito et al., 1995, 1996; Wenzel et al., 1996; Döring et al., 1998; Ocheltree et al., 2004a,b; Xiang et al., 2006; Hu et al., 2007).

6. Concentrative Nucleoside Transporters. Nucleosides are glycosylamines consisting of a sugar moiety and a purine or pyrimidine base; they include cytidine, uridine, adenosine, guanosine, thymidine, and inosine. Nucleosides are precursors for nucleotides used in DNA and RNA synthesis and are necessary for cell growth. Uptake of nucleosides by hematopoietic and other cell types is a prerequisite for nucleotide synthesis by salvage pathways because these cells lack de novo synthetic ability. Furthermore, adenosine is an important signaling molecule for neurotransmission, platelet aggregation, and other physiological events. Nucleoside analogs have been developed as drugs to treat viral infections and cancers. Nucleoside uptake transporters have been classified according to their transport properties: concentrative (high-affinity sodium-dependent transport using a physiologic sodium gradient) (*SLC28A*) and equilibrative (low-affinity facilitated carrier transport) (*SLC29A*) (for review, see Pastor-Anglada et al., 2008; Young et al., 2008) (Table 1).

CNT1–2 transporters have been cloned from multiple species and are predicted to contain 13 transmembrane helices with cytoplasmic amino termini and extracellular carboxyl termini (Huang et al., 1994; Ritzel et al., 1997, 1998; Wang et al., 1997; Baldwin et al., 1999; Patel et al., 2000; Hamilton et al., 2001; Shin et al., 2003). CNT2 was originally named the sodium-dependent purine nucleoside transporter (Wang et al., 1997; Ritzel et al., 1998). In mice and rats, Cnt1 and Cnt2 mRNA are expressed primarily in all three segments of the small intestine as well as kidneys (Cnt1) (Fig. 3) (Huang et al., 1994; Che et al., 1995; Hamilton et al., 2001; Shin et al., 2003; Lu et al., 2004). In humans, CNT1 and CNT2 mRNA are high in liver and kidneys and CNT2 mRNA is also detected in heart, brain, placenta, skeletal muscle, small intestine, and pancreas (Fig. 3) (Wang et al., 1997; Ritzel et al., 1998; Shin et al., 2003; Damaraju et al., 2007; Govindarajan et al., 2007). Immunohistochemical studies localize rat Cnt1 protein to the apical surface of multiple cell types including cortical renal tubules, hepatocytes, and enterocytes (Table 5) (Hamilton et al., 2001; Duflot et al., 2002). Cnt3 mRNA is expressed in the uterus, testes, and ovaries of mice and the lungs of rats (Fig. 3) (Lu et al., 2004). CNT3 mRNA and/or protein are expressed in multiple tissues (Fig. 3) (Ritzel et al., 2001; Damaraju et al., 2007). Within the kidneys, CNT3 localizes to the apical surface of proximal tubules and thick ascending loops of Henle along with some intracellular staining (Table 5) (Damaraju et al., 2007).

TABLE 5

Subcellular localization of uptake Pept, Cnt, Ent, and efflux Mate transporters in various species

For each transporter, the apical or basolateral localization in a particular tissue and/or species is provided. Species included rat (R), mouse (M), human (H), and bovine (B). Detailed information regarding particular cellular populations or regions of the tissue are provided for some transporter isoforms.

Cellular Localization	Tissue	Species	Cell Types	References
Pept1				
Apical	Small intestine	R	Enterocytes	Ogihara et al., 1999
Apical	Kidney	R	Proximal tubule cells	Shen et al., 1999
Apical	Liver	M	Cholangiocytes	Knutter et al., 2002
Intracellular	Pancreas	R	Acinar cells (lysosomes)	Bockman et al., 1997
Pept2				
Apical	Kidney	M, R	Proximal tubule cells	Shen et al., 1999; Rubio-Aliaga et al., 2000
Apical	Brain	R	Choroid plexus	Shu et al., 2002; Shen et al., 2004
Apical	Mammary gland	R	Glandular and ductal epithelial cells	Groneberg et al., 2002
Apical	Lung	M, R, H	Tracheal and bronchial epithelial cells, Alveolar Type 2 pneumocytes	Groneberg et al., 2001; Bahadduri et al., 2005
N.D.	Nasal mucosa	R	Epithelial cells	Quarcoo et al., 2008
N.D.	Intestine	M	Glial cells and macrophages	Ruhl et al., 2005
Cnt1				
Apical	Small intestine	R, H	Enterocytes	Hamilton et al., 2001; Govindarajan et al., 2007
Apical	Kidney	R, H	Proximal tubule cells	Hamilton et al., 2001; Govindarajan et al., 2007
Apical	Liver	R	Hepatocytes	Hamilton et al., 2001; Duflot et al., 2002
Cnt2				
Apical	Kidney	H	Proximal tubule cells	Govindarajan et al., 2007
Apical	Small intestine	H	Enterocytes	Govindarajan et al., 2007
Basolateral	Liver	R, H	Hepatocytes	Duflot et al., 2002; Govindarajan et al., 2008
Cnt3				
Apical/Intracellular	Kidney	H	Proximal tubule cells, loop of Henle	Damaraju et al., 2007; Errasti-Murugarren et al., 2007
Ent1				
Apical	Placenta	H	Syncytiotrophoblasts, endothelial cells	Govindarajan et al., 2007
Apical/Basolateral	Kidney	H	Proximal/distal tubule cells, Loop of Henle, collecting duct, corticomedullary junction	Mangravite et al., 2003; Damaraju et al., 2007; Govindarajan et al., 2007
Basolateral	Liver	H	Hepatocytes	Govindarajan et al., 2008
Lateral	Small intestine	H	Enterocytes, crypt cells	Govindarajan et al., 2007
Ent2				
Basolateral	Liver	H	Hepatocytes	Govindarajan et al., 2008
Basolateral	Kidney	H	Epithelial cells	Mangravite et al., 2003
Lateral	Small intestine	H	Enterocytes, crypt cells	Govindarajan et al., 2007
N.D.	Heart	R	Sinoatrial node, atrial and ventricular cells	Musa et al., 2002
MATE1				
Apical	Liver	M, H	Hepatocytes, cholangiocytes	Otsuka et al., 2005
Apical	Kidney	R, H	Proximal and distal tubule cells	Otsuka et al., 2005; Masuda et al., 2006; Nishihara et al., 2007
Apical	Kidney	M	Cortical collecting ducts, proximal tubules, Thin limb of loop of Henle	Otsuka et al., 2005
Mate2				
N.D.	Testes	M	Leydig cells	Hiasa et al., 2007
MATE2-K				
Apical	Kidney	H	Proximal tubule cells	Masuda et al., 2006; Tanihara et al., 2007

N.D., not determined.

Within the concentrative transporters, CNT1 transports pyrimidines (but also adenosine), CNT2 transports purines (but also uridine), and CNT3 transports both purines and pyrimidines (Table 3) (Huang et al., 1994; Fang et al., 1996; Ritzel et al., 1997, 1998, 2001; Wang et al., 1997; Schaner et al., 1999). The chemotherapeutic drug gemcitabine and the antiviral drugs stavudine, zalcitabine, and zidovudine are also substrates of CNT1 (Huang et al., 1994; Ritzel et al., 1997; Mackey et al., 1999; Graham et al., 2000; Cano-Soldado et al., 2004). Substrates of CNT2 include nucleoside analog drugs such as the hepatitis drug ribavirin (Patil et al., 1998). As the broadest nucleoside transporter, CNT3 substrates are more numerous (5-fluorouridine, zebularine, gemcitabine, cladribine, fludarabine, etc.) (Ritzel et al., 2001; Toan et al., 2003).

7. Equilibrative Nucleoside Transporters. As low-affinity, facilitated carriers, ENTs transport chemicals down concentration gradients. Intracellular levels of nucleosides are typically low because they are converted

to nucleotides. Although ENT transporters are most often considered uptake carriers, they can function bidirectionally. ENT1–4 transporters have been detected and cloned from different species (Table 1) (Griffiths et al., 1997; Yao et al., 1997; Crawford et al., 1998; Kiss et al., 2000; Baldwin et al., 2005; Zhou et al., 2007b). Hydropathy analysis suggests that Ent1–2 proteins are composed of 11 transmembrane domains with an internal amino terminus and extracellular carboxyl tail (Yao et al., 1997; Crawford et al., 1998).

The mRNA expression of Ent1 is primarily in mouse and rat liver, kidneys, lung, brain, and testes (Fig. 3) (Choi et al., 2000; Lu et al., 2004; Redzic et al., 2005). Human ENT1 expression is wide ranging, including liver, lungs, heart, ovaries, brain, kidneys, erythrocytes, fetal liver, and placenta (Fig. 3) (Griffiths et al., 1997; Anderson et al., 1999b; Pennycooke et al., 2001; Damaraju et al., 2007; Govindarajan et al., 2007). Within the kidneys, ENT1 staining is observed on the apical surface of proximal tubules and on both the apical and basal membranes of the thick ascending loops of Henle and collecting ducts (Table 5) (Damaraju et al., 2007). Similar apical localization of ENT1 is noted in human placental syncytiotrophoblasts (Govindarajan et al., 2007). Ent2 and Ent3 mRNA share similar tissue distributions with highest levels observed in kidneys, brain, gonads, and uteri of mice and rats (Fig. 3) (Anderson et al., 1999a; Lu et al., 2004; Redzic et al., 2005). The profile of ENT2 mRNA demonstrates high levels in skeletal muscle and heart and detectable amounts in other organs (Fig. 3) (Pennycooke et al., 2001). Likewise, ENT3 exhibits broad tissue distribution with prominent expression in placenta, lung, ovaries, spleen, and bone marrow (Baldwin et al., 2005). Mutations in ENT3 have been linked to H syndrome, which is characterized by skin, auditory, heart, and spleen abnormalities (Table 10) (Molho-Pessach et al., 2008). A fourth ENT isoform, ENT4, has also been cloned, although there is less information available about its tissue distribution and transport properties (Barnes et al., 2006; Xia et al., 2007; Zhou et al., 2007b).

Ent/ENT transport is sodium-independent and, like Cnt/CNT transporters, endogenous nucleosides as well as cancer and antiviral nucleoside analogs are common substrates (Table 3) (Griffiths et al., 1997; Mackey et al., 1999; Kiss et al., 2000; Baldwin et al., 2005; Damaraju et al., 2005; Nagai et al., 2007; Govindarajan et al., 2008). It is noteworthy that ENT1 is also expressed in the mitochondria, where it may be involved in the cellular toxicity of antiviral nucleoside drugs (Lai et al., 2004; Govindarajan et al., 2009).

8. Multidrug and Toxin Extrusion Transporters. For a number of years, it was understood that organic cations entered the cells via OCT transporters; however, how they exited was not clear. Transporters were first identified in bacteria and were called NorM and YdhE. They were later named the multidrug and toxin extrusion (MATE) transporters (Morita et al., 1998; Brown et al., 1999; Otsuka et al., 2005; Terada and Inui, 2008). Although MATE transporters are Slc transporters, they function as efflux proteins. Hiasa and colleagues reported that there are three subgroups of mammalian MATE transporters: class I includes rodent Mate1 and human MATE1; class II includes human MATE2 (no rodent ortholog of this subgroup); class III includes mouse and rat Mate2 (Hiasa et al., 2007; Moriyama et al., 2008). In an attempt to avoid confusion, it has been proposed that mouse and rat Mate2 be renamed Mate3 (Terada and Inui, 2008). However, for the purpose of this review, we will continue to use the existing Mate2 designation. Another MATE transporter, multidrug and toxin extrusion 2-K (MATE2-K), shows 94% amino acid similarity with MATE2 (Masuda et al., 2006). MATE2-K was first reported to be a splice variant of MATE2; however, this is currently under reconsideration, because a second attempt to clone human MATE2 has not been successful (Masuda et al., 2006; Terada and Inui, 2008). Mate1 (*SLC47A1*) and Mate2-K (*SLC47A2*) have also been cloned from rabbits (Zhang et al., 2007a) (Table 1). Recent work suggests that MATE1 and MATE2-K are composed of 13 putative transmembrane domains with amino and carboxyl termini on the intracellular and extracellular faces of the plasma membrane, respectively (Masuda et al., 2006; Zhang et al., 2007a; Terada and Inui, 2008).

Mouse Mate1 mRNA is most abundant in kidneys and is detected at lower levels in the liver and heart (Fig. 3) (Otsuka et al., 2005; Lickteig et al., 2008). Human MATE1 is expressed in heart, liver, adrenal gland, testes, skeletal muscle, and kidneys (Otsuka et al., 2005; Masuda et al., 2006). Mouse Mate2 mRNA is strongly detected in testes, whereas human MATE2-K is expressed in kidneys (but not in the testes) (Fig. 3) (Otsuka et al., 2005; Masuda et al., 2006; Hiasa et al., 2007; Lickteig et al., 2008). Differences in the tissue distributions of mouse Mate2 and human MATE2-K may be due to their classification in class II and III subgroups, respectively (Hiasa et al., 2007).

MATE1 effluxes organic cations such as tetraethylammonium, 1-methyl-4-phenylpyridinium, oxaliplatin, and paraquat using a proton-coupled electroneutral exchange (Table 3) (Otsuka et al., 2005; Terada et al., 2006; Chen et al., 2007b; Yokoo et al., 2007). Rat Mate1 also transports the histamine H_2-receptor antagonist cimetidine, the antidiabetic drug metformin, and the antibiotic cephalexin (Ohta et al., 2006; Terada et al., 2006). Mouse Mate1 prefers N^1-methylnicotinamide and guanidine as substrates, whereas mouse Mate2 prefers tetraethylammonium (Hiasa et al., 2007). MATE2-K transports organic cations including tetraethylammonium, 1-methyl-4-phenylpyridinium, cimetidine, procainamide, and metformin (Table 3) (Masuda et al., 2006).

B. ATP-Binding Cassette Transporters

1. Multidrug Resistance Proteins. ABC transporters contain ATP-binding domains that possess ATPase activity (hydrolysis of ATP to ADP) to provide energy for translocating substrates across membranes, most often against concentration gradients. Pgp was the first drug transporter described (Juliano and Ling, 1976). Pgp is encoded by multiple MDR genes, including MDR1 (*ABCB1*) and MDR3 (*ABCB4*) in humans, although Pgp most often indicates the ABCB1 gene product (Table 1) (van der Bliek et al., 1988; Dhir et al., 1990; Lincke et al., 1991). The rodent orthologs of MDR1 and MDR3 are Mdr1a/1b and Mdr2, respectively. To make things more confusing, the *Mdr1a* gene was also referred to as Mdr3 within the older literature (Devault and Gros, 1990; Dhir et al., 1990). MDR1, Mdr1a, and Mdr1b are drug transporters (Dhir et al., 1990), whereas MDR3 and Mdr2 translocate phospholipids such as phosphatidylcholine from the inner to the outer canalicular membrane (Schinkel et al., 1991; Ruetz and Gros, 1994; van Helvoort et al., 1996). The structural topology of Pgp consists of two distinct regions containing six putative transmembrane domains and one nucleotide binding domain (van der Bliek et al., 1988; Devault and Gros, 1990; Aller et al., 2009). The amino and carboxyl termini of Pgp are located intracellularly.

The tissue distribution of Mdr1a/1b and MDR1 is broad with their mRNA detected in many tissues (Fig. 4) (Chin et al., 1989; Melaine et al., 2002; Hitzl et al., 2004). Mdr1a mRNA is most prominent in the large intestine followed by the small intestine, kidneys, and brain (Fig. 4) (Cui et al., 2009c). Meanwhile, Mdr1b expression is highest in the kidneys, lungs, brain, ovaries, and placenta (Fig. 4) (Cui et al., 2009c). Within these tissues, MDR1/Mdr1a/1b proteins are detected on the apical/luminal surface (Table 6) (Schinkel et al., 1994; Lankas et al., 1998; Panwala et al., 1998; Rao et al., 1999; Miller et al., 2000; St-Pierre et al., 2000; Ushigome et al., 2003; Soontornmalai et al., 2006; Sun et al., 2006). Expression of MDR3 and Mdr2 is primarily restricted to the liver, where they localize to the canalicular membrane (Table 6) (Buschman et al., 1992; Smit et al., 1994; de Vree et al., 1998; Scheffer et al., 2000; Cui et al., 2009c). Although MDR3 and Mdr2 mRNA have been detected in additional tissues, functional protein expression has not been shown (Smit et al., 1994; Cui et al., 2009c).

Overexpression of Mdr1a and -1b confers resistance to multiple drugs by enhancing cellular extrusion (Dhir et al., 1990; Raymond et al., 1990). Early work demonstrated that cells transfected with Mdr1b were resistant to colchicine and doxorubicin whereas cells overexpressing Mdr1a were resistant to actinomycin D (Table 7) (Devault and Gros, 1990; Tang-Wai et al., 1995). In addition, MDR1-transfected cells were resistant to vincristine, colchicine, daunorubicin, doxorubicin, and actinomycin D (Schinkel et al., 1991; Tang-Wai et al., 1995).

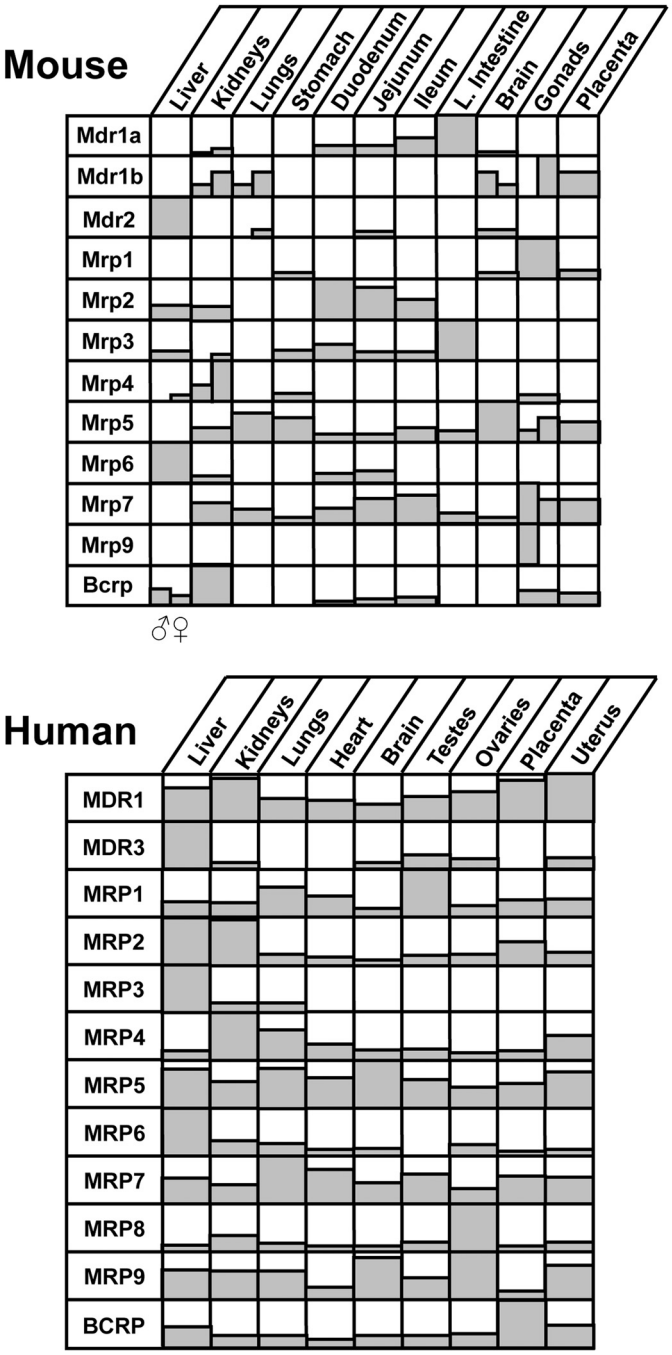

FIG. 4. Tissue distribution of Mdr, Mrp, and Bcrp mRNA in mice and humans. Top, relative mRNA levels of transporters in mouse liver, kidneys, lung, stomach, duodenum, jejunum, ileum, large intestine, brain, gonads (testes and ovaries), and placenta are shown. Male (♂) mRNA is shown on the left whereas female (♀) mRNA is shown on the right side of each box. References for mouse mRNA expression are included (Maher et al., 2005b; Cui et al., 2009c). Bottom, relative mRNA levels of transporters in human liver, kidneys, lung, heart, brain, testes, ovaries, placenta, and uterus are shown. Data for humans were obtained from GNF SymAtlas (http://symatlas.gnf.org/; now located at http://biogps.gnf.org). The GNF1H/MAS5 data set was accessed during September 2008.

Mdr2 translocates a fluorescent phosphatidylcholine analog in overexpressing yeast cells (Ruetz and Gros, 1994). In addition, MDR3 overexpression in fibroblasts

TABLE 6
Subcellular localization of efflux Mdr transporters in various species

For each transporter, the apical or basolateral localization in a particular tissue and/or species is provided. Species included rat (R), mouse (M), human (H), and bovine (B). Detailed information regarding particular cellular populations or regions of the tissue are provided for some transporter isoforms.

Cellular Localization	Tissue	Species	Cell Types	References
Mdr1a/1b/MDR1				
Apical	Liver	H, R	Hepatocytes, cholangiocytes	Gigliozzi et al., 2000; Scheffer et al., 2002c
Apical	Brain	M, R	Endothelial cells, choroid plexus	Schinkel et al., 1994; Rao et al., 1999; Miller et al., 2000
Apical	Placenta	M,H	Syncytiotrophoblasts	Lankas et al., 1998; St-Pierre et al., 2000
Apical	Fetal membranes	M	Visceral yolk sac	Lankas et al., 1998
Apical	Colon	M	Epithelial cells	Panwala et al., 1998
Apical	Pancreas	H	Small epithelial ducts	Scheffer et al., 2002b
Apical	Small intestine	R	Enterocytes (jejunum/ileum)	Ujhazy et al., 2001; Rost et al., 2002
Apical	Lung	H	Bronchial and bronchiolar epithelium	Scheffer et al., 2002c
Apical	Kidney	R, H	Proximal tubule cells	Jette et al., 1996; Ernest et al., 1997
N.D.	Testes	H	Myoid, Leydig, capillary endothelial cells	Bart et al., 2004
N.D.	Inner ear	M	Capillary endothelial cells	Zhang et al., 2000
N.D.	Adrenal gland	H	Cortex	Scheffer et al., 2002b
Mdr2/MDR3				
Apical	Liver	M,H	Hepatocytes	Buschman et al., 1992; de Vree et al., 1998

N.D., not determined.

TABLE 7
Substrates for ABC transporters

Substrates of the various transporter isoforms were identified using in vitro transport studies of human or rodent isoforms or from in vivo studies using knockout mice or mutant rats. A number of substrates are provided. Not all substrates are included in this list.

MDR1	Actinomycin D, amitriptyline, cerivastatin, colchicine, cyclosporine A, daunorubicin, digoxin, diltiazem, docetaxel, domperidone, doxorubicin, erlotinib, erythromycin, etoposide, fexofenadine, imatinib, indinavir, ivermectin, lapatinib, loperamide, losartan, lovastatin, nelfinavir, ondansetron, oseltamivir, paclitaxel, phenytoin, prazosin, quinidine, ritonavir, saquinavir, sparfloxacin, terfenadine, tetracycline, (99m)Tc-tetrofosmin, topotecan, vecuronium, verapamil, vinblastine, vincristine
MRP1	Aflatoxin B1, daunorubicin, *S*-(2,4-dinitrophenyl)-glutathione, doxorubicin, epirubicin, estradiol-17β-glucuronide, estrone-3-sulfate, etoposide glucuronide, folate, fluo-3, oxidized glutathione, glutathione-conjugated aflatoxin B1, glutathione-conjugated chlorambucil, glutathione-conjugated ethacrynic acid, glutathione-conjugated 4-hydroxynonenal, glutathione-conjugated prostaglandin A, grepafloxacin, leukotrienes C_4, D_4, and E_4 (glutathione-conjugated leukotriene C_4), methotrexate, methoxychlor, vincristine
MRP2	Acetaminophen-glucuronide, acetaminophen-sulfate, *p*-aminohippurate, arsenic-glutathione, bilirubin-glucuronide, BQ-123, diclofenac-glucuronide, *S*-(2,4-dinitrophenyl)-glutathione, estradiol-17β-glucuronide, ethinylestradiol glucuronide, glutathione-conjugated ethacrynic acid, glutathione-conjugated 4-hydroxynonenal, indinavir, leukotriene C_4, methotrexate, morphine-3-glucuronide, ochratoxin A, oxidized and reduced glutathione, PhIP, ritonavir, saquinavir, sulfotaurolithocholic acid, taurine-conjugated cholic acid, taurolithocholate sulfate, vinblastine
MRP3	Acetaminophen-glucuronide, bilirubin, estradiol-17β-glucuronide, ethinylestradiol glucuronide, etoposide, etoposide-glucuronide, folate, glycocholate, leucovorin, methotrexate, morphine-3-glucuronide, morphine-6-glucuronide, resveratrol-glucuronide, taurochenodeoxycholate-3-sulfate, taurocholate, taurolithocholate-3-sulfate
MRP4	Adefovir, *p*-aminohippurate, bimane-glutathione, cefazolin, ceftizoxime, cholic acid, cyclic AMP and GMP, dehydroepiandrosterone sulfate, edaravone sulfate, estradiol-17β-glucuronide, folate, furosemide, glycine- and taurine-conjugated bile acids, hydrochlorothiazide, irinotecan and its active metabolite, leucovorin, leukotriene B_4 and C_4, 6-mercaptopurine, methotrexate, prostaglandins E_1, E_2, and $F_2\alpha$, taurocholate, tenofovir, thromboxane B_2, topotecan, urate, zidovudine
MRP5	Adefovir, cadmium chloride, cyclic AMP and GMP, 5-fluorouracil, folate, hyaluronan, 6-mercaptopurine, methotrexate, potassium antimonyl, 6-thioguanine
MRP6	BQ-123, *S*-(2,4-dinitrophenyl)-glutathione, *N*-ethylmaleimide glutathione, etoposide, leukotriene C_4, teniposide
MRP7	Docetaxel, estradiol-17β-glucuronide, leukotriene C_4, paclitaxel, vinblastine, vincristine
MRP8	Cyclic AMP and GMP, dehydroepiandrosterone sulfate, estradiol-17β-glucuronide, estrone-3-sulfate, 5-fluorouracil, folate, glycocholate, leukotriene C_4, methotrexate, taurocholate, zalcitabine
BCRP	Abacavir, aflatoxin B, albendazole sulfoxide, ciprofloxacin, coumestrol, daidzein, dantrolene, dehydroepiandrosterone sulfate, dipyridamole, edaravone sulfate, enrofloxacin, erlotinib, estradiol-17β-glucuronide, estrone-3-sulfate, etoposide, furosemide, gefitinib, genistein, glyburide, grepafloxacin, hematoporphyrin, Hoechst, hydrochlorothiazide, imatinib, lamivudine, lapatinib, methotrexate, mitoxantrone, nitrofurantoin, norfloxacin, ofloxacin, oxfendazole, pheophorbide a, PhIP, prazosin, resveratrol 3-sulfate, resveratrol di-sulfate, riboflavin, rosuvastatin, triamterene, ulifloxacin, zidovudine

PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine.

promotes the transfer of phosphatidylcholine from the inner to outer leaflet of the plasma membrane (Smith et al., 1994). Translocation from the inner to the outer leaflet of the canalicular membrane by MDR3 enhances the availability of phospholipids for extraction into the bile canaliculi by bile acids. Phospholipids form micelles with bile acids, thereby reducing the likelihood of injury to the biliary tree (Elferink et al., 1997).

2. Multidrug Resistance-Associated Proteins. Mrp/MRP transporters constitute nine members of the ATP-

binding cassette C subfamily (*ABCC1–6, 10–12*) (Table 1). Other transporters in the *ABCC* subfamily are the cystic fibrosis transmembrane conductance regulator (*ABCC7*) and two sulfonylurea receptor isoforms (*ABCC8* and *-9*). The following nine Mrp/MRP isoforms have been cloned from various species: MRP1 (Cole et al., 1992), MRP2 (Ito et al., 1997; Keppler et al., 1997; Paulusma et al., 1997; Fritz et al., 2000), MRP3 (Kiuchi et al., 1998; Uchiumi et al., 1998), MRP4 (Kool et al., 1997; Lee et al., 1998; Chen and Klaassen, 2004), MRP5 (McAleer et al., 1999; Jedlitschky et al., 2000; Wijnholds et al., 2000b), MRP6 (Kool et al., 1999a), MRP7 (Hopper et al., 2001), MRP8, and MRP9 (Bera et al., 2001; Tammur et al., 2001; Shimizu et al., 2003). *ABCC13* is likely to be a pseudogene encoding a truncated protein of fetal origin (Yabuuchi et al., 2002; Annilo and Dean, 2004).

MRP transporters contain consensus regions named the Walker A, Walker B, and Signature C motifs that are required for ATP binding. MRP1, -2, -3, -6, and -7 contain three membrane spanning domains with a total of 17 hydrophobic transmembrane regions. For these five MRP proteins, computational analysis suggests extracellular and intracellular amino and carboxyl termini, respectively. MRP4, -5, -8, and -9 are smaller proteins with only two domains that span the plasma membrane (12 total transmembrane regions). The amino and carboxyl termini are both predicted to be intracellular for MRP4, -5, -8, and -9. MRP proteins have two intracellular nucleotide binding domains. For details of MRP transporters, including historical highlights, the reader is referred to recent reviews (Jedlitschky et al., 2006; Nies et al., 2008; Toyoda et al., 2008; Zhou et al., 2008c).

Mouse Mrp1 mRNA is observed in testes, ovaries, brain, placenta, and stomach (Fig. 4) (Maher et al., 2005b). Human MRP1 mRNA and protein is most highly expressed in testes, lungs, heart, bladder, spleen, adrenal glands, placenta, kidneys, peripheral blood mononuclear cells, and skeletal muscle (Fig. 4) (Cole et al., 1992; Flens et al., 1996; Kool et al., 1997). Within the intestine, the highest MRP1 mRNA levels are found in the ascending and transverse colon (Zimmermann et al., 2005). Overexpression of MRP1 in MDCK cells traffics this protein to the basolateral membrane similar to its localization in the choroid plexus, bronchial epithelia, and intestinal crypt cells (Table 8) (Wright et al., 1998; Peng et al., 1999; Rao et al., 1999; Zhang et al., 2004d; Roberts et al., 2008). Likewise, MRP1 is expressed on the basolateral membrane of the amnion as well as the chorionic and decidua membranes, but on the apical membrane of placental syncytiotrophoblasts and brain capillary endothelial cells (St-Pierre et al., 2000; Pascolo et al., 2003; Zhang et al., 2004d; Aye et al., 2007).

Mouse Mrp2 mRNA is detected in the small intestine, liver, and kidneys (Fig. 4) (Maher et al., 2005b). The initial identification of Mrp2/MRP2 was associated with genetic disorders in rats and humans (Table 10) (Paulusma et al., 1996). Human MRP2 mRNA is most highly expressed in liver, followed by the duodenum and kidneys (Fig. 4) (Kool et al., 1997; Uchiumi et al., 1998). The expression of Mrp2/MRP2 decreases along the intestinal tract with lower detection in the colon compared with the duodenum and ileum (Mottino et al., 2000; Maher et al., 2005b; Zimmermann et al., 2005). It is noteworthy that little difference in Mrp2 mRNA expression was observed between the proximal and distal rat intestine, whereas protein levels declined from jejunum to ileum (Mottino et al., 2000). Overexpression of the *ABCC2* gene in MDCK cells targets the MRP2 protein to the apical surface (Zhang et al., 2004d). Mrp2/MRP2 is expressed on the apical surface of hepatocytes, the amnion epithelial membrane, and proximal tubule cells (Fig. 4, Table 8) (Paulusma et al., 1996; Kinoshita et al., 1998; Scheffer et al., 2000, 2002a; van Aubel et al., 2002; Aye et al., 2007).

Mouse Mrp3 mRNA is expressed in the small and large intestine, liver, stomach, and retinal vascular endothelium (Fig. 4) (Maher et al., 2005b; Tachikawa et al., 2008). Levels of human MRP3 mRNA are highest in liver and are also detectable in duodenum, colon, pancreas, adrenal glands, kidneys, and lungs (Fig. 4) (Kool et al., 1997; Belinsky et al., 1998; Kiuchi et al., 1998; Uchiumi et al., 1998; König et al., 1999; Zimmermann et al., 2005). Typically, Mrp3/MRP3 protein localizes to the basolateral membrane of epithelial cells, including hepatocytes, cholangiocytes, distal convoluted tubules, gallbladder, pancreatic ductal cells, and enterocytes of the ileum and colon (Table 8) (Kool et al., 1999b; Scheffer et al., 2000, 2002b; Soroka et al., 2001; Rost et al., 2002; Zelcer et al., 2006). Two exceptions are localization to the lateral and apical membranes of the choroid plexus epithelial cells and placental syncytiotrophoblasts, respectively (St-Pierre et al., 2000; Soontornmalai et al., 2006).

Rodent Mrp4 mRNA is high in kidneys, prostate, and stomach (Fig. 4) (Chen and Klaassen, 2004; Maher et al., 2005b). Likewise, human MRP4 mRNA is most prominently expressed in the kidneys, followed by lungs, skeletal muscle, prostate, testes, ovaries, small intestine, bladder, platelets, and tonsil (Fig. 4) (Kool et al., 1997; Lee et al., 1998; Jedlitschky et al., 2004). Plasma membrane localization of MRP4 is dependent upon cell type (Table 8). For example, Mrp4/MRP4 localizes to the apical membrane in proximal tubule cells (van Aubel et al., 2002) and brain capillary endothelial cells (Roberts et al., 2008). In contrast, Mrp4/MRP4 protein is detected on the basolateral surface of hepatocytes (Assem et al., 2004), prostate glandular epithelial cells (Lee et al., 2000b; Rius et al., 2005), choroid plexus epithelia (Roberts et al., 2008), and visceral yolk sac epithelium (Aleksunes et al., 2008b).

Mouse Mrp5 and human MRP5 mRNA are widely expressed (Fig. 4) (Kool et al., 1997; Belinsky et al., 1998; McAleer et al., 1999; Dazert et al., 2003; Maher et

TABLE 8

Subcellular localization of efflux Mrp and Bcrp transporters in various species

For each transporter, the apical or basolateral localization in a particular tissue and/or species is provided. Species included rat (R), mouse (M), human (H), and bovine (B). Detailed information regarding particular cellular populations or regions of the tissue are provided for some transporter isoforms.

Cellular Localization	Tissue	Species	Cell Types	References
Mrp1				
Apical	Placenta	H	Syncytiotrophoblasts, endothelial cells	St-Pierre et al., 2000
Apical	Brain	H, B	Capillary endothelial cells	Nies et al., 2004; Zhang et al., 2004d
Basolateral	Choroid plexus	M, R	Epithelial cells	Rao et al., 1999; Wijnholds et al., 2000a
Basolateral	Fetal membranes	H	Amnion, chorionic, decidual membranes	Aye et al., 2007
Basolateral	Lung	M, H	Mucosal layer, bronchial epithelium	Wijnholds et al., 1998; Scheffer et al., 2002c
Basal	Testes	M, H	Leydig and Sertoli cells	Wijnholds et al., 1998; Bart et al., 2004
Basolateral	Intestine	M	Crypt cells (Paneth cells)	Peng et al., 1999
Basolateral	Heart	M	Sarcolemma	Jungsuwadee et al., 2006
N.D.	Kidney	M	Limb of Henle and collecting ducts, glomeruli	Wijnholds et al., 1998; Peng et al., 1999
Mrp2				
Apical/Basolateral	Brain	M, R	Endothelial cells	Miller et al., 2000; Soontornmalai et al., 2006
Apical	Placenta	H	Syncytiotrophoblasts	St-Pierre et al., 2000
Apical	Fetal membranes	M, H	Visceral yolk sac, amnion	Aye et al., 2007; Aleksunes et al., 2008b
Apical	Kidney	R, H	Proximal tubule cells	Schaub et al., 1997; Scheffer et al., 2000
Apical	Liver	R, H	Hepatocytes	Paulusma et al., 1996; Scheffer et al., 2000
Apical	Gallbladder	H	Epithelial cells	Rost et al., 2001
Apical	Small intestine	R	Enterocytes (jejunum)	Mottino et al., 2000; Rost et al., 2002
Mrp3				
Tight junction	Brain	M	Choroid plexus	Soontornmalai et al., 2006
Basolateral	Liver	H	Hepatocytes (periportal)	Konig et al., 1999; Scheffer et al., 2000; Nies et al., 2004
Basolateral	Liver	M, R	Hepatocytes (centrilobular)	Donner and Keppler, 2001; Soroka et al., 2001; Zelcer et al., 2006
Basolateral	Liver	R, H	Cholangiocytes	Soroka et al., 2001; Scheffer et al., 2002b
Basolateral	Pancreas	M, H	Ductal cells	Scheffer et al., 2002b; Zelcer et al., 2006
Basolateral	Kidney	H	Distal convoluted tubule cells, loop of Henle	Scheffer et al., 2002b
Basolateral	Gallbladder	H	Epithelial cells	Scheffer et al., 2002b
Basolateral	Small intestine/colon	M, R, H	Enterocytes (ileum), crypt cells	Rost et al., 2002; Scheffer et al., 2002b; Mutch et al., 2004
N.D.	Adrenal gland	H	Zona reticularis, fasciculate	Scheffer et al., 2002b
Apical	Placenta	H	Syncytiotrophoblasts, endothelium	St-Pierre et al., 2000
Mrp4				
Apical	Brain	R, H	Capillary endothelial cells	Nies et al., 2004; Roberts et al., 2008
Apical/Basolateral	Choroid plexus	R	Epithelial cells	Roberts et al., 2008
Apical	Kidney	H	Proximal tubule cells	van Aubel et al., 2002
Basolateral	Fetal membranes	M	Visceral yolk sac	Aleksunes et al., 2008b
Basolateral	Liver	M	Hepatocytes	Assem et al., 2004
Basolateral	Prostate	H	Glandular epithelial cells	Lee et al., 2000b; Rius et al., 2005
Mrp5				
Basolateral	Brain	R	Ependymal cells	Roberts et al., 2008
Apical	Brain	M, B, H	Endothelial cells, pyramidal neurons	Nies et al., 2004; Zhang et al., 2004d; Soontornmalai et al., 2006
Basolateral	Placenta	H	Syncytiotrophoblasts	Meyer Zu Schwabedissen et al., 2005
Basolateral/Apical	Fetal membranes	M, H	Visceral yolk sac, amnion	Aye et al., 2007; Aleksunes et al., 2008b
N.D.	Genitourinary	H	Corpus cavernosum, ureter, urethra, bladder	Nies et al., 2002b
N.D.	Heart	H	Auricular & ventricular cardiomyocytes, capillary endothelial cells, smooth muscle cells	Dazert et al., 2003

TABLE 8—*Continued.*

Cellular Localization	Tissue	Species	Cell Types	References
Mrp6				
Basolateral	Fetal membranes	M	Visceral yolk sac	Aleksunes et al., 2008b
Basolateral	Liver	M, R, H	Hepatocytes	Madon et al., 2000; Scheffer et al., 2002a; Gorgels et al., 2005
Basolateral	Kidney	M, H	Proximal tubule cells	Scheffer et al., 2002a; Beck et al., 2003; Gorgels et al., 2005
Apical	Tongue	M	Squamous epithelial cells	Beck et al., 2003
N.D.	Eye	M	Neuron layer	Beck et al., 2003
N.D.	Brain	M	Cerebrum neurons, Purkinje, ependymal cells	Beck et al., 2003
N.D.	Intestine	M	Mucosal cells	Beck et al., 2003
Bcrp				
Apical	Liver	M, H	Hepatocytes	Maliepaard et al., 2001; Jonker et al., 2002
Apical	Gallbladder	H	Epithelium	Aust et al., 2004
Apical	Kidney	M	Proximal tubule cells	Jonker et al., 2002
Apical	Small Intestine	M, H	Enterocytes	Maliepaard et al., 2001; Jonker et al., 2002
Apical	Brain	M, R, H	Brain capillaries, choroid plexus	Cooray et al., 2002; Hori et al., 2004; Lee et al., 2005b
Apical	Fetal membranes	M, H	Visceral yolk sac, amnion	Aleksunes et al., 2008b; Yeboah et al., 2008
Apical/Basolateral	Placenta	M, H	Syncytiotrophoblasts	Maliepaard et al., 2001; Jonker et al., 2002
Apical	Testes	M, H	Endothelial cells	Bart et al., 2004; Enokizono et al., 2007
Apical	Epididymis	M	Body, head	Enokizono et al., 2007
Apical	Mammary gland	H, R, B	Epithelia from lactating gland	Maliepaard et al., 2001; Pulido et al., 2006; Wang et al., 2008b
Apical	Eye	M	Retinal capillary endothelial cells	Asashima et al., 2006
Apical	Lung	H	Epithelium, glands, endothelial cells	Scheffer et al., 2002c
N.D.	Heart	H	Capillary endothelial cells and arterioles	Meissner et al., 2006

N.D, not determined.

al., 2005b). Overexpression of the *ABCC5* gene in MDCK cells causes MRP5 protein localization to the basolateral membrane (Wijnholds et al., 2000b). In brain, MRP5 is expressed in astrocytes, pyramidal neurons, and along the blood-brain barrier (Nies et al., 2004). MRP5 is detected on the epithelial cells of the urethra and the urogenital tract (Nies et al., 2002b). Within the placenta, MRP5 is present on the basolateral membrane of syncytiotrophoblasts as well as near fetal blood vessels (Table 8) (Pascolo et al., 2003; Meyer Zu Schwabedissen et al., 2005). It is noteworthy that placental MRP5 mRNA decreases during human gestation (Meyer Zu Schwabedissen et al., 2005). In addition, the amniotic membrane from term pregnancies expresses MRP5 on its apical and basolateral epithelial cells (Aye et al., 2007).

MRP6 was first considered the anthracycline resistance-associated gene in resistant leukemia cell lines (Longhurst et al., 1996; O'Neill et al., 1998). Subsequent cloning demonstrated that the anthracycline resistance-associated gene is a partial protein product of *ABCC6* (Belinsky and Kruh, 1999; Kool et al., 1999a). Despite expression of MRP6 in chemotherapy-resistant cell lines, it is not thought to play a role in conferring selective growth advantage to malignant cells (Kool et al., 1999a). The profiles of rodent Mrp6 and human MRP6 mRNA expression are largely similar (Fig. 4) (Kool et al., 1999a; Madon et al., 2000; Maher et al., 2005b, 2006b). In mice, rats, and humans, Mrp6/MRP6 mRNA is expressed in liver and kidneys, where their proteins are detected on the basolateral membranes of hepatocytes and proximal tubules (Table 6) (Kool et al., 1997; Belinsky and Kruh, 1999; Scheffer et al., 2002a; Maher et al., 2005b, 2006b). Likewise, overexpression of MRP6 in MDCK cells results in basolateral trafficking (Sinkó et al., 2003). MRP6 protein has also been found in enteroendocrine G cells of the stomach (Beck et al., 2005).

Mrp7/MRP7 is ubiquitously expressed (Fig. 4). Mouse Mrp7 is detected highly in testes, placenta, small intestine, kidneys, heart, and lungs (Kao et al., 2002; Maher et al., 2005b). Within the testes, Mrp7 is expressed in Sertoli cells (Augustine et al., 2005). Human MRP7 is expressed in skin, testes, stomach, spleen, colon, kidneys, brain, heart, and liver (Hopper et al., 2001). Human MRP8 is ubiquitously expressed in ovaries, heart, mammary glands, lungs, muscle, pancreas, testes, and intestine (Fig. 4) (Bera et al., 2001; Tammur et al., 2001). In the brain, MRP8 protein is located on axons in the white matter (Bortfeld et al., 2006). No mouse Mrp8 ortholog has been reported. In mice and rats, Mrp9 mRNA is only detected in testes (Fig. 4) (Maher et al., 2005b; Ono et al., 2007). Within the testes, mouse and boar sperm strongly express Mrp9 (Ono et al., 2007).

Expression of human MRP9 is more ubiquitous than rodent counterparts (Tammur et al., 2001; Ono et al., 2007).

Although identification of MDR1 drew attention to the existence of efflux pumps in chemotherapy-resistant tumors, a number of cancers did not overexpress this gene. As a result, researchers proposed the likelihood of additional efflux pumps. MRP1 was first reported in 1992 (Cole et al., 1992) and subsequently linked to anticancer drug resistance (Barrand et al., 1994; Grant et al., 1994; Stride et al., 1997). Early studies demonstrated the ability of MRP1 to transport glutathione conjugates (including oxidized glutathione), prostaglandins, and leukotrienes (Table 7) (Leier et al., 1994, 1996; Jedlitschky et al., 1996; Pulaski et al., 1996; Zaman et al., 1996; Evers et al., 1997).

Functional transport analysis demonstrates the importance of Mrp2 in the apical excretion of substrates (such as β-lactam antibiotics, methotrexate, estradiol-17β-glucuronide) from the liver and gastrointestinal tract (Table 7) (Masuda et al., 1997; Gotoh et al., 2000; Morikawa et al., 2000; Kato et al., 2008). Overexpression of MRP2 in vitro confers resistance to a number of cytotoxic drugs, including etoposide, cisplatin, doxorubicin, and epirubicin (Cui et al., 1999; Kawabe et al., 1999). The excretion of glucuronide conjugates across the canalicular surface of hepatocytes is mediated by Mrp2/MRP2 and across the sinusoidal membrane by Mrp3/MRP3. Mrp3/MRP3 transports glucuronide conjugates in addition to chemotherapeutic drugs and bile acids (Hirohashi et al., 1999; Kool et al., 1999b; Zeng et al., 1999, 2000, 2001; Li et al., 2003). Similar substrate profiles have been observed between rat and human Mrp3/MRP3 proteins (Akita et al., 2002). Although both proteins can transport bile acids, rat Mrp3 has a higher affinity for bile acids such as taurine- and glycine-conjugated cholic acid compared with human MRP3 (Zelcer et al., 2003b). Instead, it is proposed that human MRP3 may be more important in bile acid handling during cholestasis (Zelcer et al., 2003b).

Initial studies of Mrp4/MRP4 function pointed to a role for this transporter in conferring resistance to nucleoside analog antiviral drugs such as 9-(2-phosphonylmethoxyethyl)adenine as well as the anticancer drugs 6-mercaptopurine, topotecan, and methotrexate (Table 7) (Schuetz et al., 1999; Lee et al., 2000b; Chen et al., 2001; Reid et al., 2003a; Tian et al., 2005; El-Sheikh et al., 2007). In addition, Mrp4/MRP4 transports endogenous molecules such as leukotrienes, prostaglandins, folate, bile acids, urate, and cyclic nucleotides (Chen et al., 2001, 2002; Lai and Tan, 2002; Reid et al., 2003b; Zelcer et al., 2003a; Jedlitschky et al., 2004; Van Aubel et al., 2005; Rius et al., 2006, 2008; Bataille et al., 2008; Lin et al., 2008). Mrp5/MRP5 transports endogenous (cAMP, cGMP, folate, hyaluronan) and exogenous chemicals [methotrexate, 6-mercaptopurine, 6-thioguanine, 9-(2-phosphonylmethoxyethyl)adenine, 5-fluorouracil] (McAleer et al., 1999; Jedlitschky et al., 2000; Wijnholds et al., 2000b; Wielinga et al., 2002, 2003, 2005; Reid et al., 2003a; Pratt et al., 2005; Schulz et al., 2007). To date, only a limited number of MRP6 substrates have been identified, including leukotriene C_4, etoposide, and the endothelin receptor antagonist BQ-123 (Belinsky et al., 2002; Iliás et al., 2002). Likewise, MRP7 transports leukotriene C_4 and estradiol-17β-glucuronide as well as a number of chemotherapeutic drugs (Chen et al., 2003; Hopper-Borge et al., 2004). Overexpression of MRP7 confers resistance to docetaxel, paclitaxel, and vincristine (Hopper-Borge et al., 2009). Consistent with these data, high levels of MRP7 correlate with the chemotherapeutic resistance of a number of cell lines (Naramoto et al., 2007; Oguri et al., 2008; Bessho et al., 2009). MRP8 transports cyclic nucleotides, sulfated steroids, antiviral drugs, and chemotherapeutic drugs (Guo et al., 2003; Chen et al., 2005b).

3. Breast Cancer Resistance Protein. Despite the chemotherapeutic resistance conferred by MDR and MRP isoforms, resistant cancer cell lines lacking MDR/MRP over-expression suggested an additional ABC subfamily might be involved. A candidate gene named mitoxantrone resistance (MXR) was discovered in a resistant breast cancer cell line (Doyle et al., 1998; Miyake et al., 1999; Ross et al., 1999). At the same time, this transporter was also reported as the "ABC transporter highly expressed in placenta (ABCP)" (Allikmets et al., 1998). MXR/ABCP was later renamed the second member of the G subfamily of ABC transporters (*ABCG2*) or BCRP (Table 1). The BCRP protein is considered a "half-transporter" consisting of two domains: amino-terminal ATP-binding domain and carboxyl-terminal transmembrane domain (six transmembrane segments) (Wang et al., 2008a). To function, BCRP must form oligomers. Formation of a homodimer via extracellular loops between transmembrane helices 5 and 6 has been proposed (Henriksen et al., 2005a,b). Additional reports suggest that it is more likely that BCRP associates into higher order oligomers, specifically homotetramers (Xu et al., 2004).

Despite the original identification of BCRP in a breast cancer cell line, the expression of this transporter is quite variable among primary breast carcinomas, and there is no relationship between BCRP and the chemotherapeutic response to anthracyclines and/or survival of patients with breast cancer (Faneyte et al., 2002). Expression of BCRP in other tumor types is variable; detection is more frequent in adenocarcinomas of the digestive tract, endometrium, and lungs (Diestra et al., 2002). The relationship between BCRP expression and clinical outcomes in these other tumor types remains elusive.

Similar to other transporters (MDR and MRP) first associated with cancer cell resistance, BCRP is expressed not only in tumors but also in a number of organs associated with drug absorption, metabolism, and excretion. A similar distribution of mouse and rat

Bcrp expression has been reported with high Bcrp mRNA in rodent kidneys, liver, small intestine, placenta, and testes (Fig. 4) (Tanaka et al., 2005). High expression of human BCRP mRNA is detected in the placenta as well as in the brain, liver, kidneys, small intestine, colon, prostate, spinal cord, adrenal gland, uterus, and testes (Fig. 4) (Doyle et al., 1998; Fetsch et al., 2006). Within the human gastrointestinal tract, BCRP mRNA is highest in the duodenum and decreases down to the rectum (Gutmann et al., 2005). Bcrp/BCRP is almost exclusively expressed on the apical surface of epithelial cells, including hepatocytes, proximal tubules, enterocytes, trophoblasts, yolk sac, and mammary glands as well as brain and retinal capillary endothelial cells (Table 8) (Maliepaard et al., 2001; Cooray et al., 2002; Jonker et al., 2002; Aronica et al., 2005; Tachikawa et al., 2005; Asashima et al., 2006; Fetsch et al., 2006; Pulido et al., 2006; Aleksunes et al., 2008b; Roberts et al., 2008). Expression of Bcrp/BCRP on lactating mammary glands in a number of species contributes to the excretion of chemicals into breast milk (Merino et al., 2005b; van Herwaarden et al., 2006, 2007; Pérez et al., 2009).

Because BCRP was first identified from chemotherapy-resistant cancer cells, early functional analysis focused upon anticancer drugs. Overexpression of Bcrp/BCRP reduces accumulation and confers resistance to mitoxantrone, daunorubicin, doxorubicin, topotecan, and rhodamine 123 (Doyle et al., 1998; Allen et al., 1999; Litman et al., 2000; Wang et al., 2003c). Bcrp/BCRP transports a wide range of substrates, including photosensitizers, antibiotics, antivirals, natural products, statins, and carcinogens (Table 7) (Merino et al., 2005a, 2006; Robey et al., 2005; Huang et al., 2006a; Ando et al., 2007; Enokizono et al., 2007; Pan et al., 2007; Myllynen et al., 2008). BCRP also transports the fluorescent dye Hoechst 33342, which is used to label stem cell populations (Kim et al., 2002b).

C. Bile Acid, Cholesterol, Aminophospholipid, and Copper Transporters

1. Sodium Taurocholate Cotransporting Polypeptide. NTCP belongs to the *SLC10A* transporter family (Table 1). Ntcp was first cloned from rat liver (Hagenbuch et al., 1990). NTCP has seven putative transmembrane domains that are glycosylated with the carboxyl terminus oriented into the cytoplasm (Hagenbuch et al., 1991; Ananthanarayanan et al., 1994; Hagenbuch and Meier, 1994; Mareninova et al., 2005).

As part of the enterohepatic recirculation, Ntcp/NTCP is responsible for the basolateral uptake of bile acids from the portal blood into hepatocytes. Ntcp/NTCP transports bile acids such as taurocholate as well as conjugated di- and trihydroxy bile acids in a sodium-dependent manner (Hagenbuch et al., 1991; Boyer et al., 1994; Hagenbuch and Meier, 1994; Meier et al., 1997; Saeki et al., 2002). Although Ntcp was first identified in rat liver, this gene is expressed in livers of multiple species including human, mouse, rabbit, and guinea pig (Fig. 5) (Hagenbuch et al., 1991). Ntcp/NTCP proteins localize to the basolateral surface of hepatocytes in humans, rats, and mice (Table 9) (Ananthanarayanan et al., 1994; Stieger et al., 1994; Keitel et al., 2005; Aleksunes et al., 2006). It is noteworthy that Ntcp is also expressed in rat pancreas, where it traffics to the apical plasma membrane of acinar cells (Kim et al., 2002a). In addition to transporting bile acids and estrone sulfate, human NTCP (but not rat Ntcp) transports rosuvastatin (Craddock et al., 1998; Ho et al., 2006b).

2. Apical Sodium-Dependent Bile Acid Transporter. It had been known for some time that there was active transport of bile acids across the apical membrane of ileal enterocytes, but it was not until 1994, when Asbt was cloned, that this process was better understood (Wong et al., 1994). ASBT is the second member of the *SLC10A* family and shares 35% amino acid identity to

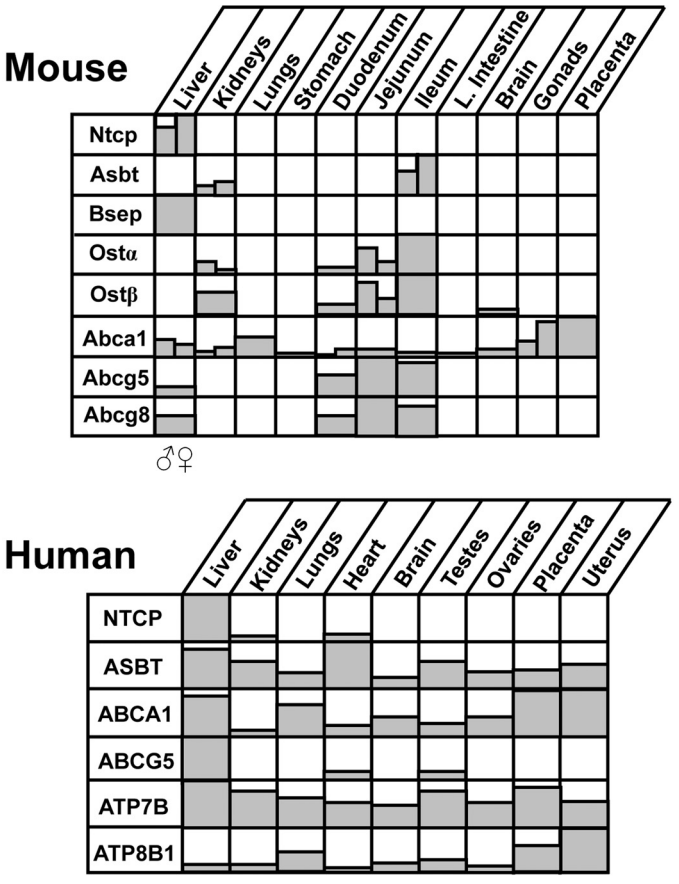

FIG. 5. Tissue distribution of Ntcp, Asbt, Bsep, Ost, Abca, and Abcg mRNA in mice and humans. Top, relative mRNA levels of transporters in mouse liver, kidneys, lung, stomach, duodenum, jejunum, ileum, large intestine, brain, gonads (testes and ovaries), and placenta are shown. Male (♂) mRNA is shown on the left, whereas female (♀) mRNA is shown on the right side of each box. References for mouse mRNA expression are included (Dieter et al., 2004; Cheng et al., 2007). Bottom, relative mRNA levels of transporters in human liver, kidneys, lung, heart, brain, testes, ovaries, placenta, and uterus are shown. Data for humans were obtained from GNF SymAtlas (http://symatlas.gnf.org/; now located at http://biogps.gnf.org). The GNF1H/MAS5 data set was accessed during September 2008.

TABLE 9

Subcellular localization of bile acid, cholesterol, aminophospholipid, and copper transporters in various species

For each transporter, the apical or basolateral localization in a particular tissue and/or species is provided. Species included rat (R), mouse (M), human (H), and bovine (B). Detailed information regarding particular cellular populations or regions of the tissue are provided for some transporter isoforms. N.D., not determined.

Cellular Localization	Tissue	Species	Cell Types	References
Ntcp				
Basolateral	Liver	M, R, H	Hepatocytes	Stieger et al., 1994; Keitel et al., 2005; Aleksunes et al., 2006
Apical	Pancreas	R	Acinar cells	Kim et al., 2002a
Asbt				
Apical	Ileum	M	Enterocytes	Dawson et al., 2005
Apical	Kidney	R	Proximal convoluted tubules	Christie et al., 1996
Apical	Liver	R	Cholangiocytes	Lazaridis et al., 1997
Bsep				
Apical	Liver	M, R, H	Hepatocytes	Childs et al., 1998; Jansen et al., 1999; Green et al., 2000
Ostα				
Basolateral	Ileum	M, R, H	Enterocytes	Ballatori et al., 2005; Dawson et al., 2005
Basolateral	Liver	M, H	Hepatocytes, cholangiocytes	Ballatori et al., 2005
Basolateral	Kidney	M, R, H	Proximal tubule cells	Ballatori et al., 2005
Ostβ				
Basolateral	Ileum	M, H	Enterocytes	Ballatori et al., 2005; Dawson et al., 2005
Abcg5				
Apical	Liver	M, H	Hepatocytes, cholangiocytes	Graf et al., 2003; Klett et al., 2004a
Apical	Small intestine	M, H	Enterocytes	Graf et al., 2003; Klett et al., 2004a
Intracellular	Gallbladder	H	Mucosal epithelial cells	Klett et al., 2004a
Abcg8				
Apical/Intracellular	Liver	H	Hepatocytes, cholangiocytes	Klett et al., 2004a
Apical	Small intestine	H	Enterocytes	Klett et al., 2004a
Intracellular	Gallbladder	H	Mucosal epithelial cells	Klett et al., 2004a
ATP7B				
Apical	Liver	R	Hepatocytes	Hernandez et al., 2008
Apical	Placenta	H	Syncytiotrophoblasts	Hardman et al., 2004; Hardman et al., 2007
Intracellular	Small intestine	M	Enterocytes	Weiss et al., 2008
Intracellular	Mammary gland	M	Ductal epithelial cells	Michalczyk et al., 2000
ATP8b1				
Apical	Liver	M, R, H	Hepatocytes	Eppens et al., 2001; Ujhazy et al., 2001
Apical	Small Intestine	R	Enterocytes	Ujhazy et al., 2001

NTCP (Table 1) (Wong et al., 1994). Asbt was first cloned from a hamster ileal cDNA library and named the ileal sodium-dependent bile acid cotransporter (Wong et al., 1994). Similar to NTCP, hydropathy analysis predicts that the ASBT protein has seven putative transmembrane domains with an extracellular amino terminus and a cytoplasmic carboxyl terminus (Banerjee and Swaan, 2006).

Asbt-mediated uptake of bile acids represents the first step in bile acid reabsorption in intestine. Contrary to Ntcp/NTCP, which localizes to the basolateral membrane of hepatocytes, Asbt is found on the apical surface of cholangiocytes, where it participates in cholehepatic recirculation (Fig. 5, Table 9) (Alpini et al., 1997; Lazaridis et al., 1997). Shuttling or localization of ASBT to the apical surface is due to its cytoplasmic tail (Sun et al., 1998). In addition to ileal enterocytes and cholangiocytes, Asbt is also an apical protein in the kidneys (Christie et al., 1996).

Like Ntcp, Asbt/ASBT transports unconjugated and conjugated bile acids in a sodium-dependent manner (Wong et al., 1994; Craddock et al., 1998). The substrate specificity of Asbt is narrower than Ntcp (Craddock et al., 1998). Human ASBT prefers taurine- and glycine-conjugated bile acids, rather than the unconjugated forms (Craddock et al., 1998). In addition, the affinity of ASBT to dihydroxy bile acids is higher than that for trihydroxy bile acids (Craddock et al., 1998).

3. Bile Salt Export Pump. Secretion of conjugated bile acids from hepatocytes into bile suggested the existence of an active transport mechanism across the canalicular membrane. In 1995, the sister of Pgp (SPGP, *ABCB11*) was cloned from a pig cDNA library (Childs et al., 1995) and later from additional species (Table 1) (Childs et al., 1998; Green et al., 2000; Lecureur et al., 2000; Byrne et al., 2002; Noe et al., 2002). SPGP was subsequently renamed Bsep (Gerloff et al., 1998). A 12-membrane-spanning domain protein containing puta-

tive glycosylation sites, nucleotide binding domains, and typical structures of ABC-transporters has been described for BSEP (Gerloff et al., 1998).

Bsep/BSEP is exclusively expressed in liver on the canalicular membrane of multiple species (Fig. 5) (Childs et al., 1995, 1998; Gerloff et al., 1998). As the primary canalicular bile acid transporter, Bsep/BSEP primarily transports conjugated bile acids (including taurochenodeoxycholate, taurocholate, tauroursodeoxycholate, glycochenodeoxycholate, and glycocholate) in an ATP-dependent manner (Gerloff et al., 1998; Green et al., 2000; Byrne et al., 2002). In contrast, Bsep does not transport cholic acid (Noe et al., 2002). Although BSEP primarily transports bile acids, it can also transport pharmaceuticals such as pravastatin (Hirano et al., 2005). A number of BSEP inhibitors have been identified (cyclosporine A, rifampicin, glibenclamide) (Byrne et al., 2002).

4. Organic Solute Transporters. Bile acids are absorbed in the small intestine as part of the enterohepatic recirculation. Uptake of bile acids from the intestinal lumen is mediated by Asbt. Once inside the enterocyte, bile acids are translocated to the basolateral membrane by the intestinal bile acid binding protein and subsequently transported across the basolateral membrane by heterodimerized OSTα/β transporters. Ostα and -β were first identified in the liver of the marine skate (Wang et al., 2001d) and subsequently in human and mouse livers (Table 1) (Seward et al., 2003). OSTα is larger than OSTβ (Wang et al., 2001d). Whereas OSTα contains seven putative membrane-spanning domains, OSTβ contains only one (Seward et al., 2003).

Mouse Ostα and -β mRNA are highest in the ileum with detectable levels also in the kidneys, duodenum, jejunum, cecum, and the proximal colon (Fig. 5) (Ballatori et al., 2005; Dawson et al., 2005; Li et al., 2007b) Likewise, human OSTα and -β are expressed to varying levels in the testes, colon, liver, small intestine, adrenal glands, kidneys, and ovaries (Seward et al., 2003). Whereas OSTα is expressed in the human liver (hepatocytes and cholangiocytes), levels are very low in mouse liver and limited only to cholangiocytes (Ballatori et al., 2005). OSTα and -β localize to the basolateral membrane of ileal enterocytes, hepatocytes, cholangiocytes, and proximal renal tubules (Table 9) (Ballatori et al., 2005). Ostα is required for the delivery of Ostβ protein to the plasma membrane; in turn, OSTα and -β need to be coexpressed to function properly (Li et al., 2007b). Ostα and -β function as a heterodimer to transport not only bile acids but also estrone sulfate, digoxin, and prostaglandin E_2 (Wang et al., 2001d; Seward et al., 2003; Dawson et al., 2005).

5. ATP-Binding Cassette Transporter A1. ABCA1 is a member of the ABC subfamily A and was cloned in 1999 (Langmann et al., 1999) at the same time that it was determined that defects in *ABCA1* cause Tangier's disease, a disorder of impaired cholesterol transport (Bodzioch et al., 1999; Brooks-Wilson et al., 1999; Marcil et al., 1999; Remaley et al., 1999; Rust et al., 1999; Schippling et al., 2008) (Tables 1 and 10). As suggested by the clinical presentation of patients with Tangier's disease, ABCA1 effluxes cholesterol and apolipoprotein A1 in vitro (Neufeld et al., 2001; Wang et al., 2001b). The absence of ABCA1 results in premature atherosclerosis, splenomegaly, and hepatomegaly in patients with Tangier's disease.

Abca1/ABCA1 is highly expressed in placenta, uterus, liver, adrenal glands, small intestine, lungs, and heart (Fig. 5) (Langmann et al., 1999). Within these tissues, ABCA1 is often expressed on macrophages in addition to epithelium (Langmann et al., 1999; Schmitz et al., 1999). In the transfected polarized hepatocyte-like WIF-B cell line, ABCA1 immunostaining is observed along the basolateral surface (Neufeld et al., 2002). These findings suggest ABCA1 participates in the regulation of intracellular cholesterol accumulation in hepatocytes. In addition to cell surface expression, ABCA1 is observed in early and late endosomes, which may participate in protein trafficking as well as shuttling cholesterol to the cell surface for efflux (Neufeld et al., 2001).

6. ATP-Binding Cassette Subfamily G Members 5 and 8. ABCG5 and ABCG8 are efflux transporters that work in concert as a heterodimer to prevent the absorption of plant sterols (Graf et al., 2003) (Table 1). Both isoforms are necessary for trafficking from the endoplasmic reticulum to the canalicular membrane and, in turn, the excretion of plant sterols and cholesterol into bile (Graf et al., 2003). ABCG5 is predicted to contain six putative transmembrane domains with cytosole-facing amino and carboxyl termini (Lee et al., 2001b). Mouse Abcg5 and -g8 mRNA are detected within the liver and small intestine (Fig. 5) (Lu et al., 2002). Within the mouse small intestine, Abcg5 and -g8 are similarly expressed among the three segments (Dieter et al., 2004). ABCG5 and -G8 mRNA are expressed in human liver, small intestine, and colon (Fig. 5) (Berge et al., 2000; Lee et al., 2001b). Abcg/ABCG5 and -g8 proteins are localized to the apical membrane of enterocytes, cholangiocytes, and hepatocytes (Table 9) (Graf et al., 2003; Klett et al., 2004a).

7. ATPase Copper-Transporting β Polypeptide. ATP7B is an ATP-dependent copper efflux transporter that is primarily expressed in liver (Petrukhin et al., 1994) (Table 1). Messenger RNA expression of ATP7B is widely expressed in multiple tissues (Fig. 5), and mice lacking Atp7b exhibit copper accumulation in kidney, brain, placenta, and lactating mammary glands (Buiakova et al., 1999). ATP7B protein is localized on the apical membrane of placenta syncytiotrophoblasts (Table 9) (Hardman et al., 2004, 2007). Likewise, ATP7B is responsible for the canalicular excretion of copper into bile (Hernandez et al., 2008). ATP7B localization changes depending upon copper con-

TABLE 10
Genetic disorders due to transporter mutations

Transporter	Disorder	Features and/or Symptoms
SLC22A5 (OCTN2)	Primary systemic carnitine deficiency syndrome	Cardiomyopathy, hypoglycemia, skeletal muscle myopathy
SLC10A2 (ASBT)	Primary bile acid malabsorption	Diarrhea, steatorrhea, low plasma cholesterol levels
SLC29A3 (ENT3)	H syndrome	Cutaneous hyperpigmentation, hearing loss, hepatosplenomegaly, heart anomalies, hypogonadism, short stature, hypertrichosis
ABCA1	Tangier's disease	Mild hypertriglyceridemia, neuropathy, enlarged tonsils, premature atherosclerosis, splenomegaly, hepatomegaly
ABCB4 (MDR3)	PFIC-III	Elevated serum γ-glutamyltranspeptidase, activity, high serum bile acid levels, hepatosplenomegaly, portal hypertension, pruritus, jaundice
ABCB11 (BSEP)	PFIC-II	Reduced bile acid secretion, progressive hepatic dysfunction at early age, normal serum γ-glutamyltranspeptidase activity
ABCC2 (MRP2)	Dubin-Johnson syndrome	Conjugated hyperbilirubinemia, chronic jaundice, relatively benign clinical course
ABCC6 (MRP6)	Pseudoxanthoma elasticum	Calcifications of elastic fibers in arteries, and retina leading to arterial skin, insufficiency and macular degeneration
ABCG5/8	Sitosterolemia	Atherosclerosis at a young age, tendon xanthomas, arthralgias
ATP7B	Wilson's disease	Liver disease due to copper accumulation, which requires transplantation, tremors, neurological and behavioral problems, brown pigment in cornea
ATP8B1	PFIC-I/Byler's disease	Elevated serum bile acids, normal serum γ-glutamyltranspeptidase activity, decreased bile acid secretion, fat malabsorption, vitamin (lipid-soluble) deficiency, diarrhea, pancreatitis, pruritus, jaundice, hearing loss

centrations. At low concentrations of copper, ATP7B is present in the trans-Golgi network. As copper accumulates, ATP7B shifts toward the apical membrane of polarized cells (Roelofsen et al., 2000; Guo et al., 2005; Lutsenko et al., 2007; Weiss et al., 2008).

8. ATPase Class I Type 8B Member 1. ATP8B1 is an ATP-dependent aminophospholipid transporter, also called the familial intrahepatic cholestasis 1 protein (Ujhazy et al., 2001) (Table 1). It is in the type 4 subfamily of P-type ATPases that are termed flippases (Paulusma and Oude Elferink, 2005). The ATP8B1 protein is predicted to contain 10 transmembrane domains (Paulusma and Oude Elferink, 2005). ATP8B1 mRNA is expressed predominantly in the small intestine, uterus, and pancreas, with moderate expression in the bladder, stomach, prostate, liver, and heart (Fig. 5) (Bull et al., 1998). ATP8B1 is expressed on the canalicular membrane of mouse, rat, and human hepatocytes, where phosphatidylserine and phosphatidylethanolamine are translocated from the outer to the inner leaflet bilayer (Table 9) (Eppens et al., 2001; Ujhazy et al., 2001). Because of ATP8B1 activity, the proportion of sphingomyelin and cholesterol in the outer leaflet is increased and is likely to enhance membrane resistance to bile acid toxicity. ATP8B1 is also expressed along the apical surface of rat enterocytes (Ujhazy et al., 2001).

There are a variety of transporters with similarities and differences in their tissue distribution and substrate affinities. In some cases, certain transporter isoforms are restricted to one or two tissues, whereas other isoforms are broadly expressed in multiple tissues. Additional insight into the function of transporters in various tissue and cell types will be addressed in the next section of this review article.

III. Transporter Function in Various Tissues

Traditional in vitro overexpression systems are used to identify substrates of individual drug transporters. The in vivo function of transport proteins can be assessed using multiple approaches. First, transporter gene knockout mice have been genetically engineered and are useful for pharmacokinetic and toxicologic studies. Because of transporter functional redundancy, double- and triple-knockout mice have also been developed. Second, defects in some transport proteins result in genetic disorders with distinct phenotypic changes that provide clues to the functional activities of the transporters (Table 10). Third, single-nucleotide polymorphisms (SNPs) in the coding region of a transporter gene may introduce amino acid substitutions, leading to altered transporter intrinsic activity by changing the protein's affinity to substrates (K_m) and/or translocation ability (V_{max}) (Tables 11-20) (Evans and Relling, 1999). Nonsynonymous SNPs may also interfere with protein folding, post-translational modifications, and/or trafficking to the cellular membrane and subsequently influence pharmacokinetics and drug response of a particular person. Findings from in vitro overexpression of nonsynonymous transporter SNPs complement clinical obser-

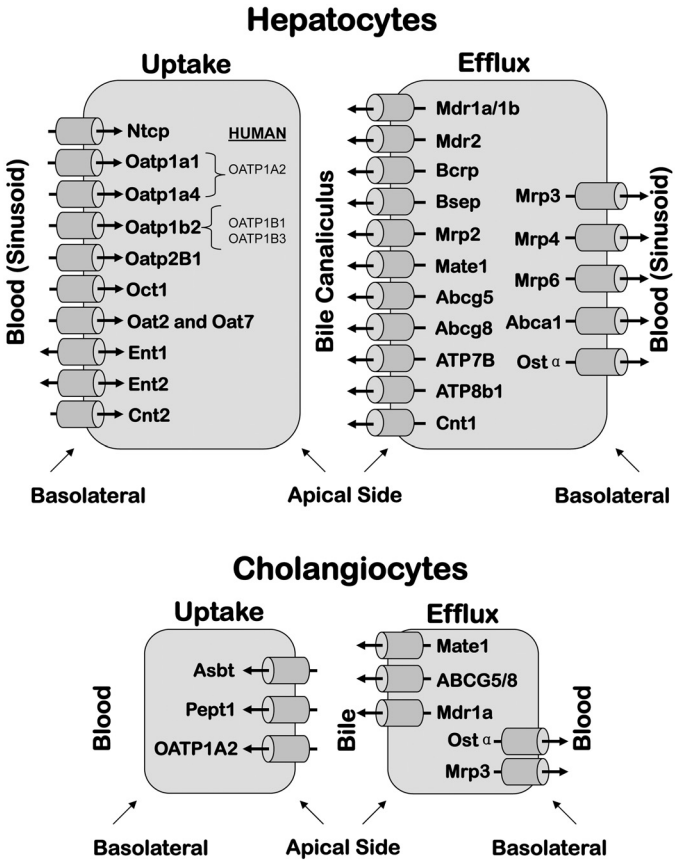

FIG. 6. Subcellular localization of uptake and efflux transport proteins in hepatocytes and cholangiocytes. The localization and orientation of uptake and efflux transporters in liver cells (primarily rodents) are shown.

vations in patients expressing the SNP on one or both alleles. Collectively, genetic disorders, genetically engineered mice, and human polymorphic variants provide valuable insights into transporter function in various tissues.

This portion of the review focuses on the biological functions of uptake and efflux transporters with regard to genetic disorders, knockout mice, and human SNP variants. For the most part, only nonsynonmous coding region polymorphisms are discussed, although recent work has highlighted important roles for intronic and synonymous polymorphisms in regulating transporter expression and/or function. Likewise, the allele frequencies for the various polymorphisms are not included but can be ascertained from the Hapmap project or PharmGKB databases. For additional in depth information regarding genetic disorders of transport (such as cystic fibrosis, surfactant deficiency, adrenoleukodystrophy, macular degeneration), knockout mice, and SNPs from specific transporter classes, the reader is referred to recent reviews (Dean, 2005; Kubitz et al., 2005; Chinn and Kroetz, 2007; Kruh et al., 2007; Gradhand and Kim, 2008; Klaassen and Lu, 2008; Vlaming et al., 2009a).

A. Liver

A variety of uptake and efflux transporters are localized to the apical and basolateral membranes of hepatocytes and cholangiocytes. Figure 6 denotes the subcellular localization of these proteins.

1. Basolateral Uptake Transporters in Liver. Ntcp (Slc10a1) is a bile acid uptake transporter that localizes to the basolateral membrane of hepatocytes (Stieger et al., 1994; Keitel et al., 2005). Its function is to take up bile acids (especially taurine-conjugated) into hepatocytes using a sodium gradient (Hagenbuch et al., 1991; Boyer et al., 1994; Hagenbuch and Meier, 1994; Saeki et al., 2002). Down-regulation of rat Ntcp using antisense oligonucleotides almost completely abolishes taurocholate transport (95% reduction) in *Xenopus laevis* oocytes (Hagenbuch et al., 1996). Four nonsynonymous *SLC10A1* (NTCP) polymorphisms exhibit reduced taurocholate, cholate, and estrone sulfate transport in vitro (Table 11) (Ho et al., 2004). Lower transport activity in only one of these variants could be explained by impaired cell surface expression (Ho et al., 2004). NTCP has a limited ability to transport pharmaceuticals (Ho et al., 2006b). In addition to *SLC10A1*, *SLCO1B1* (OATP1B1) may also contribute to bile acid uptake into the liver. *SLCO1B1* loss-of-function variants are associated with elevated serum bile acids in vivo (Xiang et al., 2009).

Basolateral uptake transporters are important determinants of liver injury induced by drugs or toxins. Rat Oatp1b2, human OATP1B1, and OATP1B3 transport the phalloidin analog demethylphalloin (Fehrenbach et al., 2003; Meier-Abt et al., 2004). Oatp1b2-null mice are resistant to hepatotoxicity caused by the mushroom toxin phalloidin and the blue-green algae toxin microcystin-LR (Lu et al., 2008). In both instances, resistance to toxicity is a result of reduced hepatic uptake of the toxins. Conversely, inhibition of NTCP-mediated bile acid uptake (as well as BSEP efflux) has also been proposed as a mechanism for hepatotoxicity induced by certain xenobiotics. It is noteworthy that some cholestatic chemicals (such as rifampicin, rifamycin SV, glibenclamide, and cyclosporin) inhibit the transport of taurocholate in NTCP- and BSEP-overexpressing polarized cells (Mita et al., 2006). Likewise, a reduced ability of the hepatotoxin bosentan to inhibit NTCP compared with

TABLE 11
In vitro characterization of genetic polymorphisms in NTCP
In vitro function was assessed using prototypical substrates for NTCP (taurocholate and cholate). Data are from Ho et al. (2004).

Nucleotide Change	Amino Acid Change	In Vitro Function	Protein Expression/Localization
SLC10A1	NTCP		
T668C	I223T	↓	Intracellular
C800T	S267F	↓	Normal
T836C	I279T	↓	Normal
A940G	K314E	↓	Normal

↓, reduced function.

rat Ntcp may explain differences in hepatotoxicity sensitivity between these two species (human > rat) by causing hepatocellular bile acid accumulation (Leslie et al., 2007).

Because of the high expression of Oatps/OATPs and the critical synthesis of cholesterol in the liver, the ability of OATP1B1 and OATP1B3 to transport anticholesterol drugs (including the statins) is an area of active research. Rifampicin and pravastatin are prototypical substrates of OATP1B1 and -1B3, respectively (Spears et al., 2005; Niemi et al., 2006b; Seithel et al., 2007). Hepatic uptake of both drugs is reduced in Oatp1b2-null mice with dramatic reductions in their liver-to-plasma ratios (Zaher et al., 2008). A conflicting report showed little difference in pravastatin pharmacokinetics between wild-type and Oatp1b2-null mice, but did observe reduced hepatic concentrations of another statin, lovastatin (Chen et al., 2008). In contrast, simvastatin uptake into liver is unchanged in Oatp1b2-null mice, demonstrating distinct differences in hepatic extraction by Oatp1b2 for this class of drugs (Chen et al., 2008). Altered drug disposition in Oatp1b2-null mice demonstrates the utility of this in vivo model for investigating the possible contributions of OATP1B1/1B3 to hepatic transport.

The pharmacokinetics of statins have been investigated in patients with *SLCO1B1* (OATP1B1) gene SNPs N130D and V174A. In vitro studies demonstrate normal and reduced pravastatin (as well as estrone sulfate) uptake in N130D- and V174A-overexpressing cells, respectively (Table 12) (Kameyama et al., 2005). The combination of N130D and V174A *SLCO1B1* SNPs leads to reduced pravastatin and pitavastatin clearance (Nishizato et al., 2003; Chung et al., 2005). The V174A SNP alone is sufficient to increase plasma concentrations of pravastatin (single dose), primarily in subjects of European American descent, suggesting delayed uptake of pravastatin into liver (Mwinyi et al., 2004; Ho et al., 2007). Furthermore, statins exhibit attenuated efficacy in lowering total cholesterol in patients with the V174A allele (Tachibana-Iimori et al., 2004). It is noteworthy that other *SLCO1B1* SNPs have opposite effects. The N130D SNP reduces the area under the curve of pravastatin after a single dose in white subjects, and seems to accelerate OATP1B1-mediated uptake of pravastatin (Mwinyi et al., 2004). Likewise, the P155T variant is associated with greater reduction in low-density lipoprotein cholesterol levels by fluvastatin than in patients with the reference allele, suggesting a gain of function for certain *SLCO1B1* alleles (Couvert et al., 2008).

The L543W *SLCO1B1* SNP has been detected only in the Japanese population. Although this variant is rare, it has been associated with pravastatin-induced myopathy (Morimoto et al., 2004). More recently, an intronic SNP in *SLCO1B1* was also identified as a strong risk factor in patients with statin-induced myopathy, using a genomewide screen (SEARCH Collaborative Group et al., 2008). In that study, more than 60% of myopathy cases in patients treated with a statin could be strongly associated with the variant *SLCO1B1* allele (SEARCH Collaborative Group et al., 2008).

TABLE 12
In vitro characterization of genetic polymorphisms in OATP1A2, -1B1, and -1B3

In vitro function was assessed using prototypical substrates for OATP1A2 (estrone-3-sulfate), OATP1B1 (estrone-3-sulfate, estradiol 17β-glucuronide, rifampin), and OATP1B3 (estrone-3-sulfate, estradiol 17β-glucuronide). Some nucleotide positions were confirmed by PharmGKB (Hewett et al., 2002). OATP1A2 data from Lee et al. (2005a) and Badagnani et al. (2006). OATP1B1 data from Tirona et al. (2001); Michalski et al. (2002); Nozawa et al. (2002); Nishizato et al. (2003); Tirona et al. (2003); Iwai et al. (2004a); Morimoto et al. (2004); Kameyama et al. (2005). OATP1B3 data from Letschert et al. (2004).

Nucleotide Change	Amino Acid Change	In Vitro Function	Protein Expression/Localization
SLCO1A2	OATP1A2		
T38C	I13T	↑ ↔	Normal
A382T	N128Y	↔	N.D.
A404T	N135I	↓ ↔	N.D.
C502T	R168C	↓	N.D.
A516C	E172D	↓	Intracellular
G559A	A187T	↓	Normal
A833-	Asn278STOP	↓	N.D.
C2003G	T668S	↔	Intracellular
SLCO1B1	OATP1B1		
T217C	F73L	↓	Intracellular
T245C	V82A	↓	Intracellular
A388G	N130D	↓ ↔	Normal
A452G	N151S	N.D.	N.D.
C463A	P155T	↔	Normal
A467G	E156G	↓	Normal
T521C	V174A	↓	Intracellular/normal
T578G	L193R	↓	Intracellular
C1007G	P336R	N.D.	N.D.
T1058C	I353T	↓	Intracellular
A1294G	N432D	↓ ↔	Normal
A1385G	D462G	↔	Normal
G1454T	C485F	N.D.	N.D.
G1463C	G488A	↓	Intracellular
T1628G	L543W	N.D.	N.D.
A1964G	D655G	↓ ↔	Normal
A2000G	E667G	↓ ↔	Normal
SLCO1B3	OATP1B3		
T334G	S112A	↑ ↔	Normal
G699A	M233I	↔	Normal
G1564T	G522C	↓ ↔	Reduced
G1748A	G583E	↓ ↔	Reduced

↓, reduced function; ↑, increased function; ↔, no change in function; N.D. not determined.

Ezetimibe is a cholesterol-lowering drug that inhibits intestinal absorption of cholesterol via the Niemann-Pick C1 like 1 protein. Ezetimibe undergoes glucuronidation and extensive enterohepatic circulation. Ezetimibe-glucuronide inhibits transport of sulfobromophthalein mediated by OATP1B1 and -2B1 (Oswald et al., 2008). Uptake of ezetimibe-glucuronide by OATP1B1 is reduced in cells transfected with the *SLCO1B1* V174A variant compared with the wild-type transporter (Oswald et al., 2008). When evaluating ezetimibe single oral dose pharmacokinetics, subjects who are homozygous for the N130D allele exhibit lower bioavailability of ezetimibe, whereas subjects who are heterozygous for the V174A allele have reduced fecal excretion of ezetimibe (Oswald et al., 2008).

Whereas OATPs mediate organic anion uptake into liver, OCT1 is responsible for the influx of organic cat-

ions. Using Oct1-null mice, the roles for this transporter in hepatic uptake have been shown. Oct1-null mice have reduced hepatic accumulation and/or biliary excretion of organic cations, such as the model substrate tetraethylammonium, the neurotoxin 1-methyl-4-phenylpyridinium, the anticancer drug metaiodobenzylguanidine, and the antidiabetic drug metformin (Jonker et al., 2001; Wang et al., 2002a; Shu et al., 2007). In addition to pharmacokinetic implications, impaired intestinal absorption and hepatic uptake of metformin have pharmacodynamic consequences (Wang et al., 2002a). Oct1-null hepatocytes are resistant to the glucose-lowering effects of metformin after glucagon challenge (Shu et al., 2007). It is noteworthy that reduced hepatic metformin uptake in Oct1-null mice is associated with lower blood lactate levels compared with wild-type mice, demonstrating that the liver is central to metformin-induced lactic acidosis (Wang et al., 2003a).

Similar to Oct1 in mice, metformin is transported by human OCT1 and OCT2 (Kimura et al., 2005; Song et al., 2008). In vitro analysis of *SLC22A1* (OCT1) variants has identified 1 deletion (Met420STOP) and six nonsynonymous polymorphisms (S14F, R61C, S189L, G220V, G401S, G465R) that exhibit reduced metformin uptake (Shu et al., 2003, 2007) (Table 13). These *SLC22A1* variants lead to impaired metformin efficacy in lowering blood glucose after an oral glucose challenge (Shu et al., 2007) and increased renal clearance (Tzvetkov et al., 2009). An intronic variant is also associated with the glucose-lowering effect of metformin (Becker et al., 2009). In addition, a study of 24 responders and 9 nonresponders to metformin (as determined by glycosylated hemoglobin A_{1c} levels) demonstrated that the frequency of the *SLC22A1* M408V allele is higher in nonresponders compared with responders (Shikata et al., 2007). Likewise, hepatic OCT1 mRNA levels are lower in livers of M408V carriers (Shikata et al., 2007). Patients with type 2 diabetes who carry the common variant M408V (allelic frequency higher than 10% in the general population) may have an insufficient therapeutic response to metformin therapy because of reduced uptake into liver, which is the major target for reducing circulating blood glucose.

TABLE 13
In vitro characterization of genetic polymorphisms in human OCT1 and -2

In vitro function was assessed using prototypical substrates for OCT1 and 2 (1-methyl-4-phenylpyridinium, tetraethylammonium, metformin). Nucleotide position was confirmed by PharmGKB (Hewett et al., 2002). OCT1 data from Kerb et al. (2002); Shu et al. (2003); Takeuchi et al. (2003); Sakata et al. (2004); Kang et al. (2007); Shu et al., 2007). OCT2 data from Leabman et al. (2002); Fukushima-Uesaka et al. (2004); Fujita et al. (2006); Lazar et al. (2006); Kang et al. (2007); Song et al. (2008); Wang et al., (2008e).

Nucleotide Change	Amino Acid Change	In Vitro Function	Protein Expression/ Localization
SLC22A1	OCT1		
C41T	S14F	↑	N.D.
C181T	R61C	↓	Reduced
T262C	C88R	↓	N.D.
C480G	F160L	↔	Normal
C566T	S189L	↔	N.D.
G659T	G220V	↓	N.D.
C848T	P283L	↓	Normal
C859G	R287G	↓	Normal
C1022T	P341L	↓↔	Normal
G1201A	G401S	↓	N.D.
A1222G	M408V	↔	N.D.
1258del	Met420STOP	↓↔	N.D.
G1393A	G465R	↓	Reduced
SLC22A2	OCT2		
C160T	P54S	↔	N.D.
T481C	F161L	↔	N.D.
A493G	M165V	↓↔	N.D.
G495A	M165I	↓↔	N.D.
C596T	T199I	↓	Normal
C602T	T201M	↓	Normal
G808T	A270S	↓	Normal
C890G	A297G	↔	N.D.
C1198T	R400C	↓	N.D.
A1294C	K432Q	↓↔	N.D.

↓, reduced function; ↑; increased function; ↔, no change in function; N.D. not determined.

2. Apical Efflux Transporters in Liver. There are a large number of transporters on the apical surface of hepatocytes that are responsible for the biliary excretion of endobiotics and xenobiotics. Mutations and polymorphisms in canalicular transporters result in genetic disorders with distinct clinical phenotypes and/or marked alterations in chemical disposition.

The ability of Mdr1a/1b, also known as Pgp, to influence the disposition and hepatotoxicity of the environmental toxicant arsenic has been investigated in Mdr1a/1b-null mice (Liu et al., 2002). Administration of sodium arsenite to Mdr1a/1b-null mice yielded interesting findings, the null mice being more susceptible to hepatic injury and mortality than the wild-type mice (Liu et al., 2002). Enhanced susceptibility is probably due to elevated arsenic tissue concentrations in liver, kidneys, small intestine, and brain (Liu et al., 2002). Similar studies in Mdr1a/1b-null mice have been conducted for the mycotoxin fumonisin, but Pgp does not seem to be important for the disposition or toxicity of this chemical (Sharma et al., 2000).

The ability of Mdr2 to transport phospholipids as well as its localization in the canalicular membrane suggested a role for this transporter in protecting the biliary tree from bile acid toxicity by forming mixed phospholipid-bile acid micelles (Elferink et al., 1997). Results from Mdr2-null mice confirmed this hypothesis (Smit et al., 1993; Leveille-Webster and Arias, 1994). Livers from mice lacking Mdr2 exhibit focal hepatocyte necrosis, bile duct proliferation and inflammation, and elevated serum biomarkers of liver injury that are similar to nonsuppurative inflammatory cholangitis (Smit et al., 1993; Mauad et al., 1994). Pathology is more severe in female than male mice, which is thought to be due to the higher levels of hydrophobic bile acids in the bile of female Mdr2-null mice (van Nieuwerk et al., 1997). By 4 to 6 months of age, Mdr2-null mice develop preneoplastic nodules that progress to liver tumors (Mauad et al., 1994). Bile acid excretion into bile is similar in wild-type and Mdr2-null mice, whereas biliary excretion of phospholipids is absent in Mdr2-null mice (Smit et al., 1993;

Oude Elferink et al., 1995). It is thought that bile duct proliferation contributes to the enhanced bile acid-independent bile flow in Mdr2-null mice (Oude Elferink et al., 1995; Elamiri et al., 2003). Mdr2-null mice are gaining utility as a rodent model of primary sclerosing cholangitis for identifying the interplay of phospholipids, sterols, and bile acids, as well as testing compounds as novel therapeutics (van Nieuwerk et al., 1997; Voshol et al., 1998; Elamiri et al., 2003; Fickert et al., 2006).

Cholestasis can be caused by genetic defects or as a secondary consequence of hepatobiliary obstruction or destruction. Progressive familial intrahepatic cholestasis (PFIC) represents a group of inherited, autosomal recessive disorders characterized by progressive liver disease with impaired bile flow but without irregularity of the hepatobiliary structure (Table 10). PFIC-III arises from mutations in the human *ABCB4* (MDR3) gene, the human ortholog of mouse Mdr2 (de Vree et al., 1998). Patients with PFIC-III display elevated serum γ-glutamyltranspeptidase levels and marked bile duct proliferation. In addition, variants of *ABCB4* are associated with the severe form of cholestasis of pregnancy, rare cases of juvenile cholesterol gallstones, and drug-induced hepatocellular and cholestatic injury (Lang et al., 2007; Wasmuth et al., 2007; Nakken et al., 2009; Bacq et al., 2009).

As the "sister" of Pgp, Bsep represents the primary bile acid exporter on hepatocyte canaliculi (Gerloff et al., 1998). Mutations in *ABCB11* (BSEP) are responsible for PFIC-II in humans (Table 10) (Strautnieks et al., 1998; Jansen et al., 1999). A recent report identifies more than 10 mutations in the *ABCB11* gene, although the functional relevance of these mutations has not been confirmed (Strautnieks et al., 2008). As expected from BSEP dysfunction, patients with PFIC-II present with high serum bile acid concentrations, normal serum γ-glutamyltranspeptidase activity and cholesterol, and low biliary bile acid concentrations. PFIC-II patients are at an increased risk of hepatobiliary malignancy (Knisely et al., 2006). Researchers have identified a number of mutations in *ABCB11* that impair BSEP insertion into the apical membrane and therefore reduce taurocholate transport in vitro (Wang et al., 2002b). In addition, autoantibodies against BSEP have been implicated in recurrent graft failure after liver transplantation in a patient with PFIC-II (Keitel et al., 2009).

In an attempt to identify individuals with a genetic predisposition to drug-induced cholestasis or intrahepatic cholestasis of pregnancy, patients with acquired cholestasis have been genotyped for *ABCB11* variants. Three highly conserved mutants/variants (V444A, D676Y, G855R) strongly associate with susceptibility to drug-induced cholestasis (Table 14) (Lang et al., 2007). Likewise, the V444A polymorphism is a risk factor for intrahepatic cholestasis of pregnancy in European patients as well as patients with contraceptive-induced cholestasis (Keitel et al., 2006; Dixon et al., 2008; Meier et al., 2008). More recent efforts have identified novel *ABCB11* variants in the Japanese population (Kim et al., 2009).

TABLE 14
In vitro characterization of genetic polymorphisms/mutations in BSEP
In vitro function was assessed using the prototypical substrate for BSEP (taurocholate). Some nucleotide positions were confirmed by PharmGKB (Hewett et al., 2002). Data from Strautnieks et al. (1998); Wang et al. (2002b); Hayashi et al. (2005); Noe et al. (2005); Lang et al. (2007).

Nucleotide Change	Amino Acid Change	In Vitro Function	Protein Expression/ Localization
ABCB11	BSEP		
N.D.	G238V	N.D.	Intracellular
A890G	E297G	↓	Intracellular
N.D.	C336S	↔	Normal
G1296C	R432T	↓	Reduced
T1331C	V444A	↔	Normal/Reduced
A1445G	D482G	↓	Normal/Reduced
G2026T	D676Y	↓	Reduced
G2563A	G855R	↓	Reduced
G2944A	G982R	↓	Intracellular
C3457T	R1153C	↓	Intracellular
G3803A	R1268Q	↓	Intracellular

In a surprising turn of events, Bsep-null mice exhibit a relatively mild cholestasis compared with humans lacking functional BSEP (Wang et al., 2001c). Bsep-null mice are viable and fertile but display growth retardation and lower liver weights compared with wild type (Wang et al., 2001c). Canaliculi from Bsep-null mice have dilated lumens, loss of microvilli, and retained biliary material (Wang et al., 2001c). Although the secretion of cholic acid is reduced in Bsep-null mice, total bile acid excretion is not abolished (~30% of wild-type mice) (Wang et al., 2001c). Feeding a cholic acid-supplemented diet to Bsep-null mice does, however, precipitate a more pronounced PFIC-II-like phenotype (Wang et al., 2003b). A less severe phenotype in Bsep-null mice compared with patients with PFIC-II suggests that mice possess an alternate canalicular bile acid transport system or further hydroxylation of bile acids in the 6 position to increase their hydrophilicity and decrease their toxicity, all of which would compensate for the loss of Bsep. Subsequent research demonstrated the overexpression of Mdr1a and Mdr2 proteins in Bsep-null mice and led to the proposition that Mdr1a transports bile acids, albeit with a lower affinity (Lam et al., 2005). Indeed, in vitro Pgp overexpression is associated with taurocholate transport (Lam et al., 2005). Furthermore, triple-null mice lacking Bsep, Mdr1a, and Mdr1b exhibit a severe degree of cholestasis as evidenced by impaired bile formation, jaundice, and increased mortality (Wang et al., 2009). Mrp2 and Mrp3 proteins are also elevated in Bsep-null mice (to a lesser degree than Mdr1a) and may compensate for bile acid excretion.

Dubin-Johnson syndrome results from mutations in the *ABCC2* (MRP2) gene (Kartenbeck et al., 1996; Paulusma et al., 1997; Tsujii et al., 1999; Keitel et al., 2000). These patients experience a benign clinical course and most notably exhibit chronic hyperbilirubinemia (Table 10). Before the development of Mrp2-null mice, re-

searchers were able to identify functional roles for Mrp2 using rats lacking this transporter (Eisai hyperbilirubinemic rats on a Sprague-Dawley background and transport-deficient (TR−) on a Wistar background) (Paulusma et al., 1996; Ito et al., 1997). Mrp2-null mice are healthy and viable (Chu et al., 2006; Vlaming et al., 2006). The only notable phenotypic characteristic of Mrp2-null mice is chronic hyperbilirubinemia, which is similar to that in the mutant rat lines (Elferink et al., 1989; Chu et al., 2006; Vlaming et al., 2006). In addition, bile flow and biliary excretion of glutathione is markedly reduced in Mrp2-null mice (Chu et al., 2006; Vlaming et al., 2006). Biliary excretion of the organic anion dibromosulfophthalein is reduced in Mrp2-null mice (Chu et al., 2006). The biliary excretion of spiramycin is lower in single-pass perfused livers from Mrp2-null mice, compared with wild type (Tian et al., 2007). Likewise, the biliary excretion of rosuvastatin is lower in Eisai hyperbilirubinemic rats compared with Sprague-Dawley rats (Kitamura et al., 2008).

The role of Mrp2 in the hepatobiliary transport of the antihistamine fexofenadine differs between mice and rats (Tian et al., 2008). The biliary excretion rate of fexofenadine is reduced 85% in Mrp2-null mice compared with wild type (Tian et al., 2008). In contrast, TR− and Eisai hyperbilirubinemic rats lacking Mrp2 function demonstrate biliary elimination of fexofenadine similar to that of their Wistar and Sprague-Dawley rat counterparts, respectively (Tahara et al., 2005; Tian et al., 2007, 2008). In addition, the biliary excretion of fexofenadine is unchanged in Mdr1a/1b-null and Bcrp-null mice, suggesting that Mrp2 is the predominant canalicular transporter responsible for fexofenadine efflux in mice (Tian et al., 2007).

An important role for Mrp2 in the biliary clearance of morphine-3-glucuronide is evident in Mrp2-null mice (van de Wetering et al., 2007). The appearance of morphine-3-glucuronide in bile is markedly reduced in Mrp2-null mice (van de Wetering et al., 2007). Instead, morphine-3-glucuronide excretion shifts from biliary to urinary (van de Wetering et al., 2007). It is likely that Mrp3 compensates for the loss of Mrp2 and enables the hepatic efflux of morphine-3-glucuronide to the sinusoidal blood.

The biliary excretion of the cholesterol-lowering drug pravastatin is lower in TR− rats lacking functional Mrp2 protein (Yamazaki et al., 1997; Fukumura et al., 1998; Kivistö et al., 2005). Increased systemic exposure to oral pravastatin in TR− rats is associated with enhanced inhibition of HMG-CoA reductase as reflected by shifts in cholesterol levels (i.e., lower lathosterol to cholesterol concentration ratios) (Kivistö et al., 2005). Pravastatin plasma concentrations are reduced in healthy volunteers carrying the C1446G synonymous *ABCC2* (MRP2) variant (Niemi et al., 2006a). This polymorphism increased hepatic MRP2 mRNA levels by 95% and, in turn, supports the link between MRP2 expression and pravastatin disposition (Niemi et al., 2006a).

Paclitaxel pharmacokinetics is altered in Mrp2-null and Mdr1a/1b-null mice as well as the triple null mice (Mrp2/Mdr1a/1b-null mice) (Lagas et al., 2006). The exact role(s) of Mrp2 and Mdr1a/1b in regulating paclitaxel pharmacokinetics depends upon the route of administration. Mdr1a/1b reduces plasma concentrations of paclitaxel when given orally (Lagas et al., 2006). It is noteworthy that intravenous administration of paclitaxel results in elevated plasma drug levels in Mrp2-null mice as well as Mdr1a/1b-null mice (Lagas et al., 2006). The biliary excretion of paclitaxel was absent in Mrp2-null mice, suggesting that Mrp2 is the principal canalicular pump for this anticancer drug (Lagas et al., 2006). These studies suggest that intestinal Mdr1a/1b and hepatic Mrp2 are important determinants of paclitaxel disposition. Docetaxel is an anticancer drug related to paclitaxel. Docetaxel-induced leucopenia/neutropenia is associated with a variant in the *ABCC2* gene (Kiyotani et al., 2008). Similar to paclitaxel, the pharmacokinetics of other anticancer drugs are influenced by the expression of Mrp2 and/or Mdr1a/1b. The biliary excretion of doxorubicin is lower in Mrp2-null mice and is almost abolished in Mrp2/Mdr1a/1b-null mice (Vlaming et al., 2006).

In addition to pumping pharmaceuticals into bile, canalicular Mrp2 also seems to influence the biliary excretion of toxins. For example, transport of the *Amanita* spp. mushroom toxin demethylphalloin is reduced in TR− rats (Gavrilova et al., 2007). Demethylphalloin levels in the bile of Mdr1a/1b-null mice and Bcrp-null mice were similar to wild type, suggesting that Mrp2 is the primary canalicular pump for this toxin (Gavrilova et al., 2007). Likewise, TR− rats are protected from α-naphthylisothiocyanate-induced biliary damage, probably by preventing exposure of cholangiocytes to this chemical (Dietrich et al., 2001b). Finally, the plasma concentrations of the food-derived carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine are elevated in Mrp2-null mice (Vlaming et al., 2006) and the intestinal absorption of 2-amino-1-methyl-6-phenylimidazo-[4,5-*b*]pyridine is limited by Mrp2 in the rat intestince (Dietrich et al., 2001a). Collectively, these findings suggest that Mrp2 functions as an intestinal and biliary transporter to protect the liver from injury. This is supported by translational studies that have associated *ABCC2* variants with liver disease including intrahepatic cholestasis of pregnancy as well as herbal and drug-induced toxicity (Choi et al., 2007; Daly et al., 2007; Sookoian et al., 2008).

Similar to Mrp2, canalicular Bcrp is important for excretion of chemicals into bile. The biliary excretion of antibiotics (nitrofurantoin, ciprofloxacin, grepafloxacin, ofloxacin, ulifloxacin) and the anticholesterol drug rosuvastatin is lower in Bcrp-null mice (Merino et al., 2005c; Ando et al., 2007; Kitamura et al., 2008). Chinese men

with one mutant Q141K *ABCG2* (BCRP) allele demonstrate higher plasma concentrations of rosuvastatin compared with those with both wild-type alleles (Table 15) (Zhang et al., 2006b). Similar findings have been reported in Finnish volunteers with the Q141K *ABCG2* (BCRP) SNP after atorvastatin or rosuvastatin administration (Keskitalo et al., 2009). Mrp2 and Bcrp both contribute to the biliary elimination of methotrexate and its toxic metabolite 7-hydroxymethotrexate after intravenous administration (Vlaming et al., 2009b). Plasma 7-hydroxymethotrexate levels are elevated in Mrp2-null mice but not Bcrp-null mice (Vlaming et al., 2009b). Double-null mice lacking both Mrp2 and Bcrp have greater than 20-fold reductions in the biliary excretion of methotrexate and its metabolite (Vlaming et al., 2009b). Therefore, it has been concluded that Mrp2 can compensate for loss of Bcrp function, whereas Bcrp can only partially compensate for loss of Mrp2 function in dictating methotrexate disposition.

The existence of a dietary cholesterol transport system was suspected before the identification of the ABCG5 and ABCG8 transporters. Sitosterolemia is a disorder of impaired clearance of plant-derived sterols that presents as tendon xanthomas, atherosclerosis at a young age, and premature coronary artery disease (Table 10) (Salen et al., 1992). This rare, autosomal recessive disorder results from mutations in *ABCG5* and *ABCG8* that consequently impair the biliary excretion of sterols (Berge et al., 2000; Lee et al., 2001b; Lu et al., 2001). Not surprisingly, disruption of both the *Abcg5* and *Abcg8* genes in mice also produces the sitosterolemia phenotype. Abcg5/g8-null mice have an increased fractional absorption of dietary plant sterols as well as plasma sitosterol levels. In addition, biliary cholesterol levels are very low in Abcg5/g8-null mice (Yu et al., 2002). Although the total sterol levels are similar in livers of wild-type and Abcg5/8-null mice, the proportion of sterols that are plant-based (as opposed to cholesterol) is much larger in Abcg5/g8-null mice (Yu et al., 2004). Single-null mice (Abcg5-null and Abcg8-null mice) have also been developed (Klett et al., 2004b; Plösch et al., 2004). Pharmacological inhibition of sterol absorption using ezetimibe ameliorates metabolic perturbations observed in Abcg5/g8-null mice (Yu et al., 2005). It is noteworthy that Mdr2-null mice also exhibit low biliary excretion of cholesterol, suggesting that all three transporters contribute to cholesterol excretion (Langheim et al., 2005). Collectively, disruption of ABCG5 and G8 in mice and humans demonstrates that these two transporters are required for efficient secretion of cholesterol into bile.

ATP7B is a critical transporter for the efflux of copper from liver to bile. Mutations in the *ATP7B* gene cause the autosomal recessive disorder Wilson's disease (Table 10) (Bull et al., 1993; Tanzi et al., 1993). This disorder typically presents in young patients, although adult onset has been reported. Patients with Wilson's disease demonstrate the sequelae of disrupted copper elimination (Lutsenko, 2008). As a result of impaired biliary excretion, copper accumulates in the liver, resulting in pathological conditions including cirrhosis, hepatitis, steatosis, and fulminant liver failure. ATP7B-null mice have been engineered; as expected, they exhibit neurological symptoms (tremor, ataxia, abnormal locomotor activity) and marked copper accumulation in the liver by 4 to 6 weeks of age (Buiakova et al., 1999). Pathological liver conditions are evident in adult ATP7B-null mice and entail swollen hepatocytes with enlarged nuclei, inflammation, necrosis, and proliferation of bile ducts. Enlarged nuclei are probably a result of copper accumulation and enhanced DNA synthesis (Huster et al., 2006). By 28 weeks, liver fibrosis and regenerating nodules are apparent (Huster et al., 2006). In addition, liver cholesterol and serum very-low-density lipoprotein levels are lower in ATP7B-null mice (Huster et al., 2007). Extrahepatic copper accumulation in ATP7B-null mice occurs in the kidneys, brain, placenta, and mammary glands (Buiakova et al., 1999).

ATP8B1 is a phosphatidylserine flippase in the canalicular membrane that transports phosphatidylserine. *ATP8B1* is also called familial intrahepatic cholestasis 1 gene and is responsible for PFIC-I as well as the milder functional defect benign recurrent intrahepatic cholestasis (Table 10). PFIC-I is also known as Byler's disease, and patients develop end-stage liver disease during the second decade of life. Other symptoms include elevated serum bile acids, fat malabsorption, diarrhea, and jaundice. Atp8b1-deficient mice carry a mutation orthologous to a human *ATP8B1* variant; surprisingly, these mice demonstrate only a mild phenotype (reduced weight at weaning, elevated serum bile acid levels, reduced bile acid excretion in bile) (Pawlikowska et al., 2004). As expected, phosphatidylserine levels are ele-

TABLE 15
In vitro characterization of genetic polymorphisms in BCRP

In vitro function was assessed using prototypical substrates BCRP (mitoxantrone, estrone-3-sulfate, dehydroepiandrosterone). Nucleotide position was confirmed by PharmGKB (Hewett et al., 2002). Data are from Honjo et al. (2002); Kondo et al. (2004); Mizuarai et al. (2004); Morisaki et al. (2005); Vethanayagam et al. (2005); Tamura et al., 2006a,b, 2007b).

Nucleotide Change	Amino Acid Change	In Vitro Function	Protein Expression/Localization
ABCG2	BCRP		
G34A	V12M	↔	Normal/intracellular
C376T	Gln126STOP	N.D.	Absent
C421A	Q141K	↓	Normal/reduced
G445C	A149P	↔	Normal
G448A	R163K	↔	Normal
C496G	Q166E	↔	Normal/reduced
A616C	I206L	↓↔	Normal
T623C	F208S	N.D.	Reduced
T742C	S248P	N.D.	Normal
C805T	P269S	↓↔	Normal
T1291C	F431L	↓	Normal/reduced
G1322A	S441N	↓	Reduced
T1465C	F489L	↓↔	Normal/reduced
A1768T	N590Y	↓↔	Increased
G1858A	D620N	↓↔	Normal

↓, reduced function; ↔, no change in function; N.D. not determined.

vated in the bile of Atp8b1-null mice after taurocholate infusion (Paulusma et al., 2006). Increased bile acid levels in Atp8b1-deficient mice are not due to changes in intestinal bile acid absorption (Groen et al., 2006, 2007). It has been hypothesized that more bile acid hydroxylation in mice accounts for the milder phenotype in Atp8b1-deficient mice compared with patients with PFIC-I (Pawlikowska et al., 2004). Furthermore, biliary cholesterol concentrations are higher in Atp8b1-null mice, not because of Abcg5/8-mediated transport, but because of nonspecific extraction of cholesterol molecules from the canalicular membrane (Paulusma et al., 2006; Groen et al., 2008).

3. Basolateral Efflux Transporters in Liver. Removal of chemicals from the hepatocyte to the sinusoidal blood is accomplished by transporters on the basolateral membrane including Mrp3, Mrp4, Mrp6, and Abca1. Ostα and Mrp3 are also expressed in the basolateral membrane of cholangiocytes.

Glucuronidation is important for the detoxification and excretion of polar chemicals. Glucuronide conjugates of morphine are substrates of MRP3 (Zelcer et al., 2005). In vivo evidence demonstrates that Mrp3-null mice are unable to efflux morphine-3-glucuronide from the liver to the blood (Zelcer et al., 2005; van de Wetering et al., 2007). Instead, morphine-3-glucuronide accumulates in liver and bile of Mrp3-null mice (Zelcer et al., 2005). A shift from urinary to fecal excretion of morphine conjugates in Mrp3-null mice corresponds with a decreased antinociceptive efficacy of morphine-6-glucuronide, probably because of reduced circulating levels (Zelcer et al., 2005). There is a similar shift in the excretion of acetaminophen-glucuronide, 4-methylumbelliferyl-glucuronide, and harmol-glucuronide from the plasma to the bile of Mrp3-null mice (Manautou et al., 2005; Zamek-Gliszczynski et al., 2006). Resveratrol is a dietary phytoestrogen that is under investigation for beneficial health effects. Mrp3 transports the glucuronide conjugate of resveratrol in vitro, and knockout mice lacking Mrp3 have reduced urinary and renal concentrations of resveratrol and its glucuronide conjugate (van de Wetering et al., 2009a). Likewise, Mrp3-null mice have been used in metabolomic experiments to identify glucuronide conjugates of dietary phytoestrogens (van de Wetering et al., 2009b).

Because of the in vitro ability of Mrp3 to transport bile acids (Hirohashi et al., 2000) and the induction of Mrp3 mRNA and protein in cholestatic livers (Scheffer et al., 2002b; Barnes et al., 2007; Slitt et al., 2007), it was hypothesized that hepatic injury would be enhanced in Mrp3-null mice. However, Mrp3-null and wild-type mice exhibit a similar extent of liver damage after bile-duct ligation (Zelcer et al., 2006). Despite similar injury, Mrp3-null mice do exhibit elevated hepatic bile acid content and reduced serum bilirubin glucuronide, which is consistent with the in vitro analysis of these substrates (Belinsky et al., 2005; Zelcer et al., 2006). Instead, Mrp4 seems to be important during extrahepatic cholestasis, as evidenced by more severe liver injury in Mrp4-null mice after bile-duct ligation (Mennone et al., 2006). Similar to MRP3, MRP4 mRNA and protein are up-regulated in cholestatic livers (Gradhand et al., 2008).

Mrp4 transports sulfate conjugates from the liver. Basolateral excretion of sulfate conjugates (including acetaminophen, harmol, and 4-methylumbelliferyl) into sinusoidal blood is reduced in Mrp4-null mice (Zamek-Gliszczynski et al., 2006). It is noteworthy that hepatic Sult2a1 mRNA is reduced in Mrp4-null mice, suggesting a conserved excretion pathway for sulfate conjugates from the liver (Assem et al., 2004).

Defects in the *ABCA1* gene cause Tangier's disease, an autosomal recessive disorder of impaired cholesterol transport (Table 10) (Bodzioch et al., 1999; Brooks-Wilson et al., 1999; Marcil et al., 1999; Remaley et al., 1999; Rust et al., 1999; Schippling et al., 2008). Patients with Tangier's disease lack high-density lipoproteins that bind cholesterol. As a result, cholesterol builds up in various tissues. Like persons with Tangier's disease, mice lacking Abca1 have reduced plasma cholesterol, phospholipids, and almost no high density lipoproteins (McNeish et al., 2000). In addition, cholesterol absorption from the intestine is diminished in Abca1-null mice (Drobnik et al., 2001). The liver attempts to compensate for these perturbations by up-regulating cholesterol synthesis (Drobnik et al., 2001). As with the whole-body knockout, plasma cholesterol and high density lipoproteins are decreased in liver-specific Abca1-null mice (Timmins et al., 2005). It is important to note that the biliary secretion of cholesterol, bile acids, and phospholipids is unaffected by the absence of Abca1 (Groen et al., 2001). Cholesterol accumulates in a variety of Abca1-null tissues, including the lungs (intraaveolar macrophages and type II pneumocytes), intestine, and feces (McNeish et al., 2000; Drobnik et al., 2001). It has also been noted that body weight is reduced in Abca1-null mice (Orsó et al., 2000). In addition, the mutant mice develop splenomegaly, enlarged adrenal glands, and deficiencies in fat-soluble vitamins (Orsó et al., 2000).

B. Kidneys

Kidney transporters (primarily in proximal tubules) participate in the secretion and reabsorption of endogenous and exogenous chemicals. Basolateral influx of organic anions and cations by Oat1, Oat3, Oct1–3, and Oatp4c1 is the first step in renal secretion (Fig. 7). After extraction of chemicals from blood, efflux transporters on the apical brush-border membrane, including Mrp2, Mrp4, Bcrp, Mate1, and Mdr1b, secrete the chemicals into urine. Reabsorption of chemicals within the kidneys can be accomplished by apical transporters Asbt, Cnt1–3, Oat2, Oat4, Oat5, Urat1, Oatp1a1, Pept1–2, and Octn1–2 and subsequently across the basolateral surface by Abca1, Ent1, Ent2, Mrp6, Ostα, and Ostβ.

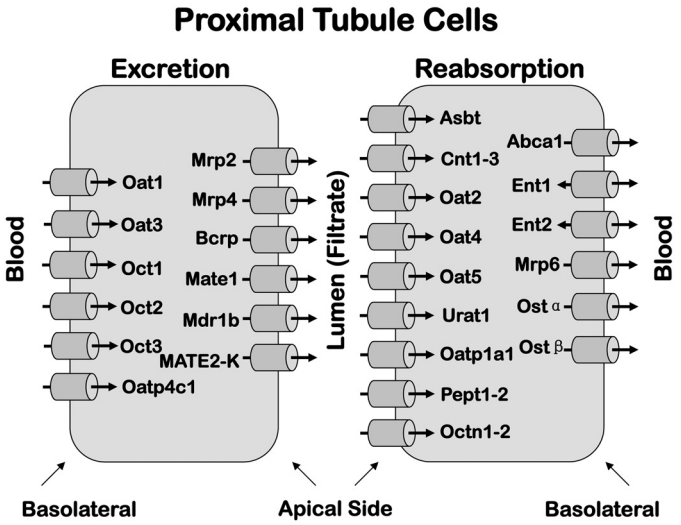

FIG. 7. Subcellular localization of uptake and efflux transport proteins in renal proximal tubules. The localization and orientation of uptake and efflux transporters in the kidneys (primarily rodents) are shown.

1. Basolateral Uptake Transporters in Kidneys. On the basolateral membrane of the kidneys, Oct1–3 are the primary cation transporters, whereas Oat1, Oat3, and Oatp4c1 are the primary anion transporters. Generation of null mice points to roles for these transporters in the active uptake of chemicals. Renal secretion of tetraethylammonium is reduced markedly in Oct1/2 double-null mice (Jonker et al., 2003). As a result, plasma tetraethylammonium levels are elevated 6-fold in Oct1/2-null mice compared with single knockouts and wild-type mice, suggesting functional overlap of these two isoforms in the kidneys (Jonker et al., 2003). As expected, Oat1-null and Oat3-null mice have deficits in renal organic anion secretion. *P*-aminohippurate uptake is absent in renal slices from Oat1-null mice (Eraly et al., 2006). Conflicting results demonstrate unchanged and reduced *p*-aminohippurate uptake in renal slices from Oat3-null mice (Sweet et al., 2002; Vanwert et al., 2007; Vallon et al., 2008b). Instead, Oat3-null mice (but not Oat1-null mice) display reduced estrone sulfate excretion (Sweet et al., 2002; Eraly et al., 2006). The plasma clearance and urinary excretion of ciprofloxacin, penicillin G, and methotrexate are reduced in Oat3-null mice (Vanwert et al., 2007, 2008; VanWert and Sweet, 2008). Urinary excretion of the diuretic furosemide and its naturetic response are lower in Oat1-null and Oat3-null mice (Eraly et al., 2006; Vallon et al., 2008b). It is noteworthy that Oat3-null mice exhibit 10 to 15% lower blood pressure than wild-type mice (Vallon et al., 2008a). Additional work is necessary to determine the mechanism of Oat3-mediated blood pressure regulation. Initial indications suggest altered blood pressure regulation may be due to accumulation of circulating endogenous organic anions (Vallon et al., 2008a).

A number of nephrotoxicants, including antivirals, antibiotics, and mercury-thiol conjugates, are transported into the kidneys by OAT transporters (Cihlar et al., 1999; Jariyawat et al., 1999; Tsuda et al., 1999; Jung et al., 2002b; Koh et al., 2002; Aslamkhan et al., 2003; Khamdang et al., 2003; Zalups and Ahmad, 2005a,b,c). As a result, OAT transporters are an important initial step in acute renal injury by accumulating toxicants within the nephron. Overexpression of OAT1–4 sensitizes cells to the cytotoxicity of the β-lactam antibiotic cephaloridine (Jariyawat et al., 1999; Jung et al., 2002b; Khamdang et al., 2003). Decreased viability of cephaloridine-exposed cells expressing OAT1, OAT3, and OAT4, but not OAT2, is reversible by the anion transporter inhibitor probenecid (Jung et al., 2002b; Khamdang et al., 2003). Like cephaloridine, OAT1-expressing kidney cells have enhanced susceptibility to cytotoxicity by the mycotoxin ochratoxin A as well as thiol-containing conjugates of inorganic and methylmercury (Tsuda et al., 1999; Koh et al., 2002; Aslamkhan et al., 2003; Zalups and Ahmad, 2005a,b,c). Additional work is necessary to confirm these findings in null mice lacking the various Oat isoforms as well as the in vivo relevance of SNPs (Table 16).

The antineoplastic drug cisplatin is both a substrate and inhibitor of OCT2 activity (Ciarimboli et al., 2005b; Yokoo et al., 2007; Filipski et al., 2008). Cisplatin accumulation and cytotoxicity are enhanced by overexpression of rat and human OCT2 and, to a lesser degree, OCT1 (Yonezawa et al., 2006; Yokoo et al., 2007). Nephrotoxicity in patients undergoing cisplatin-containing chemotherapeutic regimens often limits its therapeutic efficacy and has been demonstrated to be dependent upon basolateral organic cation transport in cultured kidney cells (Ludwig et al., 2004). Because of the prominent expression of OCT2 in kidneys, studies have started to address whether this transporter can alter

TABLE 16

In vitro characterization of genetic polymorphisms in OAT1 and -3

In vitro function was assessed using prototypical substrates for OAT1 (methotrexate, ochratoxin A) and OAT3 (estrone sulfate, cimetidine). Nucleotide position was confirmed by PharmGKB (Hewett et al., 2002). OAT1 data from Bleasby et al. (2005) and Fujita et al. (2005). OAT3 data from Erdman et al. (2006).

Nucleotide Change	Amino Acid Change	In Vitro Function	Protein Expression/ Localization
SLC22A6	OAT1		
G149A	R50H	↔	N.D.
C311T	P104L	↔	N.D.
T677C	I226T	↔	N.D.
C767T	A256V	↔	N.D.
C877T	R293W	↔	N.D.
G1361A	R454Q	↓	N.D.
SLC22A8	OAT3		
C387A	F129L	↔	N.D.
C445A	R149S	↓	N.D.
C715T	Gln239STOP	↓	N.D.
T779G	I260R	↓	N.D.
C829T	R277W	↓↔	N.D.
T842C	V281A	↔	N.D.
A913T	I305F	↓	Normal
C929T	A310V	↔	N.D.
G1195T	A399S	↔	N.D.
G1342A	V448I	↔	N.D.

↓, reduced function; ↔, no change in function; N.D. not determined.

cisplatin disposition and/or renal toxicity. Compared with wild-type mice, Oct1/2-null mice have reduced platinum excretion and are protected from cisplatin nephrotoxicity (Filipski et al., 2009). Likewise, the A270S *SLC22A2* variant was associated with protection against renal damage in a small cohort of white patients receiving cisplatin-containing chemotherapy regimens (Table 13) (Filipski et al., 2008, 2009). Coadministration of the anticancer drug imatinib prevents renal accumulation and toxicity of cisplatin, probably by interfering with OCT2-mediated transport (Tanihara et al., 2009). Cytotoxicity of another platinum-based anticancer drug, oxaliplatin, is reduced by cimetidine (general OCT inhibitor) in colon cancer cell lines, suggesting that OCT expression may contribute to the antitumor specificity of oxaliplatin (Zhang et al., 2006a). Overexpression of rat and human OCT2 and OCT3 enhances oxaliplatin accumulation and cytotoxicity (Yonezawa et al., 2006; Yokoo et al., 2007). In fact, expression of OCT3 in a human colorectal cancer-derived cell line correlates with sensitivity to oxaliplatin cytotoxicity (Yokoo et al., 2008).

2. Apical Uptake Transporters in Kidneys. Although a large number of transporters are expressed on the apical surface of the kidneys, only the abilities of Urat1, Pept2, and Octn2 to reabsorb chemicals from the urine have been demonstrated in vivo. The functional significance of Asbt, Cnts, Oats, and Oatps on the brush border membrane is hypothetical and warrants further investigation.

Urate is a product of purine metabolism and is eliminated by the kidneys. Accumulation of urate in the body leads to crystallization in the joints, resulting in gout. As the major transporter, altered URAT1 function or expression may influence the reabsorption and body burden of urate. Urat1-null mice were generated in 2008 (Eraly et al., 2008). Although Urat1-null mice have a 2-fold increase in urine urate concentration, there is no change in plasma urate levels (Eraly et al., 2008). These findings suggest that additional transporters contribute to the reabsorption of urate in mice. Messenger RNA analysis of alternate renal urate transporters (i.e., Oat and Mrp) in Urat1-null mice did not identify compensatory gene changes (Eraly et al., 2008).

It had been theorized that loss of URAT1 function in humans would reduce urate reabsorption from glomerular filtrate and decrease the likelihood of urate accumulation and crystallization (Komoda et al., 2004). For example, three *SLC22A12* (URAT1) SNPs (R90H, R477H, Trp258STOP) are associated with idiopathic hypouricemia in Japanese patients (Enomoto et al., 2002a; Iwai et al., 2004b; Komoda et al., 2004). Even heterozygous carriers of the Trp258STOP mutation exhibit low levels of serum urate (Komoda et al., 2004). In addition, the Trp258STOP SNP reduces the incidence of gout in Japanese patients (Taniguchi et al., 2005). Oocytes injected with Trp258STOP SLC22A12 mRNA demonstrate no plasma membrane protein expression, suggesting alterations in subcellular trafficking and/or degradation and probably explaining a lack of urate transport (Enomoto et al., 2002a). Two additional *SLC22A12* SNPs (T217M and E298D) exhibit reduced urate uptake despite normal protein localization (Enomoto et al., 2002a). It is surprising that Urat1-null mice demonstrate little phenotype with regard to urate reabsorption, whereas humans with *SLC22A12* SNPs exhibit pronounced hypouricemia (Eraly et al., 2008). Additional research is needed to elucidate divergent findings between species. A recent genome-wide association study identified a common single-nucleotide polymorphism in *ABCG2* (BCRP) as a determinant of serum urate levels and gout (Woodward et al., 2009). Subsequent functional analysis in vitro demonstrated that urate is indeed a substrate of BCRP and that this apical efflux transporter is important in the renal secretion of urate. After reabsorption from urine, urate seems to be transported back to the circulation via the facilitative glucose transporter 9 (Anzai et al., 2008). Similar to BCRP and URAT1, polymorphisms in facilitative glucose transporter 9 have also been linked to alterations in serum urate levels in humans (Li et al., 2007d; Matsuo et al., 2008; McArdle et al., 2008; Preitner et al., 2009).

Apical expression of Pept2 in renal tubules points to a role for this transporter in the reabsorption of di- and tripeptides (Ganapathy et al., 1997; Shen et al., 1999). In line with this hypothesis, renal accumulation of the fluorophore-conjugated dipeptide D-Ala-Lys-AMCA is markedly reduced in kidneys of Pept2-null mice (Rubio-Aliaga et al., 2003). The reabsorption of carnosine (β-alanyl-L-histidine) is impaired in Pept2-null mice, resulting in an 18-fold increase in the urinary excretion of this chemical (Kamal et al., 2009). Likewise, the total and renal clearance of glycylsarcosine is higher in Pept2-null mice, leading to reduced systemic concentrations and elevated urinary levels (Ocheltree et al., 2005; Frey et al., 2007). Pept2 accounts for 86% of glycylsarcosine reabsorption, whereas Pept1 is responsible for 14% of the reabsorbed substrate (Ocheltree et al., 2005). Additional efforts have been undertaken to identify Pept2 substrates as in vivo tracer compounds to evaluate chemical reabsorption (Nabulsi et al., 2005). Using microPET imaging, [^{11}C]glycylsarcosine clearance from the kidneys is rapid in Pept2-null mice because of impaired reabsorption (Nabulsi et al., 2005). In vitro findings for the PEPT1 and -2 SNPs in overexpression systems are shown in Table 17.

3. Apical Efflux Transporters in Kidneys. Brush-border efflux transporters Mrp2, Mrp4, Bcrp, Mate1, MATE2-K, and Mdr1b accomplish renal secretion of chemicals into urine. Most functional studies of these transporters in kidneys have focused upon Mrp4- and Bcrp-mediated transport. Diuretics (such as hydrochlorothiazide and furosemide) are in vitro substrates and inhibitors for MRP4 and BCRP (Hasegawa et al., 2007). Use of Mrp4-null mice and Bcrp-null mice suggests that

TABLE 17
In vitro characterization of genetic polymorphisms in PEPT1 and -2
In vitro function was assessed using prototypical substrates for PEPT1 (glycylsarcosine, cephalexin) and PEPT2 (glycylsarcosine). Nucleotide position was confirmed by PharmGKB (Hewett et al., 2002). PEPT1 data from Zhang et al. (2004b) and Anderle et al. (2006). PEPT2 data from Pinsonneault et al. (2004) and Terada et al. (2004).

Nucleotide Change	Amino Acid Change	In Vitro Function	Protein Expression/ Localization
SLC15A1	PEPT1		
G61A	V21I	↔	N.D.
T83A	F28Y	↓	Normal
G350A	S117N	↔	Normal
G364A	V122M	↔	Normal
G1256C	G419A	↔	Normal
G1348A	V450I	↔	Normal
C1352A	T451N	↔	Normal
C1609T	P537S	↔	N.D.
C1757T	P586L	↓	Reduced
SLC15A2	PEPT2		
G207A	R57H	↓	Normal
C1048T	L350F	N.D.	N.D.
C1225T	P409S	↔	Normal
G1526A	R509K	N.D.	N.D.

↓, reduced function; ↔, no change in function; N.D. not determined.

Mrp4 is likely to play a more significant role than Bcrp in the renal clearance of hydrochlorothiazide and furosemide (Hasegawa et al., 2007). Mrp4-null mice exhibit reduced renal clearance of both diuretics and higher kidney retention of hydrochlorothiazide during urinary cannulation studies (Hasegawa et al., 2007). The disposition and excretion of hydrochlorothiazide and furosemide are similar in wild-type and Bcrp-null mice (Hasegawa et al., 2007). An important function for Mrp4 in the renal secretion of antiviral drugs (adefovir and tenofovir) has also been demonstrated using Mrp4-null mice (Imaoka et al., 2007). Likewise, the A3463G variant of *ABCC4* (MRP4) is associated with higher tenofovir-diphosphate concentrations in the peripheral blood mononuclear cells of patients infected with HIV (Kiser et al., 2008).

Edaravone is a free radical scavenger used in Japan to treat patients with acute cerebral infarction. Urinary elimination of edaravone seems to involve OAT1- and OAT3-mediated basolateral uptake into the kidneys (Mizuno et al., 2007a). Once inside the proximal tubule cell, edaravone is conjugated with sulfate or glucuronic acid. The ability of Bcrp, as well as Mrp4, to mediate the urinary excretion of edaravone conjugates was investigated in vitro and in vivo (Mizuno et al., 2007b). Bcrp mediates the transport of edaravone-sulfate in membrane vesicles from BCRP-expressing cells, and the renal clearance of this conjugate is reduced in Bcrp-null mice (Mizuno et al., 2007b). Likewise, the glucuronide conjugate of edaravone displayed preference for MRP4 in vitro, and its urinary elimination is diminished in Mrp4-null mice (Mizuno et al., 2007b). In addition, the renal clearance of another xenobiotic conjugate, 6-hydroxy-5,7-dimethyl-2-methylamino-4-(3-pyridylmethyl) benzothiazole sulfate, is lower in Bcrp-null mice, leading to higher concentrations of this conjugate in the kidneys (Mizuno et al., 2004).

Mate1-null mice have recently been developed (Tsuda et al., 2009). The functional significance of Mate1 in the kidneys is illustrated by altered metformin pharmacokinetics (Tsuda et al., 2009). Compared with wild-type mice, Mate1-null mice have increased plasma concentrations and reduced renal clearance of metformin (Tsuda et al., 2009). Further studies in these mice should be useful for investigating the renal elimination of organic cations.

4. Basolateral Efflux Transporters in Kidneys. Efflux pumps on the basolateral membrane of the renal proximal tubule are an area of research that has largely remained unexplored. It is hypothesized that Ostα/β is responsible for the reabsorption of bile acids. In addition, Ent2 and Mrp6 may participate in the reabsorption of nucleosides and organic anions back to the blood. Initial in vitro characterization of transepithelial flux in human renal proximal tubule cells suggests that apical CNT3 and basolateral ENT2 are responsible for the reabsorption of adenosine (Elwi et al., 2009).

C. Intestine

Oral administration of drugs most often requires absorption in the small intestine. Although many drugs are thought to be absorbed by passive diffusion, extraction of chemicals from the intestinal lumen is also accomplished by a number of transporters, including Oct3, Octn1–2, Pept1, Cnt1–2, Oatps, and Asbt (Fig. 8). Likewise, there are apical efflux transporters on enterocytes (Mdr1a, Mrp2, Bcrp) that prevent the entry of chemicals into the systemic circulation and are often responsible for the poor oral bioavailability of pharmaceuticals. Additional apical efflux transporters Abcg5/8 and Atp8b1 are more important for the luminal secretion of sterols and phospholipids, respectively. Subsequent absorption of chemicals across the enterocyte basolateral surface

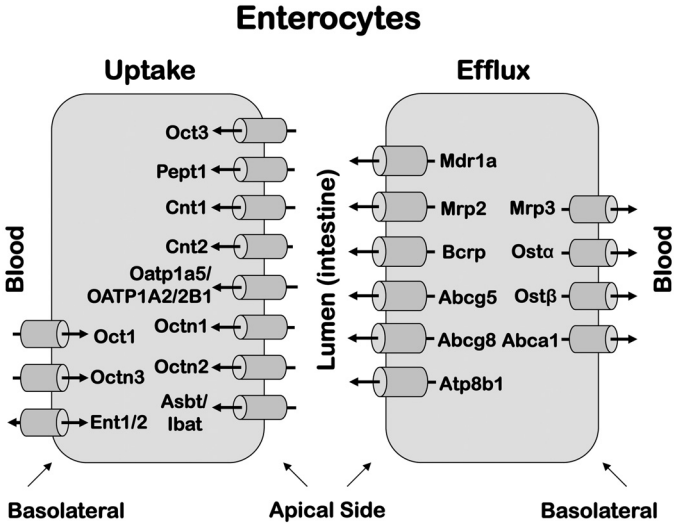

FIG. 8. Subcellular localization of uptake and efflux transport proteins in enterocytes. The localization and orientation of uptake and efflux transporters in the intestine (primarily rodents) are shown.

into the systemic circulation is accomplished via Mrp3, Ostα/β, Ent1–2, and Abca1.

1. Apical Uptake Transporters in the Intestine. Caco-2 cells express OCTN2 and transport carnitine in a sodium-dependent manner (Elimrani et al., 2003; Hirano et al., 2006). Likewise, carnitine uptake across the apical enterocyte membrane is saturable with kinetics akin to OCTN2-overexpressing cells and can be inhibited by Octn2 inhibitors (Kato et al., 2006). Consistent with these findings, carnitine uptake across the apical surface of the small intestine is almost absent in Octn2-null mice (Kato et al., 2006). By 4 weeks of age, Octn2-null mice demonstrate atrophic intestinal villi, inflammation, ulcer formation, and gut perforation (Shekhawat et al., 2007).

Inflammatory bowel disease has been linked to mutations on a locus on chromosome 5 that localizes to the region where the *SLC22A4* (OCTN1) and *SLC22A5* (OCTN2) genes exist (5q31). The L503F variant of *SLC22A4* is more frequent in white persons from New Zealand who have Crohn's disease (Leung et al., 2006) (Table 18). Moreover, the L503F variant of *SLC22A4* and the −207G<C variant of *SLC22A5* are found in adult Greek, British, and German patients with Crohn's disease, but not Italian or Hungarian patients (Gazouli et al., 2005; Török et al., 2005; Ferraris et al., 2006; Waller et al., 2006; Magyari et al., 2007; Taubert et al., 2009). Likewise, the genotype and haplotype frequencies of both of these variants are also increased in patients with ulcerative colitis (Palmieri et al., 2006). Childhood onset inflammatory bowel disease and Crohn's disease are similarly linked to variants in *SLC22A4* (L503F) and *SLC22A5* (−207G<C) in several pediatric populations (Babusukumar et al., 2006; Bene et al., 2006; Russell et al., 2006; Cucchiara et al., 2007). Polymorphisms in OCTN transporters are associated not only with the incidence of inflammatory bowel disease, but also with the pharmacological response to therapy. The −368 T>G polymorphism in the *SLC22A5* promoter corresponds to steroid resistance and inadequate response of Japanese patients with inflammatory bowel disease (Nakahara et al., 2008). These data suggest linkage between inflammatory bowel disease and *SLC22A4* and *SLC22A5* variants among different ethnic groups.

TABLE 18
In vitro characterization of genetic polymorphisms in human OCTN1 and -2

In vitro function was assessed using prototypical substrates for OCTN1 (tetraethylammonium) and OCTN2 (tetraethylammonium, carnitine). Nucleotide position was confirmed by PharmGKB (Hewett et al. (2002). OCTN1 data from Kawasaki et al. (2004); Gazouli et al. (2005); Babusukumar et al. (2006); Russell et al. (2006); Urban et al. (2007, 2008). OCTN2 data from Urban et al., 2006).

Nucleotide Change	Amino Acid Change	In Vitro Function	Protein Expression/ Localization
SLC22A4	OCTN1		
G475A	V159M	↔	N.D.
A494G	D165G	↓	Normal
G615A	M205I	↓	Normal
C844T	Arg282STOP	↓	N.D.
C917T	T306I	↔	Normal
G1385A	G462E	↓	Normal
C1507T	L503F	↑	Normal
SLC22A5	OCTN2		
C51G	F17L	↓	Intracellular
C430T	L144F	↔	Normal
T1345G	Y449D	↓	N.D.
G1441T	V481F	↓	N.D.
G1441A	V481I	↔	N.D.
T1522C	F508L	↔	N.D.
A1588G	M530V	↔	N.D.
C1645T	P549S	↔	Normal

↓, reduced function; ↑, increased function; ↔, no change in function; N.D. not determined.

Asbt is expressed on the apical surface of ileal enterocytes and transports conjugated and unconjugated bile acids in the intestine. Loss-of-function mutations in the *ASBT* gene cause primary bile acid malabsorption that is characterized by diarrhea, fat malabsorption, and malnutrition (Table 10). The first known molecular defect of human *ASBT* was a P290S substitution that abolished taurocholate transport without interfering with protein expression or subcellular distribution (Wong et al., 1995). Additional *ASBT* mutations were subsequently linked to primary bile acid malabsorption (Oelkers et al., 1997). Asbt-null mice seem healthy and physically similar to wild-type mice (Dawson et al., 2003). Fecal bile acid excretion is increased in Asbt-null mice, leading to a reduced total bile acid pool (Dawson et al., 2003). The residual bile acid pool is enriched in cholic acid. Contrary to human primary bile acid malabsorption, Asbt-null mice do not experience steatorrhea (Dawson et al., 2003). This mouse model is useful for investigating only some clinical features of primary bile acid malabsorption. Asbt-null mice exhibit reduced ileal mRNA expression of farnesoid X receptor and fibroblast growth factor 15. It is noteworthy that treatment of Asbt-null mice with either a farnesoid X receptor agonist or with fibroblast growth factor 15 reduces fecal bile acid elimination (Jung et al., 2007).

Glycylsarcosine is a dipeptide that is transported by PEPT1 (Ganapathy et al., 1995). A key role for Pept1 in the intestinal uptake of peptides was confirmed in Pept1-null mice after oral and intravenous glycylsarcosine dosing (Hu et al., 2008). Plasma concentrations of glycylsarcosine are similar in wild-type and Pept1-null mice after intravenous administration but reduced in Pept1-null mice after oral administration (Hu et al., 2008). Likewise, intestinal uptake of glycylsarcosine is lower in everted jejunal rings from Pept1-null mice than in those from wild-type mice (Hu et al., 2008).

2. Apical Efflux Transporters in Intestine. Mdr1a/Pgp is expressed at the apical surface of enterocytes (Panwala et al., 1998), where it effluxes drugs from enterocytes back into the intestinal lumen and thereby decreases the absorption of orally administered drugs. Mdr1a-null mice and/or Mdr1a/1b-null mice have increased oral absorption of vinblastine (Ogihara et al., 2006), fexofenadine (Tahara et al., 2005), and paclitaxel (Bardelmeijer et al., 2000). However, these findings do

not extend to all known Pgp substrates. For example, the well studied Pgp substrate verapamil is not absorbed in Mdr1a/1b-null mice after oral dosing (Ogihara et al., 2006). Further work is needed to classify Pgp substrates that are relevant to the disposition of orally administered drugs. In addition to using Mdr1a/1b-null mice, the human colon cancer cell line Caco-2 is routinely used to assess intestinal transporter function using general and specific inhibitors of transporter isoforms (Balimane et al., 2006).

Recent work demonstrates that regional-specific expression of intestinal drug transporters is important for dictating the intestinal permeability of the gout drug colchicine. In the rat intestine, Pgp protein expression increases from the proximal to the distal intestine, whereas Mrp2 protein expression decreases. Using Mrp2 and Pgp inhibitors in in situ single-pass intestinal perfusion of the rat proximal jejunum and distal ileum, it was shown that Pgp and Mrp2 are responsible for the proximal and distal intestinal transepithelial transport of colchicine, respectively (Dahan et al., 2009).

Maintenance of Mdr1a-null mice under specific pathogen-free conditions initiates spontaneous intestinal inflammation (including dysregulated epithelial cell growth and leukocyte infiltration in the mucosa) similar to human inflammatory bowel disease (Panwala et al., 1998). Colitis is prevented in Mdr1a-null mice after oral treatment with broad-spectrum antibiotics, suggesting intestinal microflora are necessary for this phenotype (Panwala et al., 1998). Work by another group demonstrates that Mdr1a influences the relative abundance of a subset of intraepithelial T lymphocytes in the intestines of mice (Eisenbraun et al., 2000). The consequence of a shift in T lymphocyte population with regard to colitis is not currently understood (Eisenbraun et al., 2000). The link between defective Mdr1a expression and colitis is unclear but may be important in unraveling the mechanism(s) of inflammatory bowel disease. Initial evaluation of *ABCB1* (MDR1) polymorphisms and inflammatory bowel disease has yielded mixed results (Ho et al., 2006a; Oostenbrug et al., 2006; Fiedler et al., 2007). A meta-analysis of the available findings suggests that the I1145I SNP in *ABCB1* (MDR1) is significantly associated with ulcerative colitis (Table 19) (Annese et al., 2006).

A functional role for Bcrp in the efflux of drug conjugates into the intestinal lumen has been illustrated using in situ perfusion of intestinal segments from Bcrp-null mice (Adachi et al., 2005). Similar to biliary excretion patterns, the efflux of the glucuronide and sulfate conjugates of 4-methylumbelliferone is lower in Bcrp-null small intestine segments compared with wild-type counterparts (Adachi et al., 2005). Oral bioavailability of xenobiotics such as the novel kinase inhibitor JNJ-7706621, as well as the inflammatory bowel disease drug sulfasalazine, is limited by Bcrp in the intestine (Seamon et al., 2006; Zaher et al., 2006). Oral absorption of these drugs is increased in Bcrp-null mice or wild-type mice treated with Bcrp inhibitors (Seamon et al., 2006; Zaher et al., 2006). In support of these findings, humans with the Q141K *ABCG2* (BCRP) polymorphism display increased oral bioavailability of sulfasalazine (Table 15) (Urquhart et al., 2008; Yamasaki et al., 2008). Design and development of novel therapeutics that require high oral bioavailability should be screened as potential Bcrp and Mdr1 substrates and modified to prevent intestinal efflux. There is an additional approach to bypass intestinal efflux by incorporating into oral drug formulations excipients that inhibit Bcrp function. For example, the excipients Pluronic P85 and Tween 20 improve intestinal absorption of the Bcrp substrate topotecan in wild-type but not Bcrp-null mice (Yamagata et al., 2007).

TABLE 19

In vitro characterization of genetic polymorphisms in MDR1

In vitro function was assessed using prototypical substrates for MDR1 (vinblastine, verapamil, paclitaxel). Nucleotide position was confirmed by PharmGKB (Hewett et al., 2002). Data from Kimchi-Sarfaty et al. (2002); Morita et al. (2003a); Crouthamel et al. (2006); Salama et al. (2006); Schaefer et al. (2006); Gow et al. (2008); Woodahl et al. (2009).

Nucleotide Change	Amino Acid Change	In Vitro Function	Protein Expression/ Localization
ABCB1	MDR1		
A61G	N21D	↔	N.D.
T307C	F103L	N.D.	N.D.
G1199A	S400N	↑ ↔	Normal
C2005T	R669C	↔	N.D.
G2677T	A893S	↓ ↑ ↔	Normal
G2677A	A893T	↑ ↔	Notmal
T3421A	S1141T	↓ ↔	N.D.
C3435T	I1145I	↓ ↔	N.D.
G3751A	V1251I	↓	N.D.

↓, reduced function; ↑, increased function; ↔, no change in function; N.D. not determined.

3. Basolateral Efflux Transporters in Intestine. Ostα and Ostβ are heterodimeric organic solute transporters that efflux bile acids and conjugated steroids across the basolateral membrane of epithelial cells in a variety of tissues. Despite stable expression of Ostβ mRNA, the protein expression of Ostβ in the kidneys and ileum is absent in mice lacking Ostα (Li et al., 2007b). Therefore, Ostα-null mice are essentially a "double-null" model for Ostα and -β. Ostα-null mice are viable and fertile but display growth retardation (Ballatori et al., 2008). There are a variety of pathological findings in Ostα-null mice, including hypertrophy of the small intestine and reduced bile acid pool, serum bile acid, cholesterol, and triglyceride levels (Ballatori et al., 2008). Ostα-null mice exhibit a number of compensatory gene changes, including higher intestinal, hepatic, and renal Mrp3 and lower hepatic Cyp7a1 (rate-limiting bile acid synthetic enzyme) levels. Combined loss of Ostα and Mrp3 in female Ostα/Mrp3-null mice results in nearly absent transileal transport of taurocholate (Rao et al., 2008). Ostα-null mice will continue to be a useful model for investigating enterohepatic recirculation of bile acids.

Mrp1 is expressed in intestinal proliferative crypt cells (Peng et al., 1999). Mrp1-null mice exhibit en-

hanced sensitivity to the gastrointestinal toxicity of methotrexate, as exhibited by nearly complete loss of small intestinal villi (Kato et al., 2009). Although the plasma concentration and biliary excretion of methotrexate are unchanged, immature proliferative cells from Mrp1-null mice have higher methotrexate accumulation compared with wild type (Kato et al., 2009).

The antiviral drug ribavirin is used to treat hepatitis C infection. Using Ent1-null mice, it was demonstrated that Ent1 participates in the intestinal absorption of ribavirin as well as its distribution to erythrocytes (Endres et al., 2009a,b). Therefore, Ent1 permits not only the oral absorption of ribavirin but may also enable the hemolytic anemia observed in some patients prescribed this therapy. The functional in vivo significance of the remaining apical (Oct3, Cnt1–2, Oatps) and basolateral (Oct1 and Octn3) transporters in enterocytes is not fully understood.

D. Brain

A number of uptake and efflux transporters have been identified in the brain. Some of these transporters have been localized to the apical (Mdr1a/1b, Mrp1–5, Bcrp, Oatp1a5) and basolateral (Octn2, Oatp1a4, Oatp2b1, Oat3) membranes of capillary endothelial cells (Fig. 9). The choroid plexus is also rich with drug transporters including Oatps (1a1, 1a4, 1a5, 2b1), Oat3, Pept2, Cnt2, and Oct2 as well as the efflux transporters Mrp1, -3, -4, and Mdr1b (Fig. 9). In addition, transporters have been identified in other regions of the brain.

1. Uptake Transporters in Brain. Oct3 protein staining is observed in multiple regions of the brain, including neurons in the subfornical organ of mice (Vialou et al., 2004). As part of the central nervous system, the subfornical organ participates in fluid and electrolyte exchange. Oct3-null mice exhibit increased ingestion of hypertonic saline under dehydrated and salt appetite conditions (Vialou et al., 2004). In addition, the cellular response of the subfornical organ to salt deprivation (as detected by Fos immunoreactivity) is attenuated in Oct3-null mice (Vialou et al., 2004). Collectively, these findings suggest that Oct3 participates in the response of the central nervous system to sodium depletion and water deprivation.

Treatment of mice with methamphetamine stimulates locomotor activity. Reduced Oct3 protein expression after antisense oligonucleotide administration to mice is associated with markedly higher methamphetamine-induced locomotor activity. Enhanced locomotor activity is probably due to reduced clearance of monoaminergic neurotransmitters, and thus more neuronal stimulation (Kitaichi et al., 2005). Likewise, brains from Oct3-null mice exhibit higher extracellular dopamine concentrations and greater loss of striatal nerve terminals after methamphetamine administration compared with wild type (Cui et al., 2009a). Based on the observed altered methamphetamine handling in mice with reduced expression of Oct3 (Kitaichi et al., 2005), the allelic frequencies of *SLC22A3* (OCT3) polymorphisms were determined in 213 Japanese subjects with methamphetamine dependence (Aoyama et al., 2006). Two intronic variants were associated with the development of polysubstance abuse in this population (Aoyama et al., 2006). Collectively, these data suggest a role for Oct3/OCT3 in the "uptake-2 system" of neurotransmitters in brain.

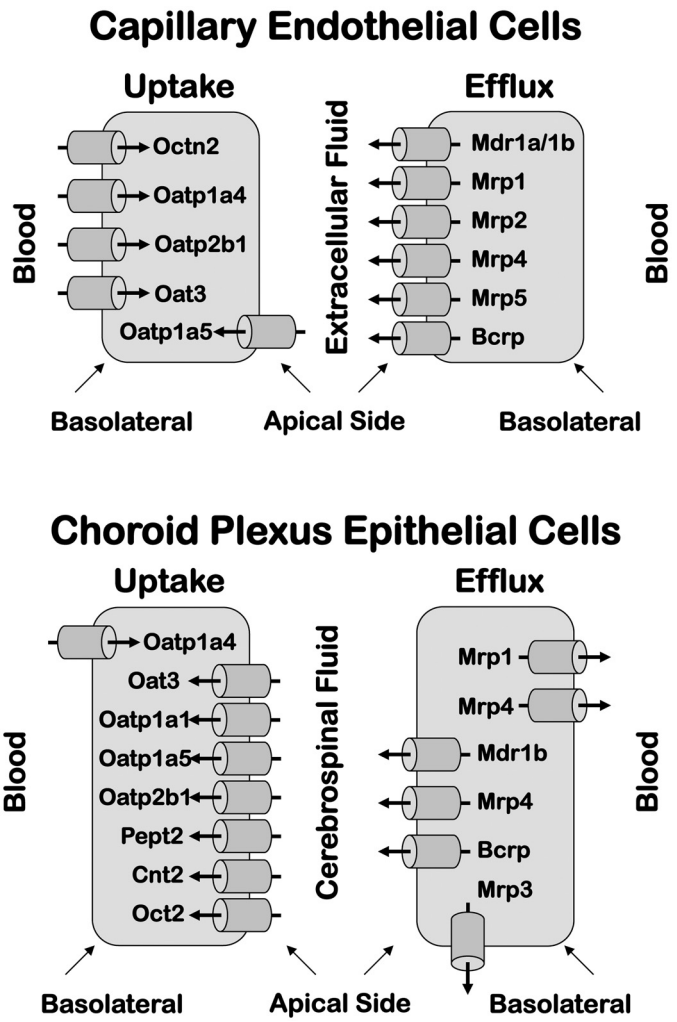

FIG. 9. Subcellular localization of uptake and efflux transport proteins in brain capillary endothelial cells and choroid plexus epithelial cells. The localization and orientation of uptake and efflux transporters in the brain (primarily rodents) are shown.

Oat3 and Pept2 are expressed on the apical membrane of the choroid plexus and participate in the extraction of chemicals from the cerebrospinal fluid into the choroid plexus epithelium (Sweet et al., 2002). Cellular uptake of the Oat3 substrate fluorescein is reduced in the choroid plexus of Oat3-null mice (Sweet et al., 2002). Likewise, levels of Pept2 substrates (cefadroxil, glycylsarcosine, 5-aminolevulinic acid, L-kyotorphin) are reduced in the choroid plexus of Pept2-null mice (Ocheltree et al., 2004b, 2005; Hu et al., 2007; Shen et al., 2007; Jiang et al., 2009). Moreover, the heme precursor

5-aminolevulinic acid is markedly elevated in the cerebrospinal fluid of Pept2-null mice, leading to enhanced neurotoxicity and mortality (Hu et al., 2007). These data indicate roles for Oat3 and Pept2 in limiting the accumulation of xenobiotics in the cerebrospinal fluid.

Adenosine is an inhibitor of mouse Ent1 function and is thought to be a substrate (Kiss et al., 2000). ENT1 protein is localized to multiple regions of the human brain, including the frontal and parietal lobes of the cerebral cortex, thalamus, midbrain, and the basal ganglia and colocalized to regions rich with the adenosine A_1 receptor (Jennings et al., 2001). Because adenosine is important in ethanol intoxication, Ent1-null mice were generated and have been shown to consume greater amounts of ethanol than wild-type mice (Choi et al., 2004). Ent1-null mice exhibit reduced hypnotic and ataxic responses in response to ethanol (Choi et al., 2004). Similar to modulating ethanol consumption, activation of adenosine receptors reduces anxiety-like behavior; therefore, the behavior of mice lacking Ent1 was tested in an open field and an elevated plus maze (Chen et al., 2007a). It is noteworthy that mice lacking Ent1 exhibit reduced anxiety-like behavior (Chen et al., 2007a). Microinjection of an ENT1 antagonist into the brains of wild-type mice also decreases anxiety-like behavior (Chen et al., 2007a). Likewise, Oct3-null mice are significantly less anxious than wild-type mice, possibly by altering serotonin signaling in the brain (Wultsch et al., 2009). Together, ENT1 and OCT3 may be important in stress and anxiety by modulating endogenous neurotransmitters.

2. Efflux Transporters in Brain. Expression of Mdr1a/1b as well as other transporters (such as Bcrp) in the blood-brain barrier restricts the accumulation of chemicals in the brain. These transporters actively efflux chemicals across the luminal surface of blood vessels (Schinkel et al., 1994; Lee et al., 2005b). Mdr1a-null mice were first developed in 1994 (Schinkel et al., 1994). Early studies highlighted the critical role of Pgp in protecting the brain from xenobiotics. Brain concentrations of the pesticide ivermectin and the anticancer drug vinblastine are elevated in Mdr1a-null mice (Schinkel et al., 1994; van Asperen et al., 1996). In turn, Mdr1a-null mice are highly susceptible to the toxicity of ivermectin as well as vinblastine (Schinkel et al., 1994).

Because of the redundancy of Mdr1a and Mdr1b transporters, mice lacking both transporters simultaneously were developed to investigate their collective transport of substrates identified in in vitro systems (such as the antiviral drug oseltamivir, the anticholesterol drug cerivastatin, and the anticancer drug paclitaxel) (Ose et al., 2008). The concentrations of oseltamivir, cerivastatin, and paclitaxel are elevated in the brains of Mdr1a/1b-null mice (Gallo et al., 2003; Kivistö et al., 2004; Ose et al., 2008). Likewise, long-term oxycodone administration to rats increases brain Pgp protein expression, thereby reducing accumulation of paclitaxel in the brain (Hassan et al., 2007). These findings suggest that opiate-mediated induction of brain efflux transporters such as Pgp may be a source of drug-drug interactions, leading to reduced chemotherapeutic drug penetration into the brain (and possibly other tissues). Likewise, accumulation of the cardiac glycoside digoxin is markedly enhanced in the brains of Mdr1a-null and Mdr1a/1b-null mice compared with wild-type mice (Schinkel et al., 1997; Kawahara et al., 1999). Despite these intriguing digoxin findings in null mice, clinical pharmacokinetic analysis of the I1145I *ABCB1* (MDR1) variant has yielded conflicting findings with regard to the disposition of a single oral digoxin dose (Table 19) (Hoffmeyer et al., 2000; Sakaeda et al., 2001; Morita et al., 2003b; Verstuyft et al., 2003; Chowbay et al., 2005).

The antihistamine drug fexofenadine is transported by MDR1 (Cvetkovic et al., 1999). When administered orally, plasma levels of fexofenadine are 6-fold higher in Mdr1a/1b-null mice compared with wild type (Tahara et al., 2005). The brain:plasma ratio of fexofenadine is elevated 3-fold in Mdr1a/1b-null mice (Tahara et al., 2005). Fexofenadine disposition is likewise altered in individuals with MDR haplotypes. Consistent with enhanced in vitro transport activity, the Ala893Ser *ABCB1* (MDR1) variant is associated with reduced plasma fexofenadine concentrations (Table 19) (Kim et al., 2001). Other investigations have observed disparate results regarding *ABCB1* genotype and fexofenadine disposition (Drescher et al., 2002; Yi et al., 2004).

The pharmacokinetics of corticosteroids such as cortisol, corticosterone, aldosterone, and progesterone are altered when administered exogenously to Mdr1a/1b-null mice (Uhr et al., 2002). In the absence of Mdr1a/1b, the four corticosteroids accumulate in mouse brains (Uhr et al., 2002). Moreover, it is hypothesized that Pgp influences the hypothalamic-pituitary-adrenal axis signaling by preventing access of glucocorticoids to the brain (Pariante et al., 2001, 2003). It is thought that antidepressants inhibit Pgp activity and in turn enhance glucocorticoid receptor function (Pariante et al., 2001, 2003). Administration of the antidepressant desipramine for 7 days induces mRNA expression of the glucocorticoid receptor in the brains of wild-type, but not Mdr1a-null mice (Yau et al., 2007). Induction of the glucocorticoid receptor corresponds with a decrease in corticosterone levels in desipramine-treated wild-type mice (Yau et al., 2007). From these findings, the authors suggest that Pgp is a molecular target of antidepressant regulation of the hypothalamic-pituitary-adrenal axis (Yau et al., 2007).

Pharmacological inhibition studies and transporter-null mice demonstrate that Mdr1a/1b and Bcrp play distinct and overlapping functions in pumping chemicals from the brain. One of the first pieces of evidence suggesting a link between these transporters in the brain is that the mRNA expression of Bcrp is elevated 3-fold in the brain microvessels of Mdr1a-null mice com-

pared with wild type (Cisternino et al., 2004). Uptake of vinblastine is higher in Mdr1a-null mice compared with wild-type mice, with little change in the accumulation of prazosin and mitoxantrone (Cisternino et al., 2004). Likewise, Bcrp-null mice do not exhibit altered mitoxantrone uptake into the brain (Lee et al., 2005b). Inhibition of Pgp and Bcrp using the dual inhibitor GF120918 in Mdr1a-null mice increases uptake of prazosin and mitoxantrone, suggesting that Bcrp partially mediates transport of these two compounds from the brain capillary endothelial cells (Cisternino et al., 2004). Overlapping functions for Bcrp and Mdr1a/1b have also been demonstrated for the anticancer drug topotecan. Topotecan plasma concentrations are higher in Bcrp-null mice administered topotecan orally (Jonker et al., 2000). There is a slight increase in the brain concentrations of topotecan in Mdr1a/1b-null and Bcrp-null mice over wild-type mice, whereas triple null Bcrp/Mdr1a/1b-null mice exhibit a 12-fold increase in topotecan in the brain (de Vries et al., 2007).

Studies on tyrosine kinase inhibitors are an active area of research as anticancer drugs. Access of tyrosine kinase inhibitors to the brain is quite limited; therefore, these compounds do not seem to be viable therapeutic options for brain tumors. A better characterization of the transporters responsible for extrusion of tyrosine kinase inhibitors from the brain may lead to the development of transporter inhibitors that permit accumulation of anticancer drugs in the brain. Uptake of imatinib into the brain is enhanced in mice lacking Bcrp or Mdr1a/1b (Dai et al., 2003; Breedveld et al., 2005). The oral bioavailability and plasma concentrations of the tyrosine kinase inhibitor, erlotinib are higher in Mdr1a/1b/Bcrp-null mice (Marchetti et al., 2008). Likewise, another tyrosine kinase inhibitor, lapatinib, is also a substrate of MDR1 and BCRP (Polli et al., 2008). Mdr1a/1b-null mice exhibit a 3- to 4-fold increase in the brain-to-plasma ratio of lapatinib after intravenous infusion, with little change in Bcrp-null mice (Polli et al., 2009). Remarkably, triple-null mice lacking Mdr1a/1b and Bcrp have a 40-fold elevation in the brain-to-plasma ratio of lapatinib, suggesting a synergistic role of these transporters in limiting entry into the brain (Polli et al., 2009). Similar findings have been observed for imatinib and dasatinib (Lagas et al., 2009; Oostendorp et al., 2009). A polymorphism in *ABCG2* (BCRP) (Q141K) is clinically associated with diarrhea as well as elevated concentrations in heterozygous patients receiving another tyrosine kinase inhibitor, gefitinib (Table 15) (Cusatis et al., 2006; Li et al., 2007a).

Initial evidence suggests novel roles for Pgp and Bcrp in the removal of amyloid-β, a hallmark of Alzheimer disease, from the brains of mice. The clearance of exogenously administered amyloid-β is reduced in the brains of Mdr1a/1b-null mice (Cirrito et al., 2005) as well as Bcrp-null mice (Xiong et al., 2009). Furthermore, administration of a Pgp inhibitor to transgenic mice that overexpress amyloid precursor protein stimulates accumulation of amyloid beta in the brain (Cirrito et al., 2005). Crossbreeding of Mdr1a/1b-null mice and amyloid precursor protein transgenic mice yields mice with higher levels of brain amyloid beta (Cirrito et al., 2005). In addition, not only do Alzheimer's patients with cerebral amyloid angiopathy overexpress BCRP mRNA and protein, but it has been shown that BCRP protein coprecipitates with amyloid-β in diseased tissue samples compared with age-matched controls (Xiong et al., 2009). These initial observations are very exciting and may reveal novel risk factors for accumulation of amyloid beta and the development of Alzheimer's disease.

The protective role of MDR1 at the blood-brain barrier led to the hypothesis that individuals with defective MDR1 might be at higher risk for the development of Parkinson's disease as a result of an impaired ability to remove environmental contaminants from the brain (Furuno et al., 2002). Although there is not a statistically significant association between screened *ABCB1* (MDR1) polymorphisms and Parkinson's disease, there was a consistent trend for early-onset Parkinson's disease in patients with the I1145I *ABCB1* variant (Table 19) (Furuno et al., 2002; Droździk et al., 2003). Conversely, there are two studies that suggest the I1145I *ABCB1* variant protects against the development of Parkinson's disease (Lee et al., 2004a; Tan et al., 2005). Further studies are clearly needed to better delineate the role of MDR1 in Parkinson's disease.

Imaging techniques for transporter function and/or inhibition at the blood-brain barrier is an area of active research. Using positron emission tomography, it has been shown that administration of the Pgp inhibitor cyclosporine A to pregnant macaques increases the penetration of radiolabeled verapamil (Pgp substrate) into brain (Eyal et al., 2009). This imaging modality may be important in screening chemicals for Mdr1a/1b inhibition. An in vivo method to analyze MRP1 function using positron emission tomography and the probe 6-bromo-7-[^{11}C]methylpurine was also recently developed (Okamura et al., 2009). Upon uptake into the brain, 6-bromo-7-[^{11}C]methylpurine is conjugated with glutathione. Efflux of the glutathione conjugate is then monitored as an indicator of MRP1 function. Specificity of this biotracker probe was confirmed using Mrp1-null mice. The efflux rate of 6-bromo-7-[^{11}C]methylpurine-glutathione from the brain is reduced markedly in Mrp1-null mice (Okamura et al., 2009).

E. Ears

Pgp protein is expressed in capillary endothelial cells of not only the brain but also the ear (Zhang et al., 2000). Doxorubicin and vinblastine drug levels are elevated in brains, inner ears, and small intestines of Mdr1a/1b-null mice (Zhang et al., 2000). It is noteworthy that doxorubicin- and vinblastine-treated Mdr1a/1b-null mice showed hearing impairment, whereas wild-type mice

did not (Zhang et al., 2000). Likewise, enhanced ototoxicity could be achieved in wild-type mice using pharmacological inhibitors of Pgp transport (Zhang et al., 2000).

ATP8b1 is expressed in the stereocilia of cochlear hair cells (Stapelbroek et al., 2009). Loss of ATP8b1/ATP8B1 expression in null mice as well as in patients with PFIC-I causes hearing loss (Stapelbroek et al., 2009). Progressive degeneration of cochlear hair cells was responsible for hearing loss in ATP8b1-null mice (Stapelbroek et al., 2009). It is thought that ATP8B1 deficiency might alter the phospholipid concentration in the inner membrane leaflet of the hair structure and thereby interfere with mechanotransduction.

There are two types of human earwax: dry and wet. The frequency of dry earwax is highest among East Asians, whereas wet earwax is observed in other populations. It is noteworthy that dry earwax has been linked to a polymorphism (G180R) in *ABCC11* (MRP8) that is more prevalent in persons of Chinese and Korean descent (Yoshiura et al., 2006; Kitano et al., 2008). An additional 27-base-pair deletion in the *ABCC11* gene is also associated with dry earwax (Yoshiura et al., 2006; Kitano et al., 2008). Subsequently, the G180R variant in *ABCC11* was associated with not only dry earwax but also lower colostrum production in Japanese women (Miura et al., 2007).

F. Lungs

Acetylcholine is a substrate of OCT1 and OCT2 but not OCT3 (Lips et al., 2005). As expected, airway epithelial acetylcholine content is higher in Oct1/2-null mice (Kummer et al., 2006). The functional consequence of this phenotype is not yet understood.

Corticosterone treatment reduces serotonin-induced bronchoconstriction. It is noteworthy that this pharmacological property is impaired in Oct3-null mice, providing novel information about the mechanism of action of corticosteroids (Kummer et al., 2006). Furthermore, OCT3 has also been implicated in the disposition of the long-acting β_2-agonist formoterol in human lung tissue (Horvath et al., 2007). Taken together, combination therapy of formoterol and corticosteroids probably elicits synergistic activity with steroids inhibiting OCT3-mediated formoterol transport, thereby causing formoterol accumulation and prolonged bronchodilator action (Horvath et al., 2007).

Recent work suggests that OATP2B1 is responsible for uptake of amiodarone into lung alveolar epithelial type II cells (Seki et al., 2009). Knockdown of OATP2B1, using small interfering RNA, reduces amiodarone influx in vitro (Seki et al., 2009). Further studies are needed to determine whether OATP2B1-mediated transport permits accumulation of amiodarone in the lungs in vivo and subsequent pulmonary toxicity.

G. Heart

mRNA profiling of human heart samples demonstrate expression of transporters including BCRP, MDR1, MRP2, -4, -5, and -7, OATP2A1 and -2B1, OCT3, OCTN1 and -2 as well as OCTN2 in the atria and ventricles (Grube et al., 2006b; McBride et al., 2009). However, the exact localization of most of these transporters is unclear. Initial in vivo studies using Octn2-null and Mrp1-null mice and in vitro studies of OCTN1 suggest roles for these transporters in the heart.

Mouse Octn1 and Octn2 proteins are present on blood vessel endothelial cells and cardiac muscle cells, respectively (Iwata et al., 2008). Human OCTN1 protein is expressed in cardiomyocytes (McBride et al., 2009). The rare ventricular arrhythmia known as torsades de pointes is associated with a prolonged QT interval on an electrocardiogram that results from antagonism of the HERG potassium channel. QT prolongation is associated with the use of drugs such as quinidine (OCTN1 substrate). Coexpression of OCTN1 and the HERG channel facilitates the HERG blockade of a number of antiarrhythmic drugs pointing to a potential role for drug transporters as a contributing factor for torsades de pointes (McBride et al., 2009).

Mutations in *SLC22A5* (OCTN2) were shown to be responsible for primary carnitine deficiency (Nezu et al., 1999; Wang et al., 1999). Primary carnitine deficiency is a disorder of fatty acid oxidation and is inherited through autosomal recessive transmission (Table 10). Patients with carnitine deficiency exhibit encephalopathy, progressive cardiomyopathy, hypoglycemia, and skeletal myopathy. More than 15 mutations in *SLC22A5* have been associated with primary carnitine deficiency (Koizumi et al., 1999; Seth et al., 1999; Wang et al., 1999, 2000a,b; Mayatepek et al., 2000; Cederbaum et al., 2002; Spiekerkoetter et al., 2003; Amat di San Filippo and Longo, 2004; Makhseed et al., 2004; Melegh et al., 2004). One of these mutations (P478L) causes complete loss of carnitine uptake but still retains transport activity of organic cations (Seth et al., 1999). Therefore, patients with primary carnitine deficiency may have normal organic cation transport function (Seth et al., 1999).

Octn2 mutant mice are also known as juvenile visceral steatosis (JVS) mice. JVS mice are deficient in carnitine, which leads to defects in fatty acid oxidation. As a result, fat accumulates in the internal organs (viscera) of JVS mice. DNA sequencing of JVS mice has revealed a missense mutation from leucine to arginine at codon 352 in the sixth transmembrane domain of Octn2 (Lu et al., 1998). The Octn2 mutation is associated with impaired L-carnitine uptake into isolated JVS mouse hepatocytes (Yokogawa et al., 1999). Heterozygous Octn2 mice are viable and fertile, but Octn2 mutant mice survive for only approximately 3 to 4 weeks without carnitine supplementation (Shekhawat et al., 2004). At 3 weeks of age, the body weight of Octn2

mutant mice is 50% of that of age-matched wild-type mice (Shekhawat et al., 2004). Deprivation of carnitine supplements from Octn2 mutant mice between 6 and 8 weeks of age markedly reduces plasma β-hydroxybutyrate levels and skeletal muscle glycogen stores (Knapp et al., 2008). Consistent with carnitine deprivation and altered fatty acid oxidation, Octn2 mutant mice develop enlarged fatty liver with steatosis (Shekhawat et al., 2004; Knapp et al., 2008).

Carnitine uptake into heart slices is blocked by Octn2 inhibitors and is absent in slices from JVS mice (Iwata et al., 2008). Over time, Octn2 mutant mice develop dilated cardiomyopathy (Shekhawat et al., 2004). Because of the severe pathological condition in Octn2 mutant mice, Octn2 heterozygous mice have been used to investigate whether Octn2 mutations might alter the cardiomyopathy risk of individual subjects (Takahashi et al., 2007). In one study, Octn2(+/−) mice were subjected to ascending aortic constriction and evaluated 4 weeks later (Takahashi et al., 2007). Compared with wild-type mice, Octn2(+/−) mice had more pronounced cardiac hypertrophy and pulmonary congestion, deterioration of left ventricular fractional shortening, and higher mortality (Takahashi et al., 2007). It is noteworthy that L-carnitine supplementation prevented these changes in Octn(2+/−) mice (Takahashi et al., 2007). Long-term studies of Octn2(+/−) mice demonstrate age-associated cardiomyopathy after 2 years of age similar to that of Octn2 mutant mice at a younger age (Xiaofei et al., 2002).

Mrp1 is expressed in sarcolemmal membranes and the mitochondria of the mouse heart (Jungsuwadee et al., 2006, 2009). Early work by Ishikawa et al. (1986, 1989) demonstrated the ATP-dependent transport of leukotriene C_4 and the glutathione conjugate of 4-hydroxynonenal in the heart via a glutathione *S*-conjugate transporter later identified as Mrp1. Hypertension induced by angiotensin II leads to an imbalance in glutathione homeostasis with elevated transport of oxidized glutathione and lower vascular levels of reduced glutathione (Widder et al., 2007). It is noteworthy that Mrp1-null mice demonstrate more favorable cardiovascular parameters after angiotensin II administration compared with wild type (Widder et al., 2007). Angiotensin II-induced increases in superoxide production and blood pressure are blunted in Mrp1-null mice (Widder et al., 2007). A critical role for Mrp1 in angiotensin II-induced hypertension may be via regulation of intracellular thiol concentrations (Leier et al., 1996). More recently, it has been suggested that Mrp1 protects the murine heart from doxorubicin-induced cardiotoxicity (Jungsuwadee et al., 2006, 2009).

H. Placenta

In an effort to understand the protection of the fetus from xenobiotic accumulation and toxicity, researchers are actively characterizing the expression of transporters in the placenta as well as supportive tissues, including the fetal membranes. Within the placenta, transporters are most often expressed in syncytiotrophoblasts. Basolateral uptake transporters Oat4, Oct3, and OATP2B1 and apical efflux transporters Mdr1a/1b, Mrp1–3, Bcrp, and ATP7B translocate chemicals from the fetus to the maternal blood (Fig. 10). Octn2, Ent1, and OATP4A1 seem to be more important in the transport of substrates from the maternal to the fetal blood. Recent attention has been placed on the presence of xenobiotic transporters in the human amnion membrane and the rodent yolk sac. For the most part, only efflux transporters (Mdr1a, Mrp1–2, Mrp4–6, Bcrp) seem to be expressed in the fetal membranes (Aye et al., 2007; Aleksunes et al., 2008b; Yeboah et al., 2008). Although the exact contribution of these transporters to fetal protection is not known, it can be hypothesized that Mdr1a, Mrp2, and Bcrp would be most important in fetal protection by transferring chemicals from fetal to maternal blood.

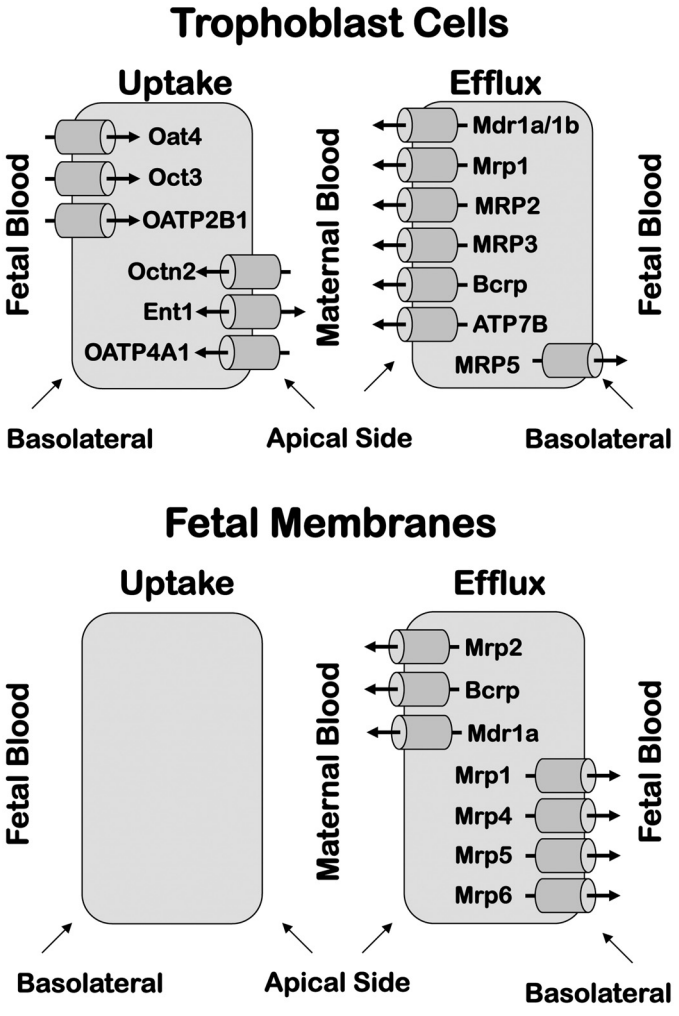

FIG. 10. Subcellular localization of uptake and efflux transport proteins in syncytiotrophoblasts and fetal membranes. The localization and orientation of uptake and efflux transporters in placenta and fetal membranes (primarily rodents) are shown.

Because milk is rich in lipids, it is presumed that carnitine is important in preparing the fetus for a postnatal milk diet. Human OCTN2 protein is localized to the apical membrane of syncytiotrophoblasts (Lahjouji et al., 2004; Grube et al., 2005). Uptake of carnitine into apical placenta membrane vesicles is sodium-dependent and is inhibited by verapamil (Lahjouji et al., 2004; Grube et al., 2005). Therefore, it is thought that OCTN2 is responsible for delivery of carnitine to the fetus during development. The placentas and fetuses of Octn2 mutant mice contain reduced carnitine levels (Shekhawat et al., 2004). In an attempt to compensate for the loss of Octn2-mediated uptake of carnitine, β-oxidation enzymes are up-regulated in Octn2 mutant placenta (Shekhawat et al., 2004). This compensatory response may be an attempt to maintain the energy status of the placenta.

Use of certain anticonvulsants during pregnancy carries a risk of fetal malformations, including congenital heart disease as well as lip and palatal deformity. Using apical membrane vesicles from human placenta, carnitine uptake is inhibited by a number of antiseizure drugs (Wu et al., 2004). It is hypothesized that interference of OCTN1 and/or OCTN2-mediated carnitine uptake across the placenta by antiseizure drugs contributes to fetal anticonvulsant syndrome. In support of this hypothesis, cells transfected with the *SLC22A4* (OCTN1) L503F variant have reduced sodium-independent uptake of the antiseizure drug gabapentin compared with wild-type OCTN1 (Table 18) (Urban et al., 2008).

Mdr1a/1b and MDR1 mRNA and protein are prominently expressed in mouse and human placenta and their expression decreases during gestation (Lankas et al., 1998; Ushigome et al., 2003; Aleksunes et al., 2008b; Cui et al., 2009c). Studies using brush border membrane vesicles from human placentas demonstrated functional Pgp activity that was blocked by Pgp inhibitors (Ushigome et al., 2003). Likewise, several *ABCB1* (MDR1) polymorphisms are associated with reduced placental Pgp expression (Tanabe et al., 2001; Hitzl et al., 2004). Use of genetically engineered Mdr1a/1b-null mice and naturally occurring Mdr1a mutant (CF-1) mice has highlighted the protective role of Mdr transporters in the placenta (Umbenhauer et al., 1997; Smit et al., 1999; Pippert and Umbenhauer, 2001). CF-1 mice lacking Mdr1a develop cleft palate after fetal exposure to the teratogenic pesticide avermectin (Lankas et al., 1998). Likewise, fetal penetration of the cardiac glycoside digoxin, the antiviral drug saquinavir, and the chemotherapeutic agent paclitaxel is enhanced in Mdr1a/1b-null mice (Smit et al., 1999). Similar to knockout mice, when pregnant macaques are administered the Pgp inhibitor cyclosporine A, the penetration of radiolabeled verapamil (Pgp substrate) into maternal brain and fetal livers increases (Eyal et al., 2009). Active efflux of potentially toxic chemicals from the fetus to the mother via Pgp may represent a protective mechanism to limit drug-induced birth defects. The consequences of reduced Pgp expression in *ABCB1* variants in the fetal to maternal transfer of xenobiotics need to be determined.

Bcrp mRNA and protein is abundantly expressed in the placenta and fetal membranes (visceral yolk sac in mice) in humans and rodents (Maliepaard et al., 2001; Grube et al., 2007; Aleksunes et al., 2008b; Cygalova et al., 2008; Yeboah et al., 2008). In both tissues, Bcrp faces the mother, suggesting that this transporter pumps chemicals from the fetus to the mother. This was first documented after topotecan accumulated in Bcrp-null fetuses to a greater extent than in wild-type fetuses (Jonker et al., 2000). It is noteworthy that a variant *ABCG2* (BCRP) gene (Q141K) is associated with reduced BCRP protein accumulation in placenta, although the functional relevance of this polymorphism has not yet been determined (Table 15) (Kobayashi et al., 2005b).

The use of glyburide to treat gestational diabetes has led investigators to question how the fetus maintains very low concentrations of glyburide. In vitro transport studies demonstrate that inhibitors of MRP1–3 and Pgp are ineffective in preventing glyburide transport across the placental membrane (Gedeon et al., 2008a,b). Instead, inhibition of BCRP disrupts glyburide efflux (Gedeon et al., 2008b). In support of this, glyburide concentrations are higher in Bcrp-null fetuses compared with wild type (Zhou et al., 2008b). Likewise, the concentration of the antibiotic nitrofurantoin is elevated 5-fold in fetuses from Bcrp-null mice (Zhang et al., 2007c). These findings are of interest because glyburide and nitrofurantoin are routinely prescribed for pregnant patients for the treatment of gestational diabetes and urinary tract infections, respectively. So far, only one BCRP variant has been screened in healthy subjects administered nitrofurantoin, and it was not associated with altered pharmacokinetics (Adkison et al., 2008). Additional work is imperative to decipher the roles of Mrp as well as Oat/Oatp transporters in the placenta as well as delineate the contribution of efflux transporters in the fetal membranes.

I. Mammary Glands

The ability of the mammary gland to concentrate pharmaceuticals such as nitrofurantoin and cimetidine in human breast milk has been recognized (Oo et al., 1995; Gerk et al., 2001). More recently, it was hypothesized that drug transporters may be important in the active transport of chemicals into breast milk. Studies have shown that Bcrp is localized to the apical epithelial surface of the mammary glands of humans, sheep, cows, and rats (Maliepaard et al., 2001; Pulido et al., 2006; Wang et al., 2008b). Pharmacological inhibition of Bcrp using GF120918 blocks excretion of nitrofurantoin into milk of lactating rats (Wang et al., 2008b). It should be noted that Pgp is not expressed in lactating mammary glands; in turn, GF120918-mediated inhibition probably

occurs via Bcrp (Wang et al., 2008b). The bioavailability of nitrofurantoin is elevated in Bcrp-null mice largely as a result of markedly reduced hepatobiliary excretion and milk secretion (Merino et al., 2005b). The milk-to-plasma ratio of nitrofurantoin is 80-fold higher in wild-type mice than in Bcrp-null mice (Merino et al., 2005b). Likewise, Bcrp transports fluoroquinolone antibiotics such as ciprofloxacin (Merino et al., 2006). Bcrp-null mice exhibit higher plasma concentrations of ciprofloxacin and a reduced milk-to-plasma ratio compared with wild-type mice (Merino et al., 2006). Endogenous molecules such as riboflavin are also actively transported into breast milk by Bcrp in the mammary gland (van Herwaarden et al., 2007). In addition to excreting pharmaceuticals and nutrients, Bcrp also transfers dietary carcinogens (aflatoxin B1 and other heterocyclic amines) into breast milk (Jonker et al., 2005b; van Herwaarden et al., 2006). Milk concentrations of aflatoxin are lower in Bcrp-null mice; instead, aflatoxin accumulates in the maternal plasma, lungs, kidneys, and brain of Bcrp-null mice (van Herwaarden et al., 2006). Bcrp function in the mammary glands is somewhat of a double-edged sword; it prevents xenobiotic accumulation in the mother and simultaneously delivers potentially toxic chemicals to newborns.

J. Testes

Transporters in the testes have been implicated in the physiological maintenance of sperm as well as the protection against xenobiotic accumulation and toxicity (Fig. 11). Carnitine is required for sperm formation, sperm maturation, and maintenance of sperm quality. Uptake of carnitine and acetylcarnitine into epididymal spermatozoa over time can be inhibited by OCTN2 substrates (Kobayashi et al., 2007). Immunohistochemical analysis demonstrates Octn2 in the distal portion of the sperm tail and Octn3 in the proximal portion of the sperm tail (near the nucleus) (Kobayashi et al., 2007). Octn2 is expressed in rat whole testes, epididymal epithelia, and primary-cultured Sertoli cells (Kobayashi et al., 2005a,c, 2007). Furthermore, Octn2 mutant mice develop obstructive azoospermia in the distal portion of the epididymis (Yakushiji et al., 2006). There are currently no reports on the relationship between OCTN2 genotype and male infertility.

Efflux transporters in the testes are probably important in restricting xenobiotic entry across the blood-testes barrier. Bcrp limits the in vivo accumulation of various pharmaceuticals (including dantrolene, triamterene, and prazosin) within the testes (Enokizono et al., 2008). Using Mrp1-null mice, it was demonstrated that methoxychlor-induced testicular damage is precipitated by the absence of Mrp1 in the testes (Tribull et al., 2003). Mrp1-null mice exhibit a reduced number of developing spermatocytes at a dose of methoxychlor that has little effect on the testes of wild-type mice (Tribull et al., 2003).

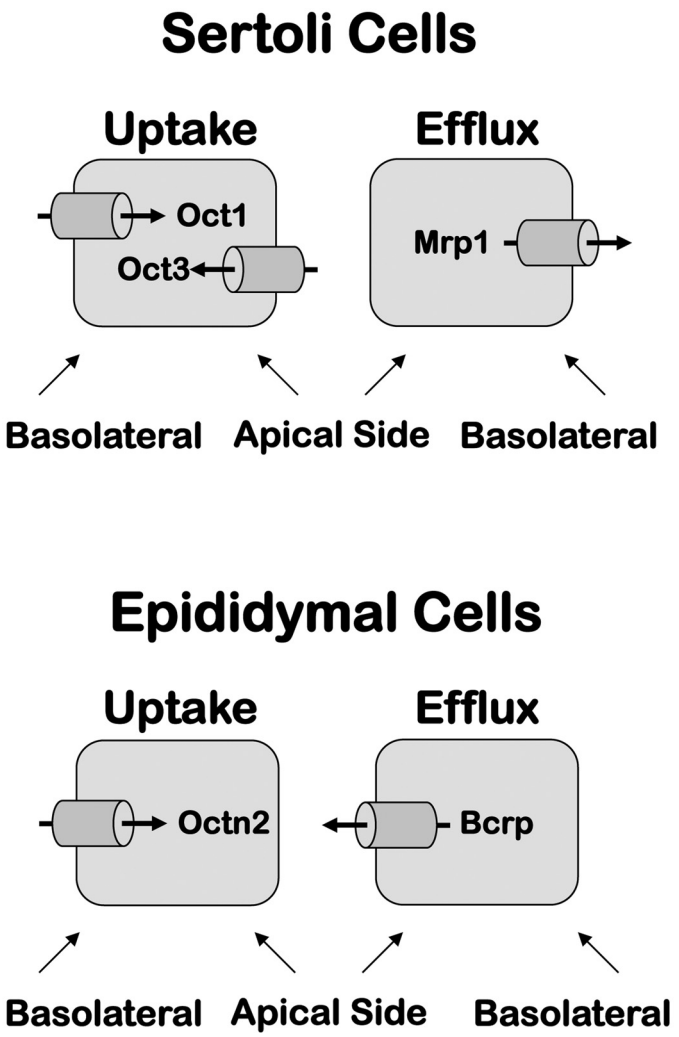

FIG. 11. Subcellular localization of uptake and efflux transport proteins in Sertoli and epididymal cells. The localization and orientation of uptake and efflux transporters in testes (primarily rodents) are shown.

Additional xenobiotic transporters (Mrp5, Mrp7, Mrp8, Ent1–2, Oatp1a5, Oat2) have been identified by mRNA profiling in rodent testes (Augustine et al., 2005). It is anticipated that we will learn more about their function in testicular homeostasis and protection in upcoming years.

K. Immune and Stem Cells

Roles for transporters in a variety of immune and stem cells have been shown. Antiviral drug transport seems to be dictated by Mrp4, Bcrp, Oct1, and Oct2 in different cell types. In addition, Mrp1 expression alters susceptibility to infectious agents. With regard to inflammation, Octn1–2 and Mrp1 play unique roles. Transporters such as Mrp2 and Mrp4 are important in the disposition of immunosuppressing drugs. Finally, efflux transporters including Bcrp and Mdr1a/1b are expressed in stem cells and may confer chemoresistance to this cell population.

1. Infections. Early studies demonstrated that MRP4 overexpression strongly correlated with drug resistance

against the purine nucleotide analog antiviral 9-(2-(phosphomethoxy)ethyl)-adenine (PMEA, also known as adefovir) in a human T-lymphoid cell line (Schuetz et al., 1999). Two *ABCC4* variants (G187W, G487E) demonstrate reduced in vitro MRP4 function as shown by higher intracellular accumulation of zidovudine and PMEA (Table 20) (Abla et al., 2008). In the case of the G187W variant, lower MRP4 function was due to reduced protein (Abla et al., 2008).

Evaluation of single- and double-null mice demonstrates that Mrp4 and Bcrp work in concert to transport PMEA in vivo. Pathological injury to the bone marrow, spleen, thymus, and gastrointestinal tract as well as lethality are increased in Mrp4-null mice treated with PMEA (Belinsky et al., 2007). PMEA markedly accumulates in the spleens and brains of Mrp4-null mice (Belinsky et al., 2007; Takenaka et al., 2007). It is noteworthy that Bcrp mRNA expression was enhanced in the spleens as well as the brains of Mrp4-null mice (Takenaka et al., 2007). Because of these findings, the role of Bcrp in dictating PMEA accumulation was investigated. Neither Mrp4-null nor Bcrp-null mice exhibited altered PMEA concentrations in livers, kidneys, or lungs (Takenaka et al., 2007). However, PMEA accumulated in the livers, kidneys, and lungs of Mrp4/Bcrp-null mice, suggesting that Mrp4 and Bcrp can each compensate for the other to enable transport of PMEA in single-null mice (Takenaka et al., 2007). These studies demonstrate how multiple organic anion transporters protect against purine analog toxicity and resistance.

OCT1- and OCT2-mediated transport of 1-methyl-4-phenylpyridinium is inhibited by the protease inhibitors nelfinavir, ritonavir, saquinavir, indinavir, and reverse transcriptase inhibitors lamivudine and zalcitabine (Jung et al., 2008). Lamivudine and zalcitabine are also transported by OCT1 and OCT2 (Jung et al., 2008). Expression of OCT1 and OCT2 mRNA is low in human lymph nodes from persons not infected with HIV but markedly increased in persons who are infected with HIV (Jung et al., 2008). It is hypothesized that OCT1 and OCT2 up-regulation may enhance delivery of antiviral drugs to infected cells.

Intranasal infection of Mrp1-null mice with *Mycobacterium tuberculosis* at 5 weeks of age results in an early increase in outgrowth of *M. tuberculosis* in the lungs and liver compared with wild-type mice (Verbon et al., 2002). However, by 4 months, the extent of mycobacterial outgrowth and animal survival is similar between genotypes, suggesting only an early role for Mrp1 in the immune response to infection (Verbon et al., 2002). In contrast, Mrp1-null mice are resistant to infection by *Streptococcus pneumoniae*, as demonstrated by diminished outgrowth of pneumococci in lungs and dramatically reduced mortality (Schultz et al., 2001). Whereas leukotriene C_4 levels are reduced in the bronchial alveolar lavage fluid of pneumococcal-infected Mrp1-null mice, the concentrations of leukotriene B_4 are elevated

TABLE 20

In vitro characterization of genetic polymorphisms in MRP1–4

In vitro function was assessed using prototypical substrates for MRP1 (leukotriene C4, estradiol 17β-glucuronide, methotrexate), MRP2 (leukotriene C4, estradiol 17β-glucuronide), MRP3 (estradiol 17β-glucuronide), and MRP4 (zidovudine, adefovir). Nucleotide position was confirmed by PharmGKB (Hewett et al., 2002). MRP1 data from Conrad et al. (2001); Conrad et al. (2002); Leslie et al. (2003); LŽtourneau et al. (2005). MRP2 data from Itoda et al. (2002); Moriya et al. (2002); Hirouchi et al. (2004); Izzedine et al. (2006); Rau et al. (2006); Haenisch et al. (2007); Sai et al. (2008). MRP3 data from Lang et al. (2004); Lee et al., 2004b; Fukushima-Uesaka et al. (2007); Kobayashi et al. (2008). MRP4 data from Abla et al. (2008) and Krishnamurthy et al. (2008).

Nucleotide Change	Amino Acid Change	In Vitro Function	Protein Expression/Localization
ABCC1	MRP1		
G128C	C43S	↑ ↔	Intracellular
C218T	T73I	↑ ↔	Normal
C257T	S92F	↓ ↔	Normal
C350T	T117M	↓ ↔	Normal
G689A	R230Q	↔	Normal
G1057A	V353M	N.D.	N.D.
G1299T	R433S	↓ ↔	Normal
G1898A	R633Q	↓ ↔	Normal
G2012T	G671V	↔	Normal
G2168A	R723Q	↓	Normal
G2965A	A989T	↓ ↔	Normal
G3140C	C1047S	↑ ↔	Normal
G3173A	R1058Q	↔	Normal
C4535T	S1512L	↔	Normal
ABCC2	MRP2		
C-24T		N.D.	N.D.
G1058A	R353H	N.D.	N.D.
G1249A	V417I	↔	Normal
C2366T	S789F	↑ ↓	Intracellular
T2780G	L927R	N.D.	N.D.
C3298T	R1100C	N.D.	N.D.
G3299A	R1100H	N.D.	N.D.
T3563A	V1188E	N.D.	N.D.
G4348A	A1450T	↔	Normal/Intracellular
G4544A	C1515Y	N.D.	N.D.
ABCC3	MRP3		
G32A	G11D	↔	Normal
C202T	H68Y	N.D.	N.D.
G296A	R99Q	N.D.	Normal
C1037T	S346F	↓	Normal
C1537A	Q513K	N.D.	N.D.
T1643A	L548Q	N.D.	N.D.
G1820A	S607N	↓	Normal
C2221T	Gln741STOP	N.D.	N.D.
G2293C	V765L	↔	Normal
G2395A	V799M	N.D.	N.D.
C2758T	P920S	↑	Normal
G2768A	R923Q	↑	Normal
C3657A	S1219R	N.D.	N.D.
C3856G	R1286G	↔	Normal
G3890A	R1297H	N.D.	N.D.
C4042T	R1348C	↑	Normal
A4094G	Q1365R	↔	Normal
C4141A	R1381S	↔	Intracellular
C4217T	T1406M	N.D.	N.D.
G4267A	G1423R	N.D.	N.D.
ABCC4	MRP4		
C52A	L18I	N.D.	N.D.
C232G	P78A	↓ ↔	Normal
T551C	M184T	N.D.	N.D.
G559T	G187W	↓	Reduced
A877G	K293E	↔	Normal
G912T	K304N	↔	Normal
C1067T	T356M	N.D.	N.D.
C1208T	P403L	↓ ↔	Normal
G1460A	G487E	↓	Normal
A1492G	K498E	↔	Normal
A1875G	I625M	N.D.	N.D.
C2000T	P667L	N.D.	N.D.
A2230G	M744V	↔	Normal
G2269A	E757K	N.D.	Intracellular
G2459T	R820I	N.D.	N.D.
G2560T	V854F	N.D.	N.D.
G2698T	V900L	N.D.	N.D.
G2867C	C956S	↑ ↔	Normal
G3211A	V1071I	↔	Normal
C3425T	T1142M	N.D.	N.D.
G3659A	R1220Q	N.D.	N.D.
A3941G	Q1314R	N.D.	N.D.

↓, reduced function; ↑, increased function; ↔, no change in function; N.D. not determined.

to levels seen in wild-type mice (Schultz et al., 2001). Given the divergent findings between mycobacterial and streptococcal exposure in Mrp1-null mice, further research is needed to understand the mechanisms of Mrp1 function during infection.

2. Inflammation. Prior work has demonstrated a strong genetic component to the inflammatory disease rheumatoid arthritis. OCTN1 mRNA is detected in human spleen, bone marrow, and blood cells with levels higher than those observed in the kidneys (Tokuhiro et al., 2003). OCTN1 and 2 mRNA are detected in fibroblast-like synoviocytes from persons with rheumatoid arthritis. It is noteworthy that stimulation of these synoviocytes with tumor necrosis factor-α increases OCTN1 mRNA (Tokuhiro et al., 2003). Likewise, Octn1 mRNA is detected in the joints of mice with collagen-induced arthritis but not in normal mice (Tokuhiro et al., 2003). In the Japanese population, there is a significant association between rheumatoid arthritis and *SLC22A4* (OCTN1) polymorphisms (Tokuhiro et al., 2003). Intron (slc2F1, slc2F2) variants of *SLC22A4* are associated with rheumatoid arthritis in Japanese patients but not British, Spanish, or Canadian patients (Tokuhiro et al., 2003; Barton et al., 2005; Newman et al., 2005; Martínez et al., 2006; Takata et al., 2008).

Mrp1 has been implicated in inflammatory and infectious diseases because of its expression on activated Th1 lymphocytes (Prechtl et al., 2000) and its ability to transport signaling mediators (such as leukotrienes and glutathione) (Leier et al., 1996; Wijnholds et al., 1997). Although Mrp1 is expressed on activated Th1 lymphocytes, it is not necessary for activation of this immune cell population (Kleemann et al., 2006). Mrp1-null mice have an impaired response to inflammatory stimuli as a result of defective leukotriene secretion (Wijnholds et al., 1997). Topical administration of arachidonic acid to mice causes ear edema and increases vascular permeability. It is noteworthy that Mrp1-null mice demonstrate attenuated responses to arachidonic acid application (Wijnholds et al., 1997). Likewise, triple-null mice lacking Mrp1 as well as Mdr1a and Mdr1b are resistant to chronic obstructive pulmonary disease-like features after exposure to cigarette smoke (van der Deen et al., 2007). Pulmonary cytokine levels as well as inflammatory cell infiltration are elevated in smoke-exposed wild-type mice with little to no change in Mrp1/Mdr1a/1b-null mice (van der Deen et al., 2007). Collectively, these models suggest a role for Mrp1 in inflammation in rodents.

3. Immunosuppression. Mycophenolic acid and its prodrug mycophenolate mofetil are immunosuppressant drugs prescribed for transplant recipients. The biliary excretion of mycophenolic acid glucuronide is reduced in TR− and Eisai hyperbilirubinemic rats, which lack Mrp2 function (Kobayashi et al., 2004; Westley et al., 2006). In addition, inhibition of Mrp2 function using cyclosporine A similarly reduces mycophenolic acid-glucuronide clearance into bile (Kobayashi et al., 2004). Patients who have undergone renal allografting who are receiving a mycophenolic acid-containing rejection regimen exhibit altered drug pharmacokinetics and experience more diarrhea if they possess the *ABCC2* C-24T variant (Table 20) (Naesens et al., 2006). The V417I *ABCC2* variant is also associated with higher plasma concentrations of mycophenolic acid-acyl glucuronide in Chinese recipients of renal transplants (Zhang et al., 2008b). Mycophenolic acid-acyl glucuronide pharmacokinetics are similarly altered in healthy volunteers with the C-24T *ABCC2* variant (Lévesque et al., 2008). In addition to mediating the disposition of antirejection drugs, Mrp2 may also influence the redox status of graft kidneys (Grisk et al., 2009). In this same study, *ABCC2* variants were associated with a delay in clinical graft function (Grisk et al., 2009).

Thiopurine drugs such as 6-mercaptopurine are used as immunosuppressants and anticancer drugs. However, the efficacy of 6-mercaptopurine is often limited by gastrointestinal and hematopoietic toxicity. MRP4 transports 6-mercaptopurine in vitro (Chen et al., 2001). Mrp4 mRNA is highly expressed in mouse monocyte and erythroid progenitors (Krishnamurthy et al., 2008). Mrp4-null mice are more sensitive to 6-mercaptopurine toxicity as evidenced by reduced survival compared with wild-type mice (Krishnamurthy et al., 2008). Enhanced mortality of Mrp4-null mice after 6-mercaptopurine is associated with reduced bone marrow cellularity and cell number as well as elevated levels of the 6-mercaptopurine active metabolite, 6-thioguanine nucleotides (Krishnamurthy et al., 2008). E757K is a frequent *ABCC4* variant in the Japanese population (Table 20) (Krishnamurthy et al., 2008). This nonsynonmous substitution reduces membrane localization of MRP4 without altering total protein levels (Krishnamurthy et al., 2008). Cells overexpressing E757K are more susceptible to 6-mercaptopurine cytotoxicity (Krishnamurthy et al., 2008). These data may explain why some Japanese patients have enhanced thiopurine sensitivity as an adverse event (Ando et al., 2001).

4. Stem Cells. Stem cells are identified by a "side population" phenotype by exhibiting low fluorescence after staining with fluorescent dyes. Efflux of these dyes (such as Hoechst and rhodamine) via Bcrp and Mdr1a/1b transporters has been implicated in the side population phenotype (Kim et al., 2002b; Uchida et al., 2002; Morisaki et al., 2005). Hepatic side population cells from Mdr1a/1b-null retain a normal ability to efflux rhodamine, suggesting involvement of other transporters in the liver side population phenotype (Uchida et al., 2002). Bcrp is prominently expressed in stem cells from various sources, including bone marrow and skeletal muscle (Zhou et al., 2001). Using single- and double-null mice, it was demonstrated that Bcrp and Mdr1a/1b account for the side population phenotype of stem cells of mammary glands (Jonker et al., 2005a). Only Bcrp conferred the

side population phenotype in bone marrow and skeletal muscle (Zhou et al., 2002; Jonker et al., 2005a). In addition, Bcrp-null hematopoietic cells are more sensitive to mitoxantrone in drug-treated transplanted mice (Zhou et al., 2002). Taken together, these findings suggest that Bcrp is a cytoprotective phenotype of stem cells to protect against xenobiotic toxicity.

L. Connective Tissue and Skin

Pseudoxanthoma elasticum is a disease of the connective tissue that results from loss-of-function mutations of MRP6 on chromosome 16p13.1 (Table 10) (Le Saux et al., 2000; Cai et al., 2001; Pulkkinen et al., 2001). Patients with pseudoxanthoma elasticum demonstrate mineralized elastic fibers with pathological findings in the skin, eyes, and cardiovascular system (Li et al., 2009a). The recent generation of Mrp6-null mice confirms the critical nature of Mrp6 in preventing calcification of blood vessel walls (primarily in the kidney, aorta, and vena cava) and in Bruch's membrane in the eyes (Gorgels et al., 2005). Pathological findings in the eyes of Mrp6-null mice are intriguing because Mrp6 protein cannot be detected in wild-type eyes, suggesting that pseudoxanthoma elasticum is a systemic disorder (Gorgels et al., 2005). Furthermore, Mrp6-null mice have reduced high-density lipoprotein cholesterol plasma levels and elevated plasma creatinine levels. These findings are consistent with the R1268Q variant of *ABCC6* in pseudoxanthoma elasticum patients that is associated with type IV hyperlipoproteinemia with hypoalphalipoproteinemia (Wang et al., 2001a).

Subsequent studies have attempted to identify additional Abcc transporters that might contribute to the pathological state of Mrp6-null mice (Li et al., 2007c). In a cohort of pseudoxanthoma elasticum patients, a number of *ABCC1* (MRP1) polymorphisms have been identified, suggesting that additional MRP transporters might contribute to this disorder (Le Saux et al., 2000). Connective tissue mineralization in Mrp1/Mrp6-null and Mrp3/Mrp6-null mice is consistent with pathological changes in Mrp6-null mice, suggesting that loss of Mrp1 and Mrp3 does not modulate the effects of Mrp6 loss in this rodent model (Li et al., 2007c). Likewise, oxidative stress does not explain the connective tissue mineralization observed in Mrp6-null mice (Li et al., 2008). It is noteworthy that recent research suggests that dietary mineral modifications may influence the phenotypic abnormalities in Mrp6-null mice (LaRusso et al., 2009). The Mrp6-null mouse model will be useful in identifying strategies to treat pseudoxanthoma elasticum.

Bcrp-null mice are generally healthy but can develop phototoxic lesions on light-exposed skin after consuming diets with a high percentage of alfalfa (Jonker et al., 2002). A similar phototoxicity can be observed in Bcrp-null mice administered the chlorophyll-breakdown product, pheophorbide-a (Jonker et al., 2002). Because of the ability of BCRP to transport porphyrins and heme, the role of Bcrp in protecting against hypoxic injury has been investigated in Bcrp-null mice (Krishnamurthy et al., 2004). Bcrp is up-regulated in progenitor cells under hypoxic conditions in an attempt to lower heme and/or porphyrin levels and ensure cell survival (Krishnamurthy et al., 2004). Moreover, in vitro expression of human BCRP variants demonstrate impaired porphyrin and pheophorbide-a transport; as such, these mutant BCRP-expressing cells are more susceptible to phototoxicity (Tamura et al., 2006b, 2007a). More research is needed to elucidate Bcrp's role in heme homeostasis and skin photosensitivity reactions.

IV. Post-Translational Regulation and Subcellular Trafficking of Transporters

There are multiple levels of transporter regulation including transcriptional (activators and repressors), post-transcriptional (splice variants), chromosomal (epigenetic modifications), translational (mRNA stability), and post-translational (alteration of proteins) modifications. A number of post-translational modifications of transport proteins, including phosphorylation, glycosylation, ubiquitination, and SUMOylation, are described in this section. These biochemical events are central to protein folding, stability, subcellular trafficking, targeted degradation, and functional activity of transporters. The second half of this section focuses on the interaction of transporters with cytosolic scaffold proteins (Table 21) and membrane rafts as well as subcellular localization of transporters to distinct regions of the plasma membrane.

A. Phosphorylation

Phosphorylation is the addition of phosphates to hydroxyl side chains on amino acids including serine, threonine, and tyrosine. Phosphorylation is accomplished by protein kinases using the hydrolysis of ATP. The removal of phosphate groups is performed by protein phosphatases, making phosphorylation a reversible process. Attachment of phosphate groups to drug transporters is thought to alter conformational structure, cellular localization, and transport function. Experimental approaches to study transporter phosphorylation include pharmacological stimulation of protein kinases, inhibition of phosphatase activity, and mutation of amino acid residues where phosphorylation occurs. There are differential effects of protein phosphorylation on transport function depending upon the transporter isoform and species. Moreover, the isoform of the protein kinase can contribute to the functional outcome of transporter phosphorylation.

The majority of research regarding the regulation of transporters by phosphorylation has focused on the OCT and OAT uptake transport families. Transport in rat Oct1- and Oct2-HEK293-overexpressing cells is stimulated by pharmacological activation of protein kinases A

and C (Mehrens et al., 2000; Wilde et al., 2009). Specifically, protein kinase C phosphorylates rat Oct1 protein at certain serine residues (Mehrens et al., 2000; Ciarimboli et al., 2005a). When individual serine and threonine residues in each of the five putative phosphorylation sites are mutated, protein kinase C activation of rat Oct1 is diminished (Ciarimboli et al., 2005a). In contrast to what has been reported for rat Oct1, protein kinase A activation reduces transport mediated by human OCT1 and OCT2 in HEK293 cells (Cetinkaya et al., 2003; Ciarimboli et al., 2004). Although the exact mechanism underlying this species difference is not entirely clear, it has been proposed that protein kinase A activation differentially affects the association of rat and human Oct2/OCT2 with additional proteins (such as calmodulin) that can influence substrate affinity (Wilde et al., 2009).

Activation of protein kinase C by various pharmacological agents inhibits Oat3 (rat and rabbit) and human OAT4 activity in kidney proximal tubule cells and placental cells, respectively (Takeda et al., 2000; Soodvilai et al., 2004; Zhou et al., 2007a). Phosphorylation of OAT by protein kinase C may have indirect effects on its activity but also has indirect effects on subcellular localization (You et al., 2000; Wolff et al., 2003; Zhou et al., 2007a). Instead, stimulation of protein kinase C causes retrieval of various OAT transporters from the cell membrane, resulting in reduced activity (Wolff et al., 2003; Zhou et al., 2007a). Upstream signals such as angiotensin II can inhibit OAT1 activity in COS-7 kidney-derived cells by activating protein kinase C and retrieving OAT1 from the cell surface to the cytoplasm (Li et al., 2009b). The retrieval of OAT1 from the plasma membrane to recycling endosomes is a constitutive activity that occurs through protein kinase C activation (Zhang et al., 2008a). Alternatively, unconventional protein kinase isoforms (such as protein kinase Cζ) increase Oat3 activity possibly by promoting insertion into the plasma membrane of rodent renal cells (Barros et al., 2009). In contrast, inhibition of protein phosphatase activity reduces mouse Oat1 transport in LLC-PK1 proximal tubule cells, at least partly as a result of direct phosphorylation (You et al., 2000).

There is limited work exploring the role of phosphorylation in regulating hepatic transporters. Incubation of hepatocytes with phosphatase inhibitors reduces Oatp1a1-mediated transport without altering subcellular localization (Glavy et al., 2000). Subsequent analysis revealed that Oatp1a1 can be phosphorylated at two serine residues, and protein kinase C is likely to participate in regulating phosphorylation status (Guo and Klaassen, 2001; Xiao et al., 2006). In a variety of cell types and/or models, the α isoform of protein kinase C increases Bsep (Noe et al., 2001) and Mrp2 (Beuers et al., 2001) transporter activity and/or membrane insertion, whereas the δ/ζ isoforms stimulate human ENT1 (Coe et al., 2002) and rat Ntcp (Sarkar et al., 2006; Schonhoff et al., 2008). It is noteworthy that cAMP stimulates rat Ntcp function by promoting Ntcp dephosphorylation at serine 226 and localization in the plasma membrane rather than the endosome (Mukhopadhayay et al., 1997; Mukhopadhyay, 1998a,b; Anwer et al., 2005). Another study demonstrates the redistribution of MRP2 protein from the canalicular to the basolateral membrane of human HepG2 cells in response to protein kinase C activation by phorbol-12-myristate-13-acetate (Kubitz et al., 2001). Subsequent studies will be needed to determine whether phosphorylation of transporter proteins is necessary for their translocation as well as other conditions responsible for insertion into a particular membrane locale.

Phosphoinositide 3-kinases catalyze the phosphorylation of lipid signaling molecules. Early work demonstrated that lipid products from phosphoinositide 3-kinases participate in the ATP-dependent transport of organic anions (including bile acids) across the canalicular membrane (Misra et al., 1999). Furthermore, phosphoinositide 3-kinases can be activated by cAMP, which stimulates bile acid secretion in vitro (Kagawa et al., 2002). Stimulation of phosphoinositide 3-kinase activity by cAMP may participate in the activation of Bsep function in rat liver but does not influence its subcellular trafficking (Misra et al., 2003). Instead, Bsep protein trafficking to the apical membrane is related to signaling and sorting of myosin-related proteins (Chan et al., 2005) and the Rab11a protein (Wakabayashi et al., 2004, 2005).

B. Glycosylation

Glycosylation is the covalent addition of sugar moieties to newly synthesized proteins. This post-translational protein modification is typically performed by enzymes in the rough endoplasmic reticulum and the Golgi apparatus that sequentially add and modify the sugar groups. Glycosylation can occur at the amide side chain of asparagine (*N*-linked glycosylation) and at the hydroxyl side chain of serine and threonine residues (*O*-linked glycosylation). Multiple approaches to investigate glycosylation of transporters are available and include the use of inhibitors of different steps of glycosylation or mutant cells lacking specific glycosylation enzymes. Interruption of glycosylation can have a range of effects on transporter expression and function, including improper protein folding, protein degradation, impaired cellular trafficking to the cell surface, and altered transporter activity.

An example of the multiple and differing effects of glycosylation on transport involves OCT2. OCT2 contains consensus sites for *N*-glycosylation at amino acid positions 71, 96, and 112 (Pelis et al., 2006). Mutation of these asparagine residues demonstrates that each site is indeed glycosylated (Pelis et al., 2006). Substitution at amino acids 96 and 112, but not 71, reduces the transport rate of OCT2. The reduced transport rate of the 112

mutant OCT2 is due to insufficient plasma membrane expression and intracellular retention (Pelis et al., 2006). The mutant protein containing a substituted amino acid at position 96 traffics properly to the cell membrane, suggesting that glycosylation of this residue reduces the rate of transport by increasing transporter turnover. It is noteworthy that substitution of the three asparagines increases the affinity of OCT2 for its prototypical substrate.

Similar mutagenesis experiments have been performed for OAT1 and OAT4 (Tanaka et al., 2004; Zhou et al., 2005). Mutation of the asparagine residue at position 39 reduces human OAT1 function without altering insertion into the cell membrane of HeLa cells (Tanaka et al., 2004). Although this position is not glycosylated in the mouse Oat1 isoform, mutation of this residue does decrease activity, suggesting that this position is important for substrate recognition by Oat1/OAT1 (Tanaka et al., 2004). Mutation of a number of asparagine residues in OAT4 prevents targeting of de novo protein to the Chinese hamster ovary cell membrane and, in turn, lowers functional transport (Zhou et al., 2005). It is noteworthy that mutant cells with altered processing of glycosylated proteins (sialic acid- and galactose-deficient oligosaccharides) exhibit normal OAT4 expression at the cell surface with reduced transport activity (Zhou et al., 2005). Therefore, glycosylation plays a critical role in not only targeting of OAT isoforms to the cell surface but also enhancing its binding affinity for substrates.

Glycosylation of Oatp1a1 protein occurs at three asparagine sites (Wang et al., 2008c). Hypoglycosylation of Oatp1a1, using the glycosylation inhibitor tunicamycin, causes intracellular retention and diminished transport of taurocholate in *X. laevis* oocytes (Lee et al., 2003). Both membrane targeting and functional activity of Oatp1a1 are regulated by the extent of *N*-glycosylation (Lee et al., 2003; Wang et al., 2008c). Similar to the post-translational regulation of uptake transporters, apically expressed efflux transporters Mrp2 (Zhang et al., 2005), BCRP (Mohrmann et al., 2005), Bsep (Mochizuki et al., 2007), and MDR1 (Schinkel et al., 1993) are regulated by glycosylation and cellular trafficking.

C. Ubiquitination and SUMOylation

Ubiquitin is a small regulatory protein of 76 amino acids that is widely expressed. Covalent addition of ubiquitin molecules (also called ubiquitination) to proteins labels them for degradation by the proteasome. Monoubiquitination tends to traffic proteins to the endosome. In addition to targeting proteins for degradation, ubiquitination can influence protein stability, function, and localization. The earliest work examining the ubiquitination of drug and bile acid transporters focused on Pgp and Asbt, respectively (Xia et al., 2004; Zhang et al., 2004e). The half-life of rat Asbt protein is reported to be approximately 6 h in stably transfected cholangiocarcinoma cells (Xia et al., 2004). Treatment of these cells with a proteasome inhibitor increases Asbt protein levels (Xia et al., 2004). In addition, Asbt and ubiquitin associate under basal conditions (Xia et al., 2004). Likewise, exposure to proteasome inhibitors increases the amount of ubiquitinated Pgp (Zhang et al., 2004e). Addition of exogenous ubiquitin to MDR1 (Pgp)-expressing breast cancer cells not only decreases Pgp expression but also enhances cellular accumulation of a Pgp substrate (Zhang et al., 2004e). More recently, it has been suggested that modulation of Pgp ubiquitination may be a novel approach for overcoming drug resistance in cancer cells (Wang et al., 2008d).

NTCP, BSEP, BCRP, and ABCA1 also undergo ubiquitination and proteasomal degradation (Kühlkamp et al., 2005; Nakagawa et al., 2008; Azuma et al., 2009; Hayashi and Sugiyama, 2009; Wakabayashi-Nakao et al., 2009). Inhibition of the proteasome alters the subcellular localization of rat Ntcp from the plasma membrane of HepG2 cells to intracellular compartments (Kühlkamp et al., 2005). NTCP colocalizes with ubiquitin in livers of patients with progressive familial intrahepatic cholestasis 3 (Kühlkamp et al., 2005). Likewise, mutations in *ABCB11* (BSEP) are associated with enhanced protein turnover by the ubiquitin-proteasome system (Hayashi and Sugiyama, 2009). It was recently reported that 4-phenylbutyrate, a drug approved in the United States to treat urea cycle disorders, promotes BSEP expression on the canalicular membrane by interfering with ubiquitination (Hayashi and Sugiyama, 2007; Hayashi and Sugiyama, 2009). These findings are of clinical importance, because patients with cholestasis often exhibit reduced or intracellular expression of BSEP protein and may point to a novel therapeutic modality.

Early findings suggest that the Mrp2 transporter can undergo SUMOylation (Minami et al., 2009). Small ubiquitin-like modifier (SUMO) proteins are a family of small proteins (~100 amino acids) that modify protein function when attached via an isopeptide linkage. Using a protein-protein interaction assay, a number of SUMO-related proteins (including SUMO-1) were pulled down using the linker region of rat Mrp2 protein (Minami et al., 2009). Subsequent work confirmed that this region of Mrp2 can undergo an in vitro SUMOylation reaction. Likewise, inhibition of SUMO-related enzymes in hepatoma cells reduces Mrp2 protein expression but does not alter its mRNA expression or canalicular localization (Minami et al., 2009). Additional research is warranted and should attempt to reveal the functional consequences of transporter SUMOylation.

From the aforementioned studies, it is evident that post-translational modifications can have diverse consequences on transport protein turnover, localization, and function. Events such as glycosylation and phosphorylation can alter localization and function of transporter proteins, whereas ubiquitination and SUMOylation lead to degradation.

D. Membrane Rafts

There is accumulating evidence that the plasma membrane is not a uniform phospholipid bilayer. Instead, it is composed of distinct and specialized regions with varying proportions of lipids and proteins. Such small microdomains (10–200 nm) that are sphingolipid- and cholesterol-enriched are called "lipid rafts" or "membrane rafts" (Zegers and Hoekstra, 1998; Pike, 2006). Because membrane rafts are highly ordered compared with surrounding areas, they are less fluid and more resistant to solubilization by nonionic detergents such as Triton X-100. A number of studies have begun to investigate whether transporters are contained within membrane rafts and, if so, which types of rafts. Early studies focused upon Pgp, which was found to localize to membrane rafts (Luker et al., 2000; Bacso et al., 2004; Radeva et al., 2005). Pgp has been reported in both low-density (Luker et al., 2000) and intermediate-density (Radeva et al., 2005) membrane microdomains. BCRP is found in detergent-resistant membranes (Storch et al., 2007). Likewise, a portion of Ntcp protein localizes to membrane rafts in mouse liver (Molina et al., 2008). Within the mouse intestine, Pept1 protein colocalizes with markers of membrane rafts (Nguyen et al., 2007). Using rat liver, it has been demonstrated that the localization of ABC family transporters (Abcg5, Bsep, Mrp2, Mdr2) is predominantly in "lubrol-microdomains" that contain the majority of canalicular cholesterol and phospholipids, as well as caveolin-1 and dipeptidyl peptidase IV proteins (Ismair et al., 2009). The designation as "lubrol-microdomains" is based upon the detergent used for solubilizing the canalicular plasma membrane.

Cholesterol is important for maintaining the order and packing of lipids and proteins in membrane rafts. Therefore, a common approach to studying membrane compartmentalization is to assess transporter function under cholesterol-depleted and replenished conditions. Depletion of membrane cholesterol enhances rat Ntcp uptake activity in transfected HEK293 cells (Molina et al., 2008). Moreover, reduced membrane cholesterol lowers BCRP (Storch et al., 2007), ASBT (Annaba et al., 2008), and Pgp (Dos Santos et al., 2007; Fenyvesi et al., 2008) transporter activity in overexpressing cell lines. In the cases of BCRP and ASBT, lower cholesterol levels did not alter cell viability or transporter subcellular localization or expression (Storch et al., 2007; Annaba et al., 2008). Supplementation of cholesterol-depleted cells with exogenous cholesterol restores transporter activity (Storch et al., 2007; Annaba et al., 2008). Exactly how cholesterol depletion influences transporter function is not clear, but may involve altered protein-protein interactions within the membrane, modulation of transporter transmembrane domains, disassembly of membrane rafts, or interference of transporter binding to lipophilic substrates (Storch et al., 2007).

The importance of canalicular membrane cholesterol content in biliary excretion was recently revealed in Atp8b1-null mice (Paulusma et al., 2009). Atp8b1-null mice have increased biliary levels of cholesterol because of nonspecific extraction from the canalicular membrane (Groen et al., 2008). Furthermore, biliary bile acid excretion is strongly impaired in Atp8b1-null mice despite normal Bsep protein expression and localization (Paulusma et al., 2006). Recent evidence suggests that the impaired Bsep activity in Atp8b1-null mice is due to the reduced cholesterol content of the canalicular membrane (Paulusma et al., 2009). In support of this hypothesis, repletion of cholesterol to membranes from Atp8b1-null mice restores Bsep transport activity (Paulusma et al., 2009).

Future studies into the functional significance of transporter expression in membrane rafts should provide insight into the complex membrane organization and compartmentalization of the plasma membrane. It should be noted that depletion of cholesterol yields conflicting results on Pept1 activity in polarized intestinal epithelial cells (increased activity) compared with intestinal apical membrane vesicles (decreased activity) (Nguyen et al., 2007). As future studies of transporters and lipid rafts are designed, these findings should be taken into consideration.

E. Scaffold Protein Interactions

A number of transporters contain PDZ domains (postsynaptic density 95/disc-large/zona occludens) for interaction with scaffold proteins (Hung and Sheng, 2002; Kato et al., 2004). Scaffold proteins connect transporters and regulatory components and influence subcellular targeting, transport activity, recruiting additional proteins, and protein stability on the cell surface. PDZ binding motifs are generally three to eight amino acids and occur at internal and/or C-terminal regions (Hung and Sheng, 2002). Cell interactions between PDZ proteins and several transporters, including OCTN, PEPT, OAT, and OATP isoforms, have been shown (Kato et al., 2004). PDZK1 and -2 and Na^+/H^+ exchanger regulatory factors (NHERF1 and 2) are well characterized PDZ proteins that interact with transporters.

A number of experimental approaches are available to study transporter-PDZ protein interactions including pull-down/direct interaction studies, cotransfection of transporter and PDZ genes (as well as mutant forms), and double immunohistochemical staining. Pull-down experiments demonstrate interaction of PDZK1 with apical URAT1, OCTN1, and OCTN2 proteins but not basolateral OCT1 or OCT2 (Anzai et al., 2004; Kato et al., 2004, 2005). Mutation of the PDZ motifs in URAT1 disrupts the physical interaction of these proteins (Anzai et al., 2004). Protein-protein interaction studies are supported by in vitro overexpression cell systems (Table 21). Cotransfection of cells with PDZK1 and OAT4 (Miyazaki et al., 2005), OCTN1 (Sugiura et al., 2006),

TABLE 21
Transporter and scaffold protein interactions

Transporter	Adaptor Protein	Cells	Observation	References
hOAT4	PDZK1/NHERF1	HEK293	↑ Transport activity/surface expression	Miyazaki et al., 2005
hOAT4	PDZK1/NHERF1	LLC-PK1	↑ Transport activity/surface expression	Zhou et al., 2008a
hOAT4	PDZK1/NHERF1	BeWo	↔ Transport activity/surface expression	Zhou et al., 2008a
OCTN1	PDZK1	HEK293	↑ Transport activity	Sugiura et al., 2006
OCTN2	PDZK1	HEK293	↑ Transport activity	Kato et al., 2005; Sugiura et al., 2006
OCTN2	PDZK2	HEK293	↑ Transport activity/surface expression	Watanabe et al., 2006
PEPT1	PDZK1	HEK293	↑ Transport activity	Sugiura et al., 2008
PEPT2	PDZK1	HEK293	↑ Transport activity	Kato et al., 2004; Sugiura et al., 2006
PEPT2	PDZK1	HEK293	↑ Transport activity/surface expression	Noshiro et al., 2006
PEPT2	NHERF2	Oocytes	↑ Transport activity/surface expression	Boehmer et al., 2008
URAT1	PDZK1	HEK293	↑ Transport activity/surface expression	Anzai et al., 2004
MRP4	NHERF1	MDCK	↑ Surface expression	Hoque et al., 2009

↑, increase; ↔, no change.

OCTN2 (Kato et al., 2005), PEPT1 (Sugiura et al., 2008), PEPT2 (Kato et al., 2004; Noshiro et al., 2006), and URAT (Anzai et al., 2004) increases transport of prototypical substrates. Likewise, cotransfection with NHERF2 and the protein kinase SGK1 enhances activity of PEPT2 in *X. laevis* oocytes (Boehmer et al., 2008). Other examples of PDZ protein interactions include PDZK2 and OCTN2 (Watanabe et al., 2006) as well as NHERF1 and OAT4 (Miyazaki et al., 2005). In most of these cases, increased transporter activity was due to enhanced cell surface expression. Mutation of either the PDZ protein or the transporter PDZ motif can reduce cell surface expression and/or activity of the transporter (Kato et al., 2005; Miyazaki et al., 2005; Sugiura et al., 2006).

Using immunohistochemical staining, the colocalization of PDZ proteins and transporters has been shown. In various cells, PDZK1 protein colocalizes with OCTN1 (Sugiura et al., 2006), URAT1 (Anzai et al., 2004), and OAT4 (Miyazaki et al., 2005). Likewise, Octn2 protein colocalizes with Pdzk1 (Kato et al., 2005) and Pdzk2 (Watanabe et al., 2006) proteins in mouse kidney. In the intestine, Pdzk1 protein colocalizes with Pept1 (Sugiura et al., 2008) and Octn2 (Kato et al., 2006) on the brush border membrane of mouse enterocytes.

There are differences in the targeting of transporters to the apical membrane by PDZ proteins between cell types. For example, PDZK1 and NHERF1 increase OAT4 cell surface expression and activity in renal cells but do not alter OAT4 activity in human placenta BeWo cells (Miyazaki et al., 2005; Zhou et al., 2008a). In addition, MRP4 protein traffics to the basolateral and apical membranes in MDCK and LLC-PK1 kidney cells, respectively (Hoque et al., 2009). Basolateral trafficking of MRP4 protein in MDCK cells is due to low expression of NHERF1 in the cell line (Hoque et al., 2009). Ectopic expression of NHERF1 in MDCK1 cells redirects MRP4 to the apical membrane (Hoque et al., 2009). These findings suggest that transporters may require an alternate set of adaptor proteins for subcellular trafficking to specific membrane domains (apical versus basolateral) in different cells.

Mice null for Pdzk1 have been developed and exhibit reduced intestinal absorption of cephalexin (Pept1 substrate) and carnitine (Octn2 substrate) (Sugiura et al., 2008). Reduced uptake of both substrates is likely to be related to lower abundance of Pept1 and Octn2 proteins in intestinal brush border membranes (Sugiura et al., 2008). Electron microscopy demonstrates retention of Pept1 protein in intracellular vesicular structures in PDZK1-null mice (Sugiura et al., 2008).

The interaction of Oatp and PDZ proteins has been investigated using in vitro and in vivo approaches. During yeast two-hybrid screening, OATP1A2, -3A1, and -1C1 bind directly to members of the PDZ family (Kato et al., 2004). Oatp1a1 is localized to the basolateral surface of hepatocytes and binds predominantly to the first and third PDZ binding domains of PDZK1. Expression of Oatp1a1 is normal in Pdzk1-null mice, yet is restricted to the intracellular compartment (Wang et al., 2005). Finally, altered localization of Oatp1a1 in Pdzk1-null mice corresponds with impaired hepatic uptake of sulfobromophthalein (Wang et al., 2005).

The current data regarding the interaction of PDZ proteins with MRP2 are unclear. PDZK1 protein interacts with the carboxyl terminal of MRP2 in a yeast two-hybrid system (Kocher et al., 1999). In line with this finding, phosphorylation of the MRP2 C-terminal increases binding to various PDZ proteins (Hegedüs et al., 2003). However, truncation of the carboxyl terminus of MRP2 protein (containing a PDZ motif) does not interfere with trafficking to the apical membrane of polarized MDCK cells (Nies et al., 2002a). Instead, a larger portion (15 amino acids) needs to be removed before cellular trafficking is impaired (Nies et al., 2002a).

Collectively, post-translational modifications, membrane rafts, and protein-protein interactions work in concert to regulate the expression, trafficking, and function of transporters. Additional reviews on intracellular trafficking of transporters are recommended (Kipp and Arias, 2000, 2002; Wakabayashi et al., 2006). A number of other biochemical events, including altered osmolarity and redox signaling, influence transporter trafficking, but they are beyond the scope of this review. Likewise,

the formation of cysteine disulfide bridges as well as homoligomerization and hetero-oligomerization are important for transport protein stabilization and function.

V. Sex Differences in Transporter Expression

Transporters exhibit sex differences in their expression, and these discrepancies probably contribute to disparities in drug disposition and toxicity between male and female subjects. Table 22 illustrates examples of sex differences in the expression of transporters in rodents. Data regarding sex differences in human transporters are quite limited; this is likely to be an active area of research.

A. Sex Differences in Various Tissues

Studies in mice demonstrate tissue-dependent regulation of transporter isoforms between the sexes. The most notable differences exist in the kidneys and liver (Table 22).

Evaluation of transporter patterns in the kidneys of male and female mice reveals an interesting pattern. There is higher mRNA expression of uptake transport-

TABLE 22
Sex differences in transporter expression in mice and rats
Sex differences in transporter mRNA expression between males and females are provided for various tissues including kidney, liver, lung, brain, and intestine.

Tissue & Transporter	Mice	Rat	References
Kidneys			
Uptake			
Oatp1a1	M > F	M > F	Li et al., 2002; Cheng et al., 2005a
Oatp3a1	M > F	N.D.	Cheng et al., 2005a
Oatp4c1	M > F	N.D.	Cheng et al., 2005a
Oat1	M > F	M > F	Buist et al., 2002, 2003; Buist and Klaassen, 2004
Oat2	M = F	F > M	Buist et al., 2002; Ljubojevic et al., 2007
Oat5	F > M	N.D.	Cheng and Klaassen, 2009
Urat1	M > F	N.D.	Hosoyamada et al., 2004
Oct2	M > F	M > F	Urakami et al., 1999; Slitt et al., 2002; Alnouti et al., 2006
Asbt	F > M	N.D.	Cheng and Klaassen, 2009
Abca1	F > M	N.D.	Cheng and Klaassen, 2009
Pept2	M = F	F > M	Lu and Klaassen, 2006
Efflux			
Ent1	F > M	M = F	Lu et al., 2004
Ent2	F > M	M = F	Lu et al., 2004
Ent3	M > F	M = F	Lu et al., 2004
Mrp3	F > M	N.D.	Maher et al., 2005b
Mrp4	F > M	N.D.	Maher et al., 2005b
Mdr1a	F > M	N.D.	Cui et al., 2009c
Mdr1b	F > M	N.D.	Cui et al., 2009c
Bcrp	M = F	M > F	Tanaka et al., 2005
Ostα	M > F	N.D.	C. Klaassen et al., unpublished
Mate1	M > F	N.D.	Lickteig et al., 2008
Liver			
Uptake			
Oatp1a1	M > F	M = F	Li et al., 2002; Cheng et al., 2005a
Oatp1a4	F > M	M = F	Guo et al., 2002b; Li et al., 2002; Cheng et al., 2005a
Oatp1a6	F > M	N.D.	Li et al., 2002; Cheng et al., 2005a
Oatp2b1	F > M	N.D.	Cheng et al., 2005a
Ntcp	F > M	M > F	Simon et al., 1999; Cheng et al., 2007
Abca1	M > F	N.D.	Cheng and Klaassen, 2009
Efflux			
Mrp3	M = F	F > M	Maher et al., 2005b; Rost et al., 2005
Mrp4	F > M	N.D.	Maher et al., 2005b
Bcrp	M > F	M = F	Merino et al., 2005c; Tanaka et al., 2005
Mate1	F > M	N.D.	Lickteig et al., 2008
Abcg5	M = F	M > F	Dieter et al., 2004
Lung			
Mdr1b	F > M	N.D.	Cui et al., 2009c
Mdr2	F > M	N.D.	Cui et al., 2009c
Brain			
Oct3	M > F	N.D.	Alnouti et al., 2006
Mdr1b	M > F	N.D.	Cui et al., 2009c
Intestine			
Abca1 (duo)	F > M	N.D.	Cheng and Klaassen, 2009
Oatp2b1 (jej)	M > F	N.D.	Cheng et al., 2005a
Cnt3 (jej)	M > F	N.D.	Lu et al., 2004
Ostα (jej)	M > F	N.D.	C. Klaassen et al., unpublished
Ostβ (jej)	M > F	N.D.	C. Klaassen et al., unpublished
Asbt (il)	F > M	N.D.	Cheng and Klaassen, 2009
Mate2 (LI)	M > F	N.D.	Lickteig et al., 2008
Abcg5 (jej)	M = F	M > F	Dieter et al., 2004
Abcg8 (jej, il)	M = F	M > F	Dieter et al., 2004

M, male; F, female; duo, duodenum; jej, jejunum; il, ileum; LI, large intestine; N.D., not determined.

ers (Oatp1a1, -3a1, -4c1, Oat1, Urat1, Oct2) in the kidneys of male mice, compared with female mice (Urakami et al., 1999; Li et al., 2002; Slitt et al., 2002; Hosoyamada et al., 2004; Cheng et al., 2005a; Alnouti et al., 2006). Conversely, female mice express higher levels of efflux transporters (Mrp3, Mrp4, Mdr1a, Mdr1b, Ent1, Ent2) in their kidneys (Lu et al., 2004; Maher et al., 2005b; Cui et al., 2009c). The net effect of these expression patterns favors lower intracellular accumulation of substrates in the renal tubule cells of female mice and could influence rates of chemical secretion and reabsorption.

A number of liver transporters demonstrate female-predominant (Oatp1a4, -1a6, -2b1, Ntcp, Mrp4, Mate1) or male-predominant (Oatp1a1, Bcrp, Abca1) mRNA expression patterns in mice (Simon et al., 1999; Guo et al., 2002a; Li et al., 2002; Cheng et al., 2005a, 2007; Maher et al., 2005b; Tanaka et al., 2005; Lickteig et al., 2008). There are relatively fewer sex differences in other mouse tissues. Compared with female mice, male mice express higher levels of Oatp2b1, Cnt3, Ostα, and Ostβ mRNA in the jejunum and Oct3 and Mdr1b in the brain (Lu et al., 2004; Cheng et al., 2005a; Alnouti et al., 2006; Lickteig et al., 2008; Cui et al., 2009c). In contrast, female-predominant expression of Mdr1b and Mdr2 mRNA is observed in mouse lungs (Cui et al., 2009c). Collectively, these data highlight the variability in sex differences depending upon the tissue and transporter isoform.

B. Sex Differences among Species

Sex differences are not always consistent among species. Male-predominant expression of Oatp1a1, Oat1, and Oct2 is similarly observed in the kidneys of mice and rats (Urakami et al., 1999; Buist et al., 2002; Slitt et al., 2002; Buist and Klaassen, 2004; Alnouti et al., 2006; Groves et al., 2006). In contrast, hepatic Ntcp demonstrates female-predominant mRNA expression in mice and male-predominant expression in rats (Simon et al., 1999; Cheng et al., 2007). There is more NTCP mRNA in female human livers, although it is not statistically significant because of large interindividual variation (Cheng et al., 2007). Likewise, hepatic Bcrp/BCRP mRNA is higher in male mice and humans, respectively, compared with female counterparts (Merino et al., 2005c). As a result, Bcrp substrates (nitrofurantoin and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine) exhibit greater biliary excretion in male wild-type mice relative to female mice (Merino et al., 2005c). It is noteworthy that there are no differences in the pharmacokinetics of these two chemicals in Bcrp-null mice, suggesting that the transporter is indeed responsible for the sex-divergent pharmacokinetics (Merino et al., 2005c). Similarities in the sex-dependent expression of Ntcp/NTCP and Bcrp/BCRP data suggest that mice may be an appropriate model for evaluating functional outcomes of sex differences in human transporters (Merino et al., 2005c; Cheng et al., 2007).

Kidney Oat1 mRNA and protein expression are higher in male mice and rats than in female mice and rats (Buist et al., 2002; Buist and Klaassen, 2004), and corresponds with more *p*-aminohippurate transport (Cerrutti et al., 2002; Ljubojevic et al., 2004). In contrast, no sex difference in Oat1 is observed in renal proximal tubule suspensions from rabbits (Groves et al., 2006). Evaluation of human OAT1 expression patterns in both sexes is necessary before extrapolating from rodent data.

Whereas the majority of sex difference studies have focused upon mRNA expression, additional work is needed at the protein and functional levels to better understand the in vivo significance. Moreover, there is a clear need for characterization of sex differences in human transporters.

C. Regulatory Mechanisms of Sex Differences

1. Growth Hormone. Sex differences in the regulation of transporters are dictated by sex hormones as well as sex-dimorphic growth hormone secretion patterns. Experimental data investigating the mechanistic role of hormones in regulating sex-divergent transporter expression are summarized in Table 23. Male rats secrete growth hormone in high-amplitude pulses at regular intervals, whereas female rats exhibit lower and more frequent growth hormone pulses (Terry et al., 1977). In turn, circulating levels of growth hormone exhibit fewer fluctuations in female rats.

Surgical removal of the pituitary gland (hypophysectomy) followed by growth hormone supplementation is one approach to assess the contribution of growth hormone secretion patterns to the regulation of renal and hepatic transporters (Table 23). The pituitary gland produces not only growth hormone but also luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone, and prolactin. Therefore, hypophysectomy diminishes multiple hormone signaling pathways. Another approach to assess the contribution of growth hormone to transporter regulation is the use of lit/lit mice (Table 23). Lit/lit mice have a spontaneous mutation in the growth hormone-releasing hormone receptor (Beamer and Eicher, 1976). Using these approaches, it has been shown that the female-predominant expression of hepatic Ntcp and renal Mrp4 is due to the inhibitory effects of male-pattern growth hormone secretion (Maher et al., 2006a; Cheng et al., 2007). In the case of Ntcp, exogenous administration of growth hormone (male-type patten) to hypophysectomized or lit/lit mice reduced hepatic mRNA levels (Cheng et al., 2007). Likewise, male-predominant Oatp1a1 expression in mouse liver is caused by the stimulatory effects of male-pattern growth hormone secretion (Cheng et al., 2006). The influence of growth hormone secretion patterns on the female-predominant expression of hepatic Mrp2 mRNA in rat liver has also been reported (Simon et al., 2006).

TABLE 23

Hormonal regulation of transporter mRNA expression in rodent livers and kidneys

The tissue, species, and predominant gender are provided for each transporter. Hormonal regulation was determined using gonadectomy (GNX), hypophysectomy (HPX), lit/lit mice, and hormone replacement (estrogen and 5α-dihydroxytesterone, DHT) in gonadectomized mice. Changes in estrogen- and DHT-treated mice should be compared with those in GNX mice.

Transporter	Tissue	Species	Gender Predominant	Female				Male				References
				GNX	HPX	Lit/Lit	Estrogen	GNX	HPX	Lit/Lit	DHT	
Mdr1a	Kidney	Mice	Female	↓	↔	↓	↔	↑	↑	↑	↓	Cui et al., 2009c
Mdr1b	Kidney	Mice	Female	↔	↑	↓	↔	↑	↑	↑	↓	Cui et al., 2009c
Mrp3	Kidney	Mice	Female	↓	↓	↓	↑	↑	↔	↑	↓	Maher et al., 2006a
Mrp4	Kidney	Mice	Female	↔	↑	↑	↔	↑	↑	↑	↓	Maher et al., 2006a
Bcrp	Liver	Mice	Male	↔	N.D.	N.D.	↔	↓	N.D.	N.D.	↑	Tanaka et al., 2005
Ntcp	Liver	Mice	Female	↓	↔	↔	↔	↔	↔	↔	↔	Cheng et al., 2007
Oatp1a1	Liver	Mice	Male	↓	↓	↓	↔	↓	↓	↓	↑	Cheng et al., 2006
Oatp1a1	Kidney	Mice	Male	↔	↔	↔	↔	↓	↓	↓	↑	Cheng et al., 2006
Oatp1a4	Liver	Mice	Female	↔	↑	↑	↓	↑	↑	↑	↓	Cheng et al., 2006
Oatp3a1	Kidney	Mice	Male	↔	↔	↔	↔	↓	↓	↔	↑	Cheng et al., 2006
Oatp4c1	Kidney	Mice	Male	↑	N.D.	↔	↔	↓	N.D.	↔	↑	Cheng and Klaassen, 2009
Oat1	Kidney	Rat	Male	↔	↔	N.D.	N.D.	↓	↓	N.D.	N.D.	Buist et al., 2003
Oat2	Kidney	Rat	Female	↓	↓	N.D.	N.D.	↔	↔	N.D.	N.D.	Buist et al., 2003
Oat3	Liver	Rat	Male	↔	↑	N.D.	N.D.	↓	↓	N.D.	N.D.	Buist et al., 2003
Oat5	Kidney	Mice	Female	↓	N.D.	↓	↑	↑	N.D.	↓	↓	Cheng and Klaassen, 2009
Urat1	Kidney	Mice	Male	↔	N.D.	↔	↓	↔	N.D.	↔	↑	Cheng and Klaassen, 2009
Oct2	Kidney	Mice	Male	↔	N.D.	N.D.	↔	↓	N.D.	N.D.	↑	Alnouti et al., 2006

↑, increased mRNA levels; ↓, reduced mRNA levels; ↔, no change in mRNA levels; N.D., not determined.

Although Oat2 mRNA levels in kidneys are similar in male and female mice (Buist and Klaassen, 2004), protein expression is higher in female mice (Ljubojević et al., 2007). Hypophysectomy of female rats reduces Oat2 mRNA expression in the kidneys that is partially restored by growth hormone injection (Buist et al., 2003).

2. Sex Steroids. Testosterone and estrogen can have both stimulatory and inhibitory influences on the mRNA expression of various transporters. Gonadectomy is the surgical removal of the testes or ovaries, thereby reducing circulating levels of sex hormones. One approach to confirming the role(s) of individual sex hormones in regulating sex-divergent expression is to include a subset of mice that receive hormone replacement after surgical intervention (Table 23). Using gonadectomy, it has been shown that the female-predominant expression of renal Mdr1a, Mdr1b, and Mrp4, as well as hepatic Oatp1a4 in mice, is due to an inhibitory effect by androgens (Cheng et al., 2006; Maher et al., 2006a; Cui et al., 2009c). In contrast, female-predominant expression of renal Mrp3 and Oat5 in mice and Oat2 in rats is due to estradiol (Buist et al., 2002, 2003; Kobayashi et al., 2002a; Maher et al., 2006a; Ljubojević et al., 2007; Cheng and Klaassen, 2009).

Testosterone stimulates Oat3 mRNA expression in male rat livers (Kobayashi et al., 2002a; Buist et al., 2003) and represses Pgp and Mrp2 protein levels in female rat livers (Suzuki et al., 2006). In kidneys, male-predominant Oatp1a1, Oatp3a1, Oatp4c1, Oat1, Urat1, and Oct2 expression is androgen-dependent (Isern et al., 2001; Buist et al., 2003; Ljubojevic et al., 2004; Alnouti et al., 2006; Cheng et al., 2006; Cheng and Klaassen, 2009). For example, gonadectomy of male rodents reduces expression of kidney Oct2 to levels comparable with that in sham-operated female mice and rats (Slitt et al., 2002; Alnouti et al., 2006). Treatment of gonadectomized male and female mice with 5α-dihydroxytestosterone induces renal Oct2 in both sexes, whereas estradiol has little influence on renal Oct2 (Alnouti et al., 2006). Likewise, treatment of intact male and female rats with testosterone increases Oct2 mRNA, protein, and transport in the kidneys (Urakami et al., 2000).

Researchers have only begun to report sex differences in transporter expression. Mice are the most characterized rodent model. Future emphasis should be placed on quantifying sex differences in humans. Until such efforts are accomplished, only predictions can be made regarding the clinical implications of sex-divergent transporter regulation. For example, Urat1 mRNA and protein levels are expressed at a higher level in male mouse kidneys compared with female mouse kidneys (Hosoyamada et al., 2004). If this sex difference exists in humans, it may explain in part the increased incidence of gout in men compared with women. In addition, a polymorphism in *ABCA1* in women is associated with an increased risk of developing late-onset Alzheimer's disease (Sundar et al., 2007). This is a unique risk factor and highlights the future direction of research into sex-specific polymorphisms in transporters.

VI. Ontogeny of Transporters

Developmental changes in metabolism and transport govern drug pharmacokinetics in humans and laboratory animals. These changes critically determine the systemic clearance of drugs and in turn influence the pharmacodynamic responses of newborns. Early studies focused upon the ontogenic development of drug-metabolizing enzymes as the underlying mechanism for altered drug disposition in juveniles. With the discovery of drug and bile acid transporters, attention has been placed on variations in their expression and/or function with age. This section will focus primarily on the peri-

natal to adulthood mRNA expression of transporters in rodents (mostly, mice) and humans in various tissues (Fig. 12).

A. Liver

Hepatic drug clearance is low in neonatal rats, leading to increased circulating plasma levels of chemicals and enhanced susceptibility to drug toxicity (such as ouabain) (Klaassen, 1972). Likewise, human newborns and infants are at risk of jaundice because of the physiological immaturity of the liver (Suchy et al., 1981). During ontogeny, hepatocytes become polarized allowing for distinct localization of transporters on the basolateral and apical membranes and the vectorial transport of endo- and xenobiotics. Hepatic uptake transporters vary in the timing at which they reach adult mRNA levels (Fig. 12). Before birth, Oatp2a1 is the only transporter expressed at mature levels in mouse liver (Cheng et al., 2005a). It is noteworthy that Ntcp and Ent1 exhibit a spike in mRNA expression at birth (0 days) and then decrease (Cheng et al., 2007). Likewise, Ntcp mRNA levels increase in the fetal rat liver near birth (St-Pierre et al., 2004). It is hypothesized that the elevation of Ntcp mRNA at day 0 is a response to the development of the enterohepatic recirculation of bile acids in newborns (Cheng et al., 2007).

The remaining Oat/Oatp transporters reach adult mRNA levels at early (5–10 days: Oatp1a4, Oatp1a6, Oat2), middle (15–22 days: Oatp1b2, Oatp2b1, Oct1), and late (30–45 days: Oatp1a1) periods of liver development (Cheng et al., 2005a; Alnouti et al., 2006). The hepatic mRNA patterns of Oatp1a1, -1a4, and -1b2 ontogeny in rats are similar to mice (Li et al., 2002; Gao et al., 2004). For uptake transporters exhibiting sex-divergent expression (Oatp1a1, Oatp1a4, and Ntcp), differences between male and female mice are evident by 30 to 45 days of age (Fig. 12). Hepatic expression of rat Cnt2 mRNA does not increase until 21 days after birth (del Santo et al., 2001).

Liver efflux transporters demonstrate an intriguing initiation of mRNA expression in mice at birth (Figs. 13 and 14). These canalicular and sinusoidal transporters include Mrp2, Mrp4, Mate1, Mdr2, Bcrp, Bsep, Ostα, and Ostβ (Maher et al., 2005b; Cheng et al., 2007; Cui et al., 2009c). It is noteworthy that stimulation of Bsep, Mrp4, Ostα, Ostβ, and Mdr2 expression at birth corresponds with increased Ntcp mRNA and may represent the constitution of the enterohepatic recirculation of bile acids in mice. Likewise, Bsep and Mrp2 mRNA levels increase in the fetal rat liver perinatally and are fol-

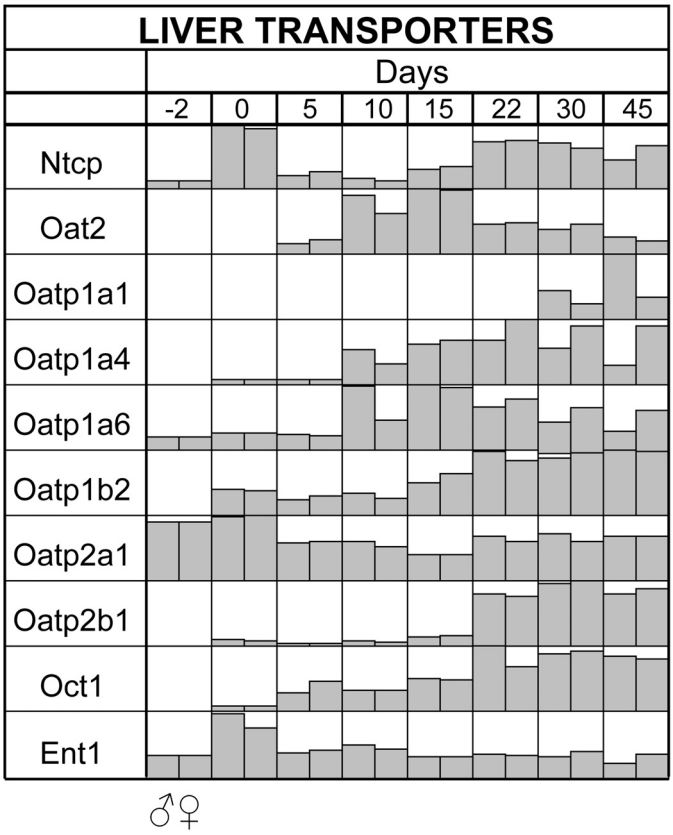

FIG. 12. Ontogeny of mouse basolateral uptake transporter mRNA expression in liver. Tissues from C57BL/6 mice were obtained at −2, 0, 5, 10, 15, 22, 30, and 45 days. Day −2 represents gestational day 17. Male (♂) mRNA is shown on the left, whereas female (♀) mRNA is shown on the right side of each box. Data are summarized from unpublished observations (C. Klaassen) and previous publications (Cheng et al., 2005a, 2007; Alnouti et al., 2006).

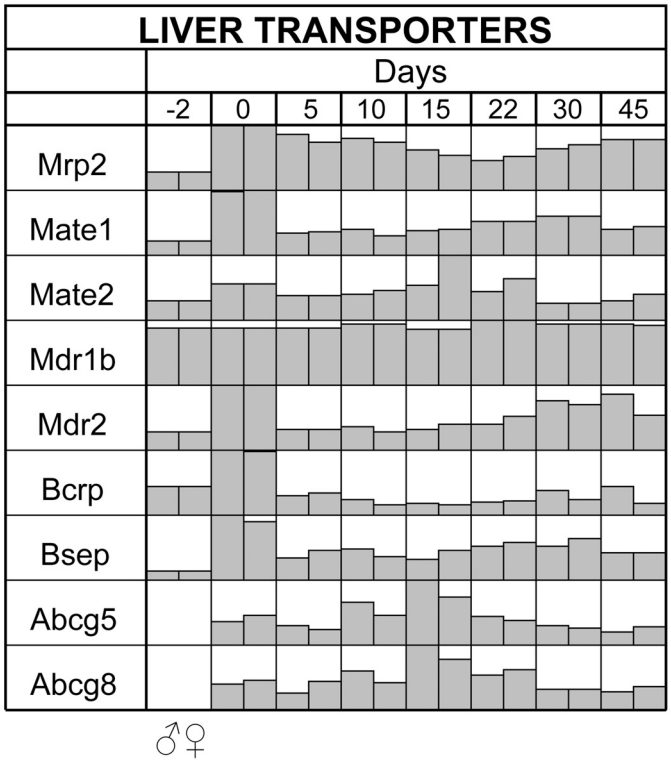

FIG. 13. Ontogeny of mouse canalicular efflux transporter mRNA expression in liver. Tissues from C57BL/6 mice were obtained at −2, 0, 5, 10, 15, 22, 30, and 45 days. Day −2 represents gestational day 17. Male (♂) mRNA is shown on the left, whereas female (♀) mRNA is shown on the right side of each box. Data are summarized from unpublished observations (C. Klaassen) and previous publications (Maher et al., 2005b; Cheng et al., 2007; Cui et al., 2009c).

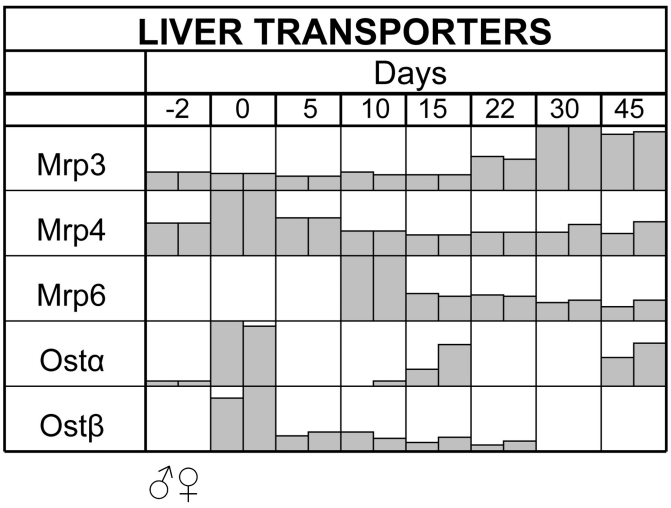

FIG. 14. Ontogeny of mouse basolateral efflux transporter mRNA expression in liver. Tissues from C57BL/6 mice were obtained at −2, 0, 5, 10, 15, 22, 30, and 45 days. Day −2 represents gestational day 17. Male (♂) mRNA is shown on the left, whereas female (♀) mRNA is shown on the right side of each box. Data are summarized from unpublished observations (C. Klaassen) and previous publications (Maher et al., 2005b).

lowed by elevated protein expression between 1 and 4 weeks of age (Zinchuk et al., 2002; Rosati et al., 2003; Tomer et al., 2003; Gao et al., 2004; St-Pierre et al., 2004). Weak canalicular Bsep and Mrp2 protein immunostaining is observed in the fetal rat liver and becomes diffuse in appearance in newborns, suggesting subapical localization (Zinchuk et al., 2002). It is not until after 1 week of age that Bsep and Mrp2 protein are sharply localized to the rat canalicular membrane (Zinchuk et al., 2002).

Messenger RNA levels of mouse Mrp4, Ostα, Ostβ, Bsep, Bcrp, and Mate1 quickly decrease by 5 days of age (Figs. 13 and 14). Shortly after birth (10 days), peak levels of Mrp6 mRNA are observed in mouse and rat liver (Gao et al., 2004; Maher et al., 2005b). Maximal mRNA expression of Mate2, Abcg5, and Abcg8 is not observed until later in development (15–22 days). By 30 days, mouse Mrp3 mRNA approximate adult levels (Ma-

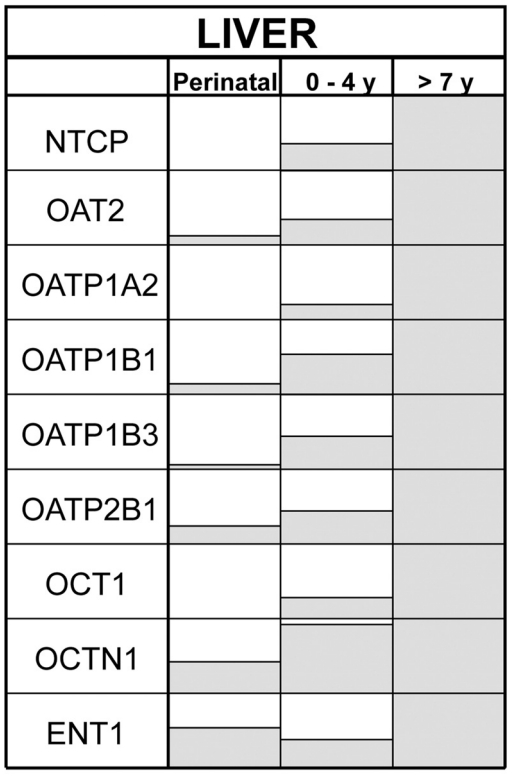

FIG. 15. Ontogeny of human uptake transporter mRNA expression in liver. Human liver specimens are from various time periods: perinatal (prenatal to postnatal day 30, $n = 6$), 0 to 4 years ($n = 8$), and more than 7 years old ($n = 6$). Data from male and female human livers are combined (C. Klaassen, unpublished observations).

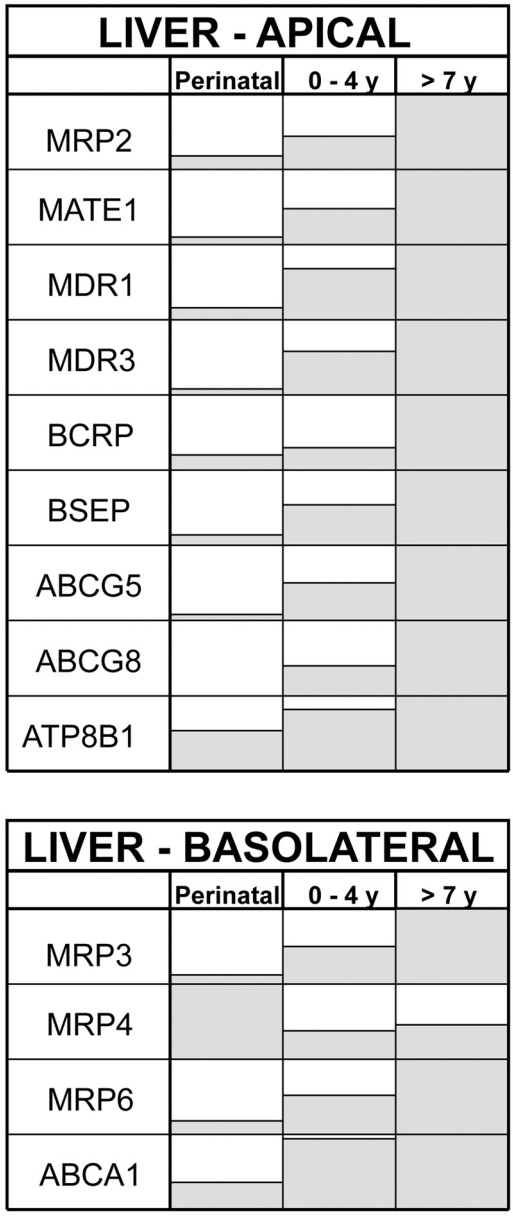

FIG. 16. Ontogeny of human efflux transporter mRNA expression in liver. Human liver specimens are from various time periods: perinatal (prenatal to postnatal day 30, $n = 6$), 0 to 4 years ($n = 8$), and more than 7 years old ($n = 6$). Data from male and female human livers are combined (C. Klaassen, unpublished observations).

her et al., 2005b). Mouse Mdr1b mRNA in liver is unchanged from gestation throughout adulthood (Cui et al., 2009c).

Initial studies have begun to examine the developmental expression of hepatobiliary transporters in humans. Our laboratory recently screened the mRNA expression of uptake and efflux transporters in human livers from three developmental periods: perinatal (gestation through 30 days), 0 to 4 years of age, and 7 to 17 years of age (Figs. 15 and 16). Only a small number of transporters (OCTN1, ENT1, ATP8B1, MRP4, and ABCA1) were detected in the perinatal livers. In general, mRNA expression of uptake and efflux transporters (with the exception of MRP4) increased from 0 to 4 years and was even higher in livers of persons over 7 years old. Similar to our findings, it has previously been reported that canalicular transporters BSEP, MRP2, and MDR3 tend to increase from the fetal period to adulthood (Chen et al., 2005a). As in rat liver development, the immunostaining patterns of MRP2, BSEP, and MDR3 proteins in the human fetal liver are diffuse with intracellular and canalicular staining (Chen et al., 2005a). Insufficient trafficking of canalicular transporters in the immature liver may be one reason for the heightened susceptibility of newborns to cholestasis.

B. Kidneys

Excretion by prenatal and juvenile rodent kidneys is functionally immature. Renal transport of the organic anion *p*-aminohippurate in rat kidney slices increases after birth and continues through adulthood (Nakajima et al., 2000). Maturation of renal excretion parallels the appearance of organic anion and cation transporters in developing kidneys. In mice, renal uptake transporters on the brush-border membrane seem to develop before those on the basolateral surface (Figs. 17 and 18). Before and at birth, the fetal mouse kidney expresses Oatp1a4, -2a1, and -2b1 (Cheng et al., 2005a). Although the subcellular localization of these transporters has not been determined, Oatp isoforms are presumed to be expressed on the apical surface of the kidneys, suggesting that only reabsorption is functional during gestational development. It is not until 15 to 22 days of postnatal life that the mRNA of mouse Oct1–2, Octn1–2, Oatp1a6, Oatp4c1, Oat5, Cnt1, Pept2, and Urat1 are sufficiently expressed in developing kidneys (Choudhuri et al., 2001; Cheng et al., 2005a; Alnouti et al., 2006; Cheng and Klaassen, 2009). Mice and rats exhibit similar increases in Pept2 mRNA postnatally (Shen et al., 2001). In-

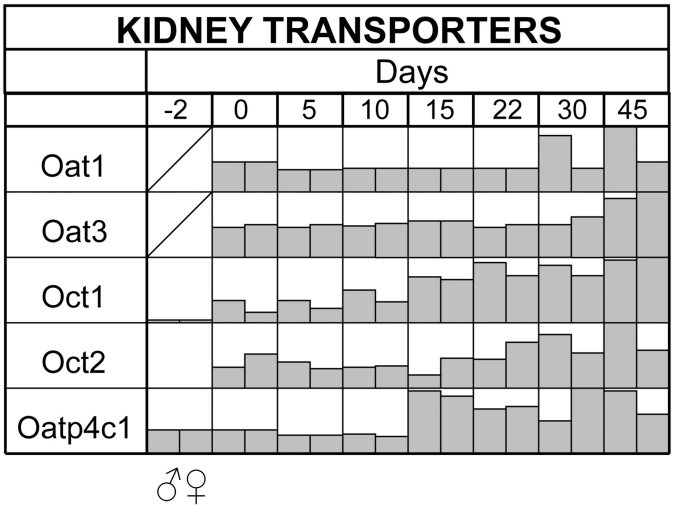

FIG. 17. Ontogeny of mouse basolateral uptake transporter mRNA expression in kidneys. Tissues from C57BL/6 mice were obtained at −2, 0, 5, 10, 15, 22, 30, and 45 days. Day −2 represents gestational day 17. Male (♂) mRNA is shown on the left, whereas female (♀) mRNA is shown on the right side of each box. It is noteworthy that Oat1 and Oat3 mRNA expression was not quantified at day −2. Data are summarized from previous publications (Buist and Klaassen, 2004; Cheng et al., 2005a; Alnouti et al., 2006; Cheng and Klaassen, 2009).

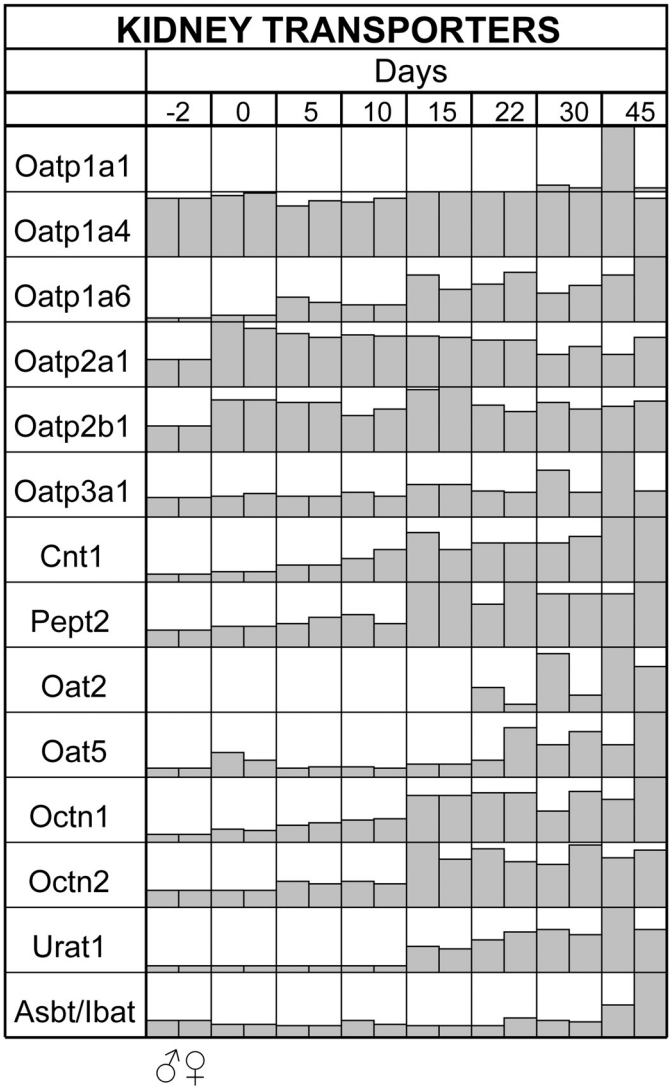

FIG. 18. Ontogeny of mouse apical uptake transporter mRNA expression in kidneys. Tissues from C57BL/6 mice were obtained at −2, 0, 5, 10, 15, 22, 30, and 45 days. Day −2 represents gestational day 17. Male (♂) mRNA is shown on the left, whereas female (♀) mRNA is shown on the right side of each box. Data are summarized from unpublished observations (C. Klaassen) and previous publications (Cheng et al., 2005a; Alnouti et al., 2006; Cheng and Klaassen, 2009).

creased Octn2 mRNA at 16 to 18 days in rat kidney corresponds with increased carnitine transport in brush border membrane vesicles (García-Delgado et al., 2009). By later in development (30+ days), Oat1–3, Oatp1a1, Oatp3a1, and Asbt are detected at adult levels (Choudhuri et al., 2001; Buist and Klaassen, 2004; Cheng et al., 2005a; Cheng and Klaassen, 2009). Similar delays in Oat and Oct expression are observed in developing rat kidneys at which time male-predominant Oat1, Oat2 (mouse only), and Oct2 expression is noticed, typically around 30 days of age (Buist et al., 2002; Slitt et al., 2002; Buist and Klaassen, 2004; Alnouti et al., 2006). Likewise, Oat1 and Oat3 mRNA is higher in renal proximal tubule suspensions from 15- to 20-week-old rabbits compared with 8-week-old rabbits (Groves et al., 2006). Oat1 and Oat3 mRNA is first expressed during late gestation in the renal cortex of sheep and remains elevated postnatally (Wood et al., 2005). In contrast to mice, Asbt mRNA is observed earlier (7 days) in the development of rat kidneys (Christie et al., 1996).

The efflux transporters involved in reabsorption appear earlier in mouse renal development compared with those that participate in chemical secretion (Figs. 19 and 20). Ent2 and Mrp6 mRNA are detected in fetal kidneys and are accompanied by increases in Mrp1 and Mrp5 at birth (Fig. 20) (Maher et al., 2005b). Brush border efflux transporters (Mrp2, Mrp4, Mdr1b, Bcrp, and Mate1) and additional retrograde basolateral transporters (Ent3 and Mrp3) mature slowly and are not maximally expressed until the mid-juvenile stage of mouse renal development (15–22 days) (Figs. 19 and 20) (Maher et al., 2005b; Lickteig et al., 2008; Cheng and Klaassen, 2009; Cui et al., 2009c). The ontogeny of Mdr1a and -1b in mouse kidneys corresponds with increased renal excretion of the Pgp substrate, digoxin, from postnatal days 0 to 21 (Pinto et al., 2005). Similar maturation of Mdr1a, Mdr1b, and Mrp2 mRNA in rat kidneys occurs postnatally (Rosati et al., 2003; Garrovo et al., 2006).

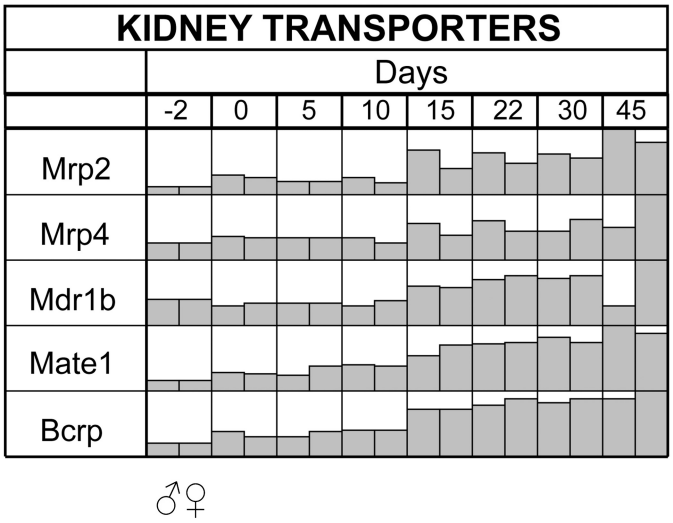

FIG. 19. Ontogeny of mouse apical efflux transporter mRNA expression in kidneys. Tissues from C57BL/6 mice were obtained at −2, 0, 5, 10, 15, 22, 30, and 45 days. Day −2 represents gestational day 17. Male (♂) mRNA is shown on the left, whereas female (♀) mRNA is shown on the right side of each box. Data are summarized from unpublished observations (C. Klaassen) and previous publications (Maher et al., 2005b; Lickteig et al., 2008; Cheng and Klaassen, 2009; Cui et al., 2009c).

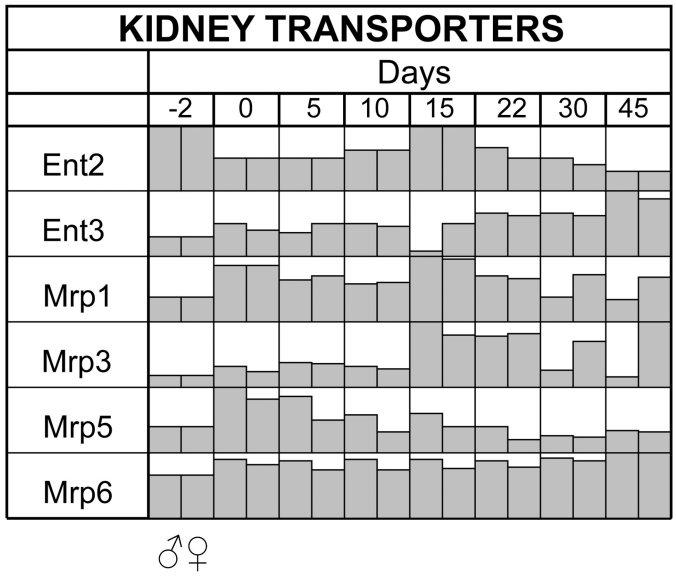

FIG. 20. Ontogeny of mouse basolateral efflux transporter mRNA expression in kidneys. Tissues from C57BL/6 mice were obtained at −2, 0, 5, 10, 15, 22, 30, and 45 days. Day −2 represents gestational day 17. Male (♂) mRNA is shown on the left, whereas female (♀) mRNA is shown on the right side of each box. Data are summarized from unpublished observations (C. Klaassen) and previous publications (Maher et al., 2005b; Cheng and Klaassen, 2009).

C. Intestine

Development of the small intestine in animals is not complete at birth. Intestinal expression of transporters seems to be elevated after birth and again at weaning (transition from milk to solid food). Dietary exposure to lipids, peptides, and carnitine necessitate the expression of intestinal transporters for efficient absorption. Likewise, enterohepatic circulation of bile acids is important to solubilize dietary lipids.

Expression of Asbt mRNA in rat and mouse ileum is biphasic with increased mRNA prenatally (gestation day 22) and increased levels again at weaning (19–21 days after birth) (Shneider et al., 1995, 1997; Christie et al., 1996; Håkansson et al., 2002). During the intervening period (day 7 after birth), Asbt mRNA expression is suppressed (Shneider et al., 1997). Asbt mRNA expression at all three time points (gestation day 22, postnatal days 7 and 21) corresponds with apical protein expression and taurocholate uptake in isolated ileal vesicles (Christie et al., 1996; Shneider et al., 1997). The second dramatic increase in Asbt mRNA is a result of weaning; early (day 15) or late (day 22) weaning of rat pups accelerates (at day 19) or decelerates (at day 22) Asbt up-regulation, respectively (Hwang and Henning, 2001).

Rat Pept1 mRNA increases in all three segments of the small intestine 1 day after birth and peaks between 3 and 5 days with a dramatic decline afterward (Shen et

al., 2001). An additional report suggests that the decline in Pept1 mRNA occurs later in rat development (around postnatal day 50) (Rome et al., 2002). The rise in Pept1 mRNA after birth is mirrored by an increase in protein. It is noteworthy that Pept1 protein expression in the small intestine is biphasic, with a dramatic decrease at day 14 followed by a rise to adult rat levels after weaning (Shen et al., 2001). It should be noted that Pept1 mRNA and protein disappears from the rat colon between 3 and 5 days after birth and remains undetectable through 75 days of age (Shen et al., 2001).

Octn2 mRNA in the rat jejunum and ileum is expressed higher perinatally and decreases 1 day after birth through 6 months of age (García-Miranda et al., 2005). This pattern of mRNA expression parallels the decline in sodium-dependent uptake of L-carnitine with advancing age (García-Miranda et al., 2005).

D. Brain

A number of transporters have been detected in different regions of the developing brain. The protein expression of Pept2 is highest in rat cerebral cortex during embryonic development and steadily decreases through 75 days after birth (Shen et al., 2004). The decline in Pept2 protein is due to loss of the transporter in astrocytes (Shen et al., 2004). Pept2 staining is maintained in the choroid plexus throughout development (Shen et al., 2004).

From gestation through adulthood, there are increases in the mRNA expression of rodent Mdr1a, Mdr1b, and Mrp2 in brain (Rosati et al., 2003; Garrovo et al., 2006; Cui et al., 2009c). Pgp protein reaches adult levels in mouse brain by 21 days (Ose et al., 2008). As Pgp expression increases with age, the brain accumulation of Pgp substrates oseltamivir, digoxin, and cyclosporine declines (Goralski et al., 2006; Ose et al., 2008). It was recently shown that human Pgp protein can be detected on microvessel endothelial cells of the brain as early as 22 weeks of gestation, and staining intensity increases with development (Daood et al., 2008). Conversely, Mrp1 mRNA is similar in the rat fetal, newborn, and adult brain (Garrovo et al., 2006). Human MRP1 protein staining in the choroid plexus and ventricular ependyma is observed early in development (Daood et al., 2008). Human and mouse BCRP protein is also consistently detected in fetal and adult choroid plexus and capillary endothelial cells, respectively (Tachikawa et al., 2005; Daood et al., 2008).

During the prenatal and postnatal periods, organ development is incomplete. Therefore, the pharmacokinetics of drugs changes as various tissues mature. The consequences of variation in drug disposition may be inadequate therapeutic efficacy and/or a heightened incidence of adverse events. Although maturation of drug metabolizing enzyme expression is important, it is likely that establishment of polarized epithelia and vectorial transport across membranes during development also influences drug pharmacokinetics. Furthermore, transporter expression may be a marker of tissue differentiation as newborns develop. Although beyond the scope of this discussion, it is important to consider alterations in transport isoforms with advanced age. There are limited studies addressing transporter expression in older rodents and/or patients.

VII. Regulation of Hepatic Transporters by Xenobiotic-Activated Transcription Factors

A number of transporters are relatively highly expressed in mouse and human livers including Ntcp, Oatp1a1, -1a4, -1b2 (and their human orthologs) as well as Mrp2, Abcg5/8, Mdr2, Bcrp, and Bsep. Other transporters (Mrp3, Mrp4, Ostα, and Ostβ) are expressed at lower levels but have the potential to be induced by chemicals or during pathological conditions. Early work by our laboratory demonstrated that xenobiotics known to induce microsomal enzyme activity also altered the hepatobiliary disposition of chemicals (Klaassen, 1970, 1974, 1976). Although induction of drug metabolizing enzymes is an important pharmacological phenomenon, differential expression of hepatobiliary transporters after chemical treatment also contributes to changes in drug disposition. Coordinated up-regulation of drug-metabolizing enzymes and transporters is mediated by a number of hepatic transcription factors and has been discussed in greater detail in previous review articles (Handschin and Meyer, 2003; Klaassen and Slitt, 2005; Xu et al., 2005). Transcription factor-mediated up-regulation of hepatobiliary transporters has been reported to be mediated by the aryl hydrocarbon receptor (AhR), constitutive androstane receptor (CAR, NR1I3), pregnane X receptor (PXR, NR1I2), peroxisome proliferator-activated receptor (PPAR, NR1C1), and farnesoid X receptor (FXR, NR1H4). These receptors (with the exception of AhR) function by heterodimerizing with the retinoid X receptor α (RXRα, NR2B1). Other transcription factors involved in transporter regulation include the oxidative stress sensor, NFE2-related factor 2 (Nrf2, NFE2L2) and the liver-specific regulators known as hepatocyte nuclear factors (HNF). Mice lacking these transcription factors have been developed and are useful tools in evaluating the physiological and chemical regulation of transporters (Fig. 21, Table 24).

A. Aryl Hydrocarbon Receptor

AhR is a transcription factor that typically resides in an inactive form in the cytosol. In response to ligand binding to chemicals, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), AhR dissociates from repressive chaperones and translocates to the nucleus, where it dimerizes with the AhR nuclear translocator, resulting in gene transcription. AhR binds to xenobiotic responsive elements and mediates the induction of cytochrome P450 1A1 by TCDD (Whitlock et al., 1989). In addition to

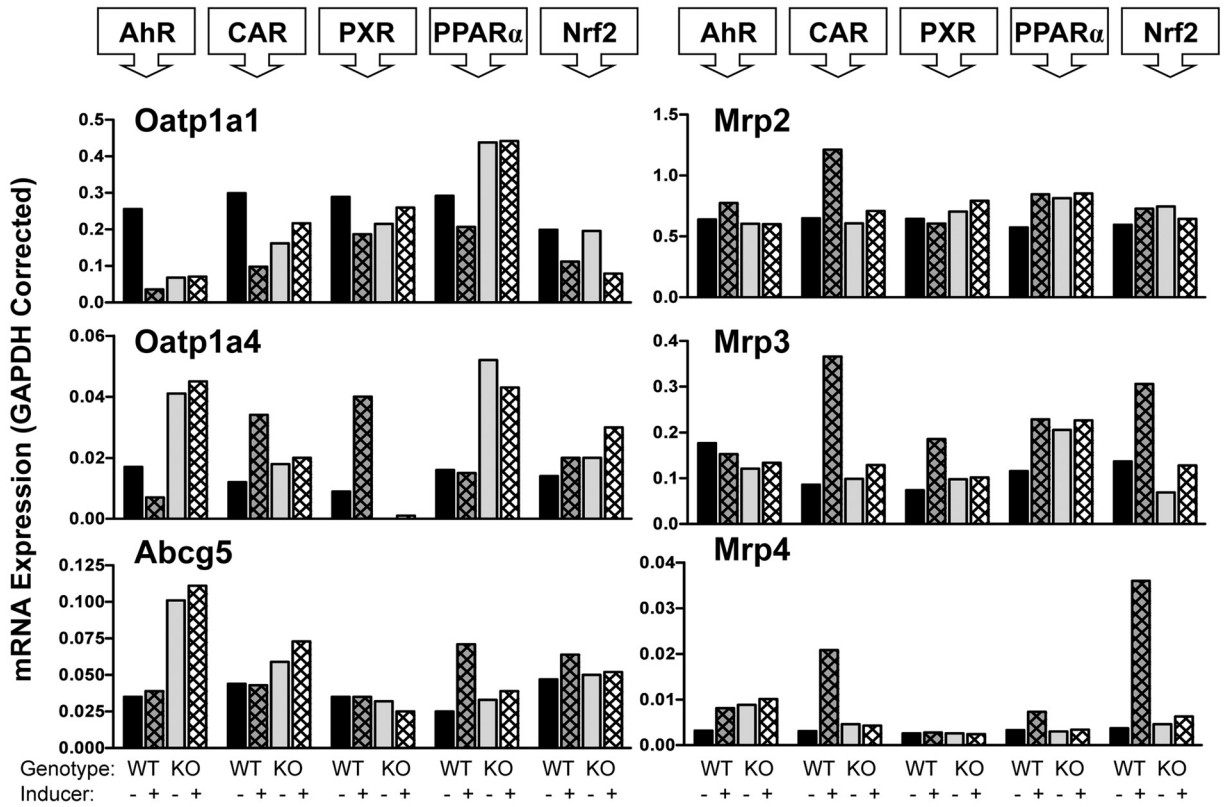

FIG. 21. Hepatic transporter mRNA expression in male transcription factor-null mice after chemical inducer treatment. Wild-type (WT) and knockout (KO) mice lacking AhR, CAR, PXR, PPARα, and Nrf2 were treated for 4 days with prototypical inducers (or corn oil vehicle) for each transcription factor. WT and AhR-null mice were administered TCDD (40 μg/kg i.p.). WT and CAR-null mice were administered TCPOBOP (300 μg/kg i.p.). WT and Nrf2-null mice were administered oltipraz (150 mg/kg i.p.). WT and PPARα-null mice were administered clofibrate (500 mg/kg i.p.). WT and PXR-null mice were administered PCN (200 mg/kg i.p.). Livers were removed 24 h after the final chemical inducer treatment. Transporter mRNA expression was quantified using multiplex mRNA expression analysis.

TCDD, other AhR ligands include polychlorinated biphenyls, 3-methylcholanthrene, and β-naphthoflavone (Safe et al., 1985; Köhle and Bock, 2006). AhR ligands elevate hepatic expression of Mrps as well as Oatp2b1 and -3a1 mRNA in mice and decrease Oatp1a4 mRNA in rats (Figs. 21 and 22) (Rausch-Derra et al., 2001; Guo et al., 2002a; Cheng et al., 2005b; Maher et al., 2005a). Down-regulation of hepatic Oatp1a1 and -1a4 mRNA in mouse livers by TCDD is dependent upon AhR expression as demonstrated in Fig. 21 (Cheng et al., 2005b). It is noteworthy that AhR-null mice have elevated constitutive expression of Oatp1a4 and Abcg5 mRNA (Fig. 21). Furthermore, exposure of human hepatocytes to TCDD increases mRNA levels of MDR1 and represses BSEP, OCT1, OATP1B1, OATP1B3, OAT2, and NTCP (Fig. 22) (Jigorel et al., 2006).

B. Constitutive Androstane Receptor

CAR is a nuclear hormone receptor that is responsible for detoxifying xenobiotics. As its name implies, CAR is constitutively active in the absence of administered ligand but can be regulated by chemical agonists and inverse agonists. Upon ligand activation, CAR translocates to the nucleus where it heterodimerizes with RXRα and transactivates genes containing the phenobarbital response element and various direct repeat sites (Masahiko and Honkakoski, 2000; Handschin and Meyer, 2003). Isoforms from the cytochrome P450 2B subfamily are associated with CAR activation in rodents and humans (Wang and Negishi, 2003). There are numerous CAR activators with differential affinity and activity for rodent and human CAR and include phenobarbital, 1,4-bis-[2-(3,5,dichloropyridyloxy)] benzene (TCPOBOP), diallyl sulfide, and *trans*-stilbene oxide (Klaassen and Slitt, 2005).

CAR ligands reduce expression of Oatp1a1 mRNA and increase Oatp1a4 and Mrp2–6 mRNA in rat and mouse livers (Fig. 22) (Cherrington et al., 2002; Guo et al., 2002a; Xiong et al., 2002; Cheng et al., 2005b; Maher et al., 2005a; Petrick and Klaassen, 2007). Induction of Oatp1a4 mRNA as well as Mrp2–4 mRNA in livers of mice treated with TCPOBOP is absent in CAR-null mice (Fig. 21) (Maglich et al., 2002). It is noteworthy that phenobarbital induces mouse Mrp3 mRNA independent of CAR (Cherrington et al., 2003), whereas Mrp3 induction in this model depends upon RXRα expression and function (Cherrington et al., 2003).

Incubation of human liver slices with phenobarbital increases the mRNA expression of efflux transporters (BSEP, BCRP, MRP2, MRP3, MDR1) and decreases lev-

	Uptake Transporters		Efflux Transporters	
	Rodent In vivo	Human In vitro	Rodent In vivo	Human In vitro
AhR	↓ Oatp1a1 ↓ Oatp1a4 ↑ Oatp2b1 ↑ Oatp3a1	↓ NTCP ↓ OATP1B1 ↓ OATP1B3 ↓ OAT2 ↓ OCT1		↓ BSEP ↑ MDR1
CAR	↓ Oatp1a1 ↑ Oatp1a4	↓ NTCP ↓ OATP1B3 ↓ OAT2 ↓ OCT1	↑ Mrp2-6	↑ MRP2-3 ↑ BSEP ↑ MDR1 ↑ BCRP
PXR	↑ Oatp1a4	↓ NTCP ↑ OATP1A2 ↓ OAT2 ↓ OCT1	↑ Mrp3 ↑ Mdr1a/1b ↑ Abca1 ↑ Abcg5/8	↑ MRP2-3 ↑ MDR1 ↓ BSEP ↑ BCRP
PPARα	↓ Oatp1a1 ↓ Oatp1a6 ↓ Oatp2a1 ↓ Oatp4a1 ↑ Octn1-2		↑ Mrp3-4 ↑ Mdr1a/1b ↑ Mdr2 ↑ Bcrp	
FXR	↓ Ntcp	↑ OATP1B3	↑ Bsep ↑ Mrp2 ↑ Ostα/β	↑ BSEP

FIG. 22. Transporter regulation by the AhR, CAR, PXR, PPARα, and FXR transcription factors. Hepatic mRNA and/or protein expression of rodent (in vivo studies) and human (in vitro studies) transporters is increased (↑) or decreased (↓) in response to transcription factor activation.

els of uptake transporters (OCT1, OATP1B3, OAT2, NTCP) (Kiuchi et al., 1998; Jigorel et al., 2006; Olinga et al., 2008; Richert et al., 2009). In addition, constitutive levels of MRP2 mRNA in normal human livers correlates with CAR mRNA expression (Aleksunes et al., 2009). These findings correspond with the known induction of Mrp2 mRNA in phenobarbital-exposed rat hepatocytes (Kast et al., 2002).

C. Pregnane X Receptor

PXR is a major chemical sensor known to activate expression of cytochrome P450 3A enzymes in humans and rodents. Foreign substances (ligands) trigger PXR heterodimerization with RXRα and binding to response elements in the promoter/enhancer regions of genes involved in detoxification and transport (Staudinger et al., 2001a). The ability of CAR and PXR to coordinately regulate expression of metabolic and transport genes has been linked to pharmacological protection of the liver in a variety of pathological models including bile acid toxicity (Staudinger et al., 2001b; Zhang et al., 2004c; Stedman et al., 2005; Uppal et al., 2005).

Treatment of mice and rats with PXR ligands such as pregnenolone-16α-carbonitrile (PCN) increases mRNA expression of Oatp1a4 in liver (Fig. 22) (Rausch-Derra et al., 2001; Guo et al., 2002a; Cheng et al., 2005b; Cheng and Klaassen, 2006). Up-regulation of Oatp1a4 mRNA is absent in livers from PXR-null mice (Fig. 21) (Staudinger et al., 2001b, 2003; Cheng and Klaassen, 2006). In addition to Oatp1a4, PCN increases Mrp3, Mdr1a, and Mdr1b mRNA in liver and Abca1, Mdr1a, and Mrp2 mRNA in the small intestines of wild-type mice but not in mice lacking PXR expression (Figs. 21 and 22) (Maglich et al., 2002; Staudinger et al., 2003; Teng et al., 2003; Maher et al., 2005a; Cheng and Klaassen, 2006). A wide range of PXR agonists transactivate the *Abcc3* (Mrp3) gene (Teng et al., 2003). Furthermore, the fact that PXR ligands alter mRNA expression of Abca1 as well as Abcg5 and -g8 in human and rodent cells suggests that this receptor can regulate cholesterol trafficking (Dieter et al., 2004; Sporstøl et al., 2005).

Not all of the effects of PXR ligands are observed at the transcriptional level. In fact, PCN treatment increases Mrp2 protein expression in rat livers in the absence of mRNA changes (Johnson and Klaassen, 2002). Increases in Mrp2 protein after PCN are due to de novo protein synthesis and not to changes in mRNA stability or protein degradation (Jones et al., 2005). Whether PXR is specifically involved in this response is not known. Additional studies have focused upon the translational regulation of MRP2 and provide insight into the mechanisms the role(s) of various open reading frames (Zhang et al., 2007b, 2009).

PXR activation can up-regulate human MDR1 expression in hepatocytes and intestinal cells in vitro (Synold et al., 2001). Using human liver slices and hepatocytes, it was demonstrated that rifampicin (a PXR ligand) induces MRP2, MRP3, BCRP, and MDR1 mRNA (Fig. 22) (Kast et al., 2002; Jigorel et al., 2006; Olinga et al., 2008; Richert et al., 2009). Exposure of human breast cancer cells to rifampin increases OATP1A2 mRNA levels (Meyer zu Schwabedissen et al., 2008). In addition, rifampicin decreases human BSEP, OCT1, OAT2, and NTCP (Jigorel et al., 2006). More recent work demonstrates the ability of various PXR ligands to alter OATP1B1 and -1B3-mediated transport, which may result in drug-drug interactions at the transporter level (Gui et al., 2008).

D. Peroxisome Proliferator-Activated Receptor

PPARs are a group of nuclear receptors that are important for cell differentiation and metabolism (notably, carbohydrates and lipids). The three main PPAR isoforms include α, γ, and δ (often termed β). Endogenous ligands for PPARs include free fatty acids and eicosanoids (Dreyer et al., 1993; Wahli et al., 1999). The name of this class of receptors reflects the fact that chemicals that activate PPAR isoforms increase the number and size of peroxisomes in cells (Dreyer et al.,

1992). Pharmacological activation of the α and γ isoforms can be achieved by fibrate and thiazolidinedione drugs, respectively (Willson and Wahli, 1997). In addition to fibrate drugs (such as clofibrate and ciprofibrate), PPARα is also activated by a number of environmental chemicals, including phthalates [plasticizers such as di(2-ethylhexyl) phthalate] and perfluorinated fatty acids [stain- and heat-resistant chemicals such as perfluorooctanoic acid and perfluorodecanoic acid (PFDA)]. Like CAR and PXR, PPARs heterodimerize with RXRα and bind to peroxisome proliferator response elements in the promoter regions of genes (Dreyer et al., 1993). Of the drug-metabolizing enzymes, the cytochrome P450 4A subfamily is most sensitive to PPAR signaling (Johnson et al., 1996).

The development of PPARα-null mice has greatly enhanced investigations into the regulation of transporters by various exogenous ligands. PPARα ligands decrease expression of multiple Oatp isoforms in mouse livers (Cheng et al., 2005b). Down-regulation of Oatp1a1 mRNA by clofibrate is observed in wild-type but not in PPARα-null mice (Figs. 21 and 22). It is noteworthy that Oatp1a4 mRNA is not altered by clofibrate administration but is more highly expressed in PPARα-null mice (Fig. 21). Treatment of mice with clofibrate increases Mdr1a, Bcrp, Mrp3, and Mrp4 mRNA in a PPARα-dependent manner (Figs. 21 and 22) (Maher et al., 2005a; Moffit et al., 2006). Like clofibrate, ciprofibrate differentially alters transporter expression. Ciprofibrate increases Mdr1a, -1b, and -2 mRNA and protein in wild-type mouse livers but not in PPARα-null mice (Fig. 22) (Kok et al., 2003). In addition, ciprofibrate decreases Bsep, Oatp1a1, and Ntcp protein expression in a PPARα-dependent manner (Kok et al., 2003). Likewise, the perfluorinated chemicals perfluorooctanoic acid and PFDA decrease mRNA levels of Oatp1a1, -1a4, -1b2, and Ntcp (PFDA only) and increase Mrp3 and Mrp4 (Cheng and Klaassen, 2008; Maher et al., 2008). It is noteworthy that these changes are absent in PPARα-null mice treated with PFDA (Cheng and Klaassen, 2008; Maher et al., 2008). PPARα agonists also increase hepatic Bcrp mRNA in a PPARα-dependent manner (Hirai et al., 2007). Taken together, these findings from null mice demonstrate similarity among PPARα agonists in their regulation of hepatobiliary transporters.

In addition to regulating transporters involved in drug disposition, PPARα is important for controlling carnitine homeostasis. Hepatic and intestinal carnitine levels are increased after PPARα agonist (clofibrate and Wy14643) treatment of rodents and pigs (van Vlies et al., 2007; Ringseis et al., 2008). Increased carnitine levels are due to enhanced carnitine biosynthesis and uptake (Ringseis et al., 2008). Treatment of mice with PPARα agonists increase hepatic and intestinal Octn2 mRNA expression and carnitine levels in wild-type mice but not in PPARα-null mice (Fig. 22) (Ringseis et al., 2007; Maeda et al., 2008). Clofibrate up-regulates Octn1 (liver) and Octn2 mRNA (liver, duodenum, jejunum) in mice (Fig. 22) (Ringseis et al., 2007). Likewise, fibrate drugs elevate Octn2 mRNA in rat hepatocytes (Maeda et al., 2008). In line with these findings, freshly isolated hepatocytes from fenofibrate-treated rats demonstrate increased [^{3}H]carnitine uptake (Maeda et al., 2008).

E. Farnesoid X Receptor

FXR is an intracellular bile acid sensor that controls bile acid and lipid homeostasis. By coordinately regulating bile acid synthesis and transport, FXR signaling provides one mechanism for reducing the bile acid burden of liver. FXR heterodimerizes with RXRα and binds to inverted nucleotide repeat motifs in the promoter sequences of *SLCO1B3* (OATP1B3) and *ABCB11* (BSEP) (Fig. 22) (Ananthanarayanan et al., 2001; Jung et al., 2002a). Inverted repeat response elements are essential for transactivation of the *SLCO1B3* and *ABCB11* promoters in response to bile acids (Ananthanarayanan et al., 2001; Jung et al., 2002a). Functional transactivation of the *SLCO1B3* gene has been demonstrated in hepatocyte-derived cells incubated with bile acids (Ohtsuka et al., 2006). Furthermore, a polymorphism in the FXR promoter corresponds with reduced hepatic mRNA expression of human OATP1B1 and -1B3 (Marzolini et al., 2007). In addition to human OATP1B3 and BSEP, the rat Mrp2 promoter can be transactivated by FXR and its ligands (Fig. 22) (Kast et al., 2002).

Additional clues for identifying transporters regulated by FXR can be ascertained from FXR-null mice. FXR-null mice have reduced levels of hepatic Bsep mRNA and renal Oat3, Oatp1a1, Oatp1a4, Oct2, and Octn1 mRNA (Maeda et al., 2004).

Bile acids stimulate FXR and induce expression of the small heterodimer partner (Shp, NR0B2), which in turn down-regulates Ntcp gene expression in isolated hepatocytes (Denson et al., 2001). Likewise, bile acid treatment and bile-duct ligation repress Ntcp mRNA in wild-type, but not FXR-null mice (Zollner et al., 2005). At the same time, FXR is responsible for the bile acid and oxysterol-induced transactivation of the *Abcb11*/*ABCB11* (Bsep/BSEP) gene in mouse liver (Maeda et al., 2004) and hepatocytes (Plass et al., 2002; Deng et al., 2006). Impaired regulation of Bsep mRNA in FXR-null mice during intrahepatic cholestasis probably contributes to increased hepatic necrosis observed in these animals (Zollner et al., 2003; Cui et al., 2009b). In addition to Ntcp and Bsep, the other bile acid transporters Ostα and Ostβ are regulated by FXR (Fig. 22). In 2006, Ostα and β were identified as novel FXR targets (Boyer et al., 2006; Zollner et al., 2006). Feeding with bile acids increases Ostα and β in livers, kidneys, and ilea of wild-type mice but not FXR-null mice (Zollner et al., 2006). Similar results have been observed in wild-type and FXR-null mice after bile-duct ligation (Boyer et al., 2006). Ostα contains two functional FXR binding motifs, whereas only one motif is found in the *Ost*β gene (Landrier et al.,

2006). Finally, the fibroblast growth factors 15 and 19, which are FXR target genes, repress the expression of Asbt protein in mouse ileum and gallbladder and in human cholangiocarcinoma cells (Sinha et al., 2008). Secondary signaling of FXR via fibroblast growth factors may be important in the regulation of additional hepatic and ileal transporters.

F. Hepatocyte Nuclear Factors

HNF1α and -4α are liver-enriched transcription factors that regulate the basal expression of many genes and are commonly referred to as "master" transcription factors because of their ability to regulate other nuclear receptors and transcription factors. HNF1α is expressed in livers, kidneys, intestines, and stomach and is implicated in the regulation of bile acid, fatty acid, and drug metabolism.

To better characterize additional roles for HNF1α in regulating transporters, hepatic, renal, and intestinal expression of xenobiotic and bile acid transporters was quantified in HNF1α-null mice (Maher et al., 2006c; Kikuchi et al., 2007) (Table 24). The most dramatic changes in mRNA expression in HNF1α-null mice include down-regulation of hepatic Oatp1a1, 1b2, and Asbt and renal Urat1, Oat1, Oat2, and Oat3 (Shih et al., 2001; Maher et al., 2006c; Kikuchi et al., 2007). A number of genes are up-regulated in HNF1α-null mice including hepatic Mrp4, Oatp1a4, renal Mrp3, Mrp4, Mdr1a, Mdr1b, Abcg5, as well as duodenal Oat3 and Mdr1a (Maher et al., 2006c). Up-regulation of these transporters may reflect repression by HNF1α or compensation to hepatic dysfunction in HNF1α-null mice.

TABLE 24
Expression of liver, kidney, and duodenal transporters in HNF1α-null mice

Differences in transporter mRNA between wild-type and HNF1α-null mice in liver, kidneys, and duodenum.

	Liver	Kidney	Duodenum
Oat1	↔	↓	N.D.
Oat2	↓	↓	N.D.
Oat3	↔	↓	↑
Urat	N.D.	↓	N.D.
Oatp1a1	↓	↓	N.D.
Oatp1a4	↑	↔	N.D.
Oatp1a5	↓	N.D.	N.D.
Oatp1a6	N.D.	↑	N.D.
Oatp1b2	↓	↔	N.D.
Oatp2a1	↔	↔	↓
Oatp2b1	↓	↑	↔
Oatp3a1	N.D.	↓	N.D.
Oatp4c1	N.D.	↑	N.D.
Oct1	↔	↔	↓
Oct2	↑	↑	↔
Oct3	↑	↔	↔
Octn1	↔	↔	↔
Octn2	↑	↓	↔
Octn3	↔	↓	↔
Mrp1	↔	↑	↔
Mrp2	↔	↑	↔
Mrp3	↔	↑	↔
Mrp4	↑	↑	↔
Mrp5	↑	↑	↔
Mrp6	↓	↔	↓
Mdr1a	↑	↑	↑
Mdr1b	↔	↑	N.D.
Mdr2	↑	↑	N.D.
Ntcp	↔	↔	N.D.
Bsep	↓	↔	N.D.
Asbt	↓	↓	↔
Bcrp	↔	↔	↔
Abcg5	↔	↑	↑
Abcg8	↔	↔	↓

↑, increased mRNA levels in HNF1α-null mice; ↓, mRNA levels in HNF1α-null mice; ↔, no change in mRNA levels between genotypes; N.D., not determined.

Regulation of Ntcp and Oatp genes by HNF1α may be one mechanism for the liver-predominant expression of these transporters. Moreover, HNF1α seems to regulate these uptake transporters during various pathological conditions of the liver. Rats treated with carbon tetrachloride, endotoxin, or 17α-ethinylestradiol have reduced hepatic HNF1α binding activity and lower Ntcp mRNA levels (Trauner et al., 1998; Geier et al., 2002, 2003a). HNF1α seems to be important in modulating rat Ntcp but not the mouse or human genes (Fig. 23) (Karpen et al., 1996; Jung et al., 2004). HNF1α binding to the mouse Oatp1b2 promoter is decreased within 2 h after endotoxin administration (Li and Klaassen, 2004). HNF1α-mediated regulation of hepatic bile acid and organic anion transport probably has implications in enterohepatic recirculation under basal and pathological conditions.

HNF1α and 1β positively regulate OAT1, OAT3, URAT1, OATP1B1, and OATP1B3 by directly binding to and transactivating their promoters (Fig. 23) (Jung et al., 2001; Kikuchi et al., 2006, 2007; Ohtsuka et al., 2006; Furihata et al., 2007; Saji et al., 2008). Furthermore, OATP1B1 mRNA levels correlate with *HNF1α* gene expression in livers from adult Japanese subjects (Furihata et al., 2007). In addition, a polymorphism in the proximal promoter of human CNT2 increases the binding and transactivation of HNF1α and -1β (Yee et al., 2009).

Like HNF1α, HNF4α is important in regulating drug transporters. HNF4α binds to response elements and transactivates the promoters of the *CNT1*, *OCT1*, *OAT1*, and *OAT2* genes (Fig. 23) (Popowski et al., 2005; Saborowski et al., 2006; Ogasawara et al., 2007; Klein et al., 2009). Likewise, HNF4α increases mouse Ntcp promoter transactivation in cultured cells by binding to a conserved distal *cis*-element (Geier et al., 2008). In addition, down-regulation of HNF4α using small interfering RNA suppresses Ntcp RNA expression up to 95% in mouse Hepa1–6 cells (Geier et al., 2008) and reduces MDR1, BSEP, MRP2, OATP1B1, and OCT1 mRNA in human hepatocytes (Kamiyama et al., 2007). Taken together, these data suggest that HNF1α and -4α are master regulators for the expression of hepatic drug and bile acid transporters and they may be important determinants for interindividual variation in drug pharmacokinetics (Wortham et al., 2007).

G. Nuclear Factor-E2-Related Factor 2

Nrf2 belongs to the basic region-leucine zipper family of transcription factors and is activated in response to

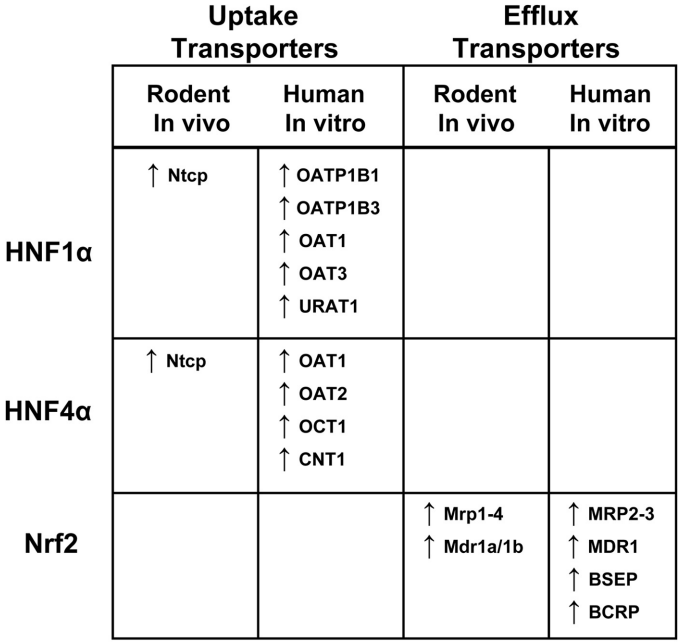

FIG. 23. Transporter regulation by the HNF1α, HNF4α, and Nrf2 transcription factors. Hepatic mRNA and/or protein expression of rodent (in vivo studies) and human (in vitro studies) transporters is increased (↑) or decreased (↓) in response to transcription factor activation.

electrophiles and oxidative stress. During periods of oxidative stress, Nrf2 is released from sequestration in the cytoplasm and translocates to the nucleus. Nrf2 binds antioxidant response elements in the regulatory regions of target genes and activates transcription (Aleksunes and Manautou, 2007). NADPH:quinone oxidoreductase 1 is a prototypical target gene of Nrf2 signaling (Venugopal and Jaiswal, 1996; Nioi et al., 2003). Antioxidant response element sequences have been identified in mouse *Abcc1–4* (Mrp1–4) promoters (Fig. 23) (Hayashi et al., 2003; Vollrath et al., 2006; Maher et al., 2007). Treatment of mice with Nrf2-activating chemicals coordinately induces hepatic Mrp2–6 mRNA (Maher et al., 2005a, 2007) and some Oatp isoforms (Cheng et al., 2005b). The Nrf2 activator oltipraz induces Mrp3, Mrp4, Mdr1a, and Mdr1b mRNA in rat livers (Cherrington et al., 2002; Merrell et al., 2008) and MDR1, MRP2, MRP3, and BCRP in human hepatocytes (Fig. 23) (Jigorel et al., 2006). Small interfering RNA knockdown of Nrf2 in HepG2 cells prevents pharmacological induction of MRP2 mRNA (Adachi et al., 2007). Likewise, induction of BSEP mRNA and protein expression in HepG2 cells after oltipraz treatment is attenuated when small interfering RNAs are used to lower NRF2 expression (Weerachayaphorn et al., 2009). In addition, up-regulation of liver Mrp3 and 4 mRNA and protein after oltipraz treatment is observed in wild-type, but not Nrf2-null mice (Fig. 21) (Maher et al., 2007). Induction of Mrp3 and Mrp4 mRNA and protein during hepatotoxicity has also been shown to be dependent upon Nrf2 expression (Aleksunes et al., 2008c; Maher et al., 2008; Okada et al., 2008). There is additional evidence that Nrf2 can work in concert with CAR to regulate metabolism and transport (Slitt et al., 2006).

Mice with low expression of the Nrf2 repressor protein Kelch-like ECH-associated protein 1 (Keap1), not only have higher Nrf2 activation, but also elevated levels of Mrp2–4 mRNA and protein (Okada et al., 2008; Reisman et al., 2009b). Increased Mrp2–4 expression in Keap1-knockdown mice has functional consequences in the disposition of acetaminophen conjugates (Reisman et al., 2009a). Regulation of Mrp transporters via Nrf2 suggests that enhanced efflux is a component of the coordinated response to cellular oxidative stress.

VIII. Regulation of Hepatic Transporters in Pathophysiological Conditions

Transporters are highly expressed on hepatocytes and cholangiocytes and, in turn, are quite important in the biotransformation and disposition of toxicants. This section discusses the regulation of drug transporters in the liver in response to a variety of pathological conditions. It is generally thought that differential changes in the mRNA, protein, and/or function of transporters in damaged livers are an adaptive response to reduce cellular accumulation of substrates. Evidence supporting this notion includes the similar patterns of transporter expression among diverse conditions including cholestasis, drug-induced hepatotoxicity, liver regeneration, and ischemia-reperfusion injury (Fig. 24). There are likely to be consequences for changes in transporter expression and function. One possibility is drug-disease interactions in which a pathological condition alters the expression of a particular transporter responsible for the excretion of one of the patient's medications. In addition, this section provides examples of how transporters influence susceptibility to liver injury either by interfering with endogenous systems (such as bile acid transport) or directly altering uptake or efflux of toxicants from the liver.

A. Acetaminophen Hepatotoxicity

Acetaminophen (APAP) hepatotoxicity is the leading cause of drug-induced liver failure in the United States. APAP is a commonly used analgesic and antipyretic that is safe when taken at therapeutic doses. When suprathrapeutic doses are ingested, detoxification pathways (sulfation and glucuronidation) can be overwhelmed, and APAP is bioactivated by cytochrome P450 enzymes to a toxic, reactive metabolite. The reactive APAP electrophile is detoxified by conjugation with glutathione; however, when intracellular glutathione stores are depleted, the metabolite reacts with sulfhydryl groups of cellular proteins. The formation of protein covalent adducts, in addition to oxidative stress, results in centrilobular hepatocyte damage that can ultimately lead to fulminant hepatic failure.

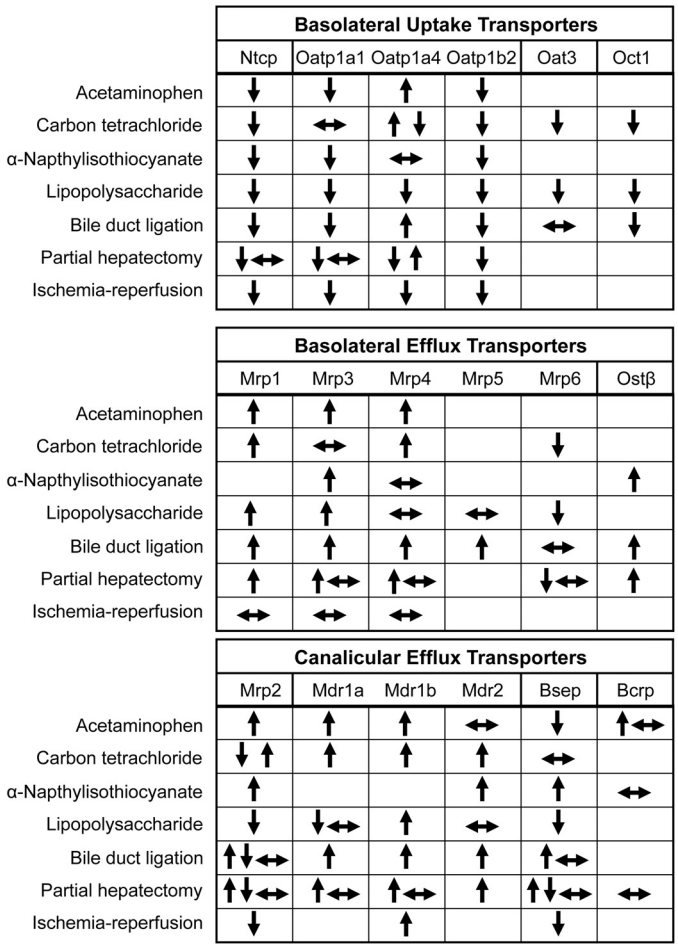

FIG. 24. Pathophysiological regulation of hepatic transporters. Hepatic mRNA and/or protein expression of rodent uptake and efflux transporters is increased (↑), decreased (↓), and/or unchanged (↔) in response to various toxicants and pathological conditions. The time points at which mRNA and protein transporter changes are observed vary among experimental models.

Because of the similar responses of rodents and humans to APAP, laboratory animals have been used to study the effects of chemical-induced liver injury on transporter expression and function. In general, hepatobiliary transporters are similarly regulated in rodents and humans in response to APAP. Exposure of rats to APAP increases hepatic Mrp2 and Pgp protein expression (Ghanem et al., 2004). Administration of a single toxic dose of APAP to mice lowers mRNA expression of the basolateral uptake transporters Oatp1a1, Oatp1b2, and Ntcp (Aleksunes et al., 2005, 2007). Concurrently, basolateral (Mrp1, Mrp3, Mrp4) and canalicular (Mrp2, Mdr1a, Mdr1b) efflux transporter mRNA levels are elevated in APAP-treated mice (Aleksunes et al., 2005, 2007). Protein expression patterns mirror mRNA changes. Livers from APAP-treated mice exhibit reduced Oatp1a1, Oatp1b2, and Ntcp and increased Mrp2, Mrp3, and Mrp4 protein expression (Aleksunes et al., 2006; Campion et al., 2008). It is noteworthy that Mrp3 and Mrp4 proteins are selectively up-regulated in hepatocytes surrounding the central vein and adjacent to regions of hepatic damage (Aleksunes et al., 2006). In these studies, transporter expression was largely unchanged by nonhepatotoxic APAP doses, suggesting a dependence on hepatic injury to alter transporter levels (Aleksunes et al., 2005). Like rats and mice, explant liver specimens from patients with fulminant hepatic failure caused by APAP exhibit elevated expression of efflux transporters. Human MRP1 and MRP4 mRNA levels are significantly higher in liver specimens from APAP overdoses compared with normal liver controls (Barnes et al., 2007). In addition, MRP4, MRP5, BCRP, and Pgp proteins are increased in livers from patients after APAP overdose.

A single low dose of APAP protects rodents against a subsequent higher dose of APAP (a process known as autoprotection) (Aleksunes et al., 2008a). It is noteworthy that Mrp4 up-regulation is localized to proliferating hepatocytes and may contribute to APAP resistance in mice (Aleksunes et al., 2008a). Interruption of hepatocyte proliferation using an antimitotic chemical not only inhibits APAP autoprotection, but also prevents induction of Mrp4 (Aleksunes et al., 2008a). Functional studies to dissect the role of Mrp4 in APAP hepatotoxicity are under way, although it is purported that Mrp4 may reduce hepatotoxicity by removing byproducts of cellular injury and/or facilitating hepatocyte recovery by exporting signaling molecules to adjacent hepatocytes and nonparenchymal cells. This hypothesis is supported by the fact that Kupffer cells participate not only in protecting the liver from APAP toxicity but also in up-regulating hepatocellular Mrp4 protein (Campion et al., 2008). Work by Ghanem et al. (2005) has provided an additional explanation for APAP autoprotection in rodents. Pretreatment of rats with increasing doses of APAP alters the excretion of the final high dose of APAP and corresponds to reduced hepatotoxicity (compared with rats receiving only the high dose). Up-regulation of Mrp3 in response to APAP pretreatment shifts excretion of APAP-glucuronide from bile to urine (Ghanem et al., 2005). Using Mrp3-null mice, APAP-glucuronide has been shown to be an in vivo substrate for Mrp3 (Manautou et al., 2005; Zamek-Gliszczynski et al., 2006). More recently, it has been suggested that the diversion of APAP-glucuronide from bile to urine by Mrp3 prevents the enterohepatic recirculation of APAP and reduces exposure of the liver to APAP (Ghanem et al., 2009). Likewise, rat Mrp3 is induced in other pathological conditions such as nonalcoholic fatty liver disease (induced by a methionine and choline-deficient diet) and bile-duct ligation (Lickteig et al., 2007a; Villanueva et al., 2008). Induction of Mrp3 protein in both models corresponds with higher urinary excretion of APAP-glucuronide in rats (Lickteig et al., 2007a; Villanueva et al., 2008). These studies collectively point to potentially novel roles for Mrp3 and Mrp4 transporters in liver adaptation to APAP hepatotoxicity.

B. Carbon Tetrachloride Hepatotoxicity

Carbon tetrachloride (CCl_4) is a chemical that was previously used as a dry-cleaning solvent, a refrigerant, and a fire retardant. Its industrial use has been largely abandoned because of well documented adverse health effects, including centrilobular hepatotoxicity. CCl_4 is bioactivated to a highly reactive free radical that stimulates lipid peroxidation and subsequent hepatocyte damage (Manibusan et al., 2007).

Like APAP, CCl_4 influences the expression of hepatobiliary transporters. Messenger RNA and/or protein expression of uptake transporters (Ntcp, Oatp1a1, Oatp1b2, Oat3, Oct1) is decreased in mouse and rat livers after CCl_4 (Geier et al., 2002; Aleksunes et al., 2005; Okumura et al., 2007). Meanwhile, CCl_4 increases canalicular efflux transporters (Mdr1a, Mdr1b, Mdr2) mRNA and/or protein expression in rat livers that corresponds with enhanced transport activity (Nakatsukasa et al., 1993; Song et al., 2003; Minami et al., 2005; Okumura et al., 2007). Administration of a single hepatotoxic dose of CCl_4 to mice increases Mrp2 mRNA, whereas multiple low doses of CCl_4 in rats reduce hepatic Mrp2 mRNA (Aleksunes et al., 2006; Okumura et al., 2007). On the basolateral membrane, Mrp1 and Mrp4 are elevated in livers of CCl_4-treated mice and rats (Aleksunes et al., 2006; Okumura et al., 2007). Similar to the immunostaining distribution of Mrp4 protein in APAP livers, up-regulation of Mrp4 protein after CCl_4 exposure is observed on hepatocytes adjacent to the central vein (Aleksunes et al., 2006). It is noteworthy that enhanced Mrp1 staining in rat livers exposed to CCl_4 for 2 weeks is not only localized to hepatocytes but also to stellate cells (Hannivoort et al., 2008). Therefore, expression of efflux transporters in multiple cell types and in different regions may be important in recovery of the liver from chemical injury. More data in rodent and human livers after chemical-induced injury may help to delineate the extent of transporter changes with varying degrees of hepatotoxicity.

C. α-Naphthylisothiocyanate Cholestasis

Cholestasis is the disruption of bile flow that can occur at the cellular level of the hepatocyte, at the level of the intrahepatic biliary ductules, or as a result of extrahepatic obstruction of the bile ducts. Interruption of bile flow leads to the accumulation of bile acids and other bile components in hepatocytes, and ultimately hepatobiliary toxicity. Cholestasis is often designated as intrahepatic or extrahepatic (i.e., obstructive), depending upon the etiology.

α-Naphthylisothiocyanate (ANIT) damages bile ductules and causes intrahepatic cholestasis in rodents. After glutathione conjugation, ANIT is transported into bile by Mrp2 (Dietrich et al., 2001b). Upon release into the bile, ANIT-glutathione rapidly dissociates, and ANIT injures bile duct epithelial cells. Damage to the biliary tract reduces bile flow leading to hepatic accumulation of bile acids and subsequent hepatocyte necrosis and neutrophil infiltration. In addition, ANIT can be reabsorbed into the cell and again conjugated with glutathione leading to depletion of glutathione within the cell.

Because glutathione conjugates have a high affinity for Mrp2 transport, it was not surprising that rats lacking Mrp2 are protected from ANIT-induced injury. However, it was surprising that the liver adapts to ANIT injury by up-regulating Mrp2 mRNA and protein (Cui et al., 2009b). It can be hypothesized that this response would lead to higher exposure of the biliary tract to ANIT upon a subsequent dose. A number of other canalicular (Mdr2, Bsep, Atp8b1) and basolateral transporters (Mrp3 and Ostβ) are also induced by ANIT in rodents (Ogawa et al., 2000; Liu et al., 2005; Cui et al., 2009b; Tanaka et al., 2009). Up-regulation of Mrp3 and Ostβ may redirect bile acids from bile to blood and help to limit the accumulation within hepatocytes. Likewise, Ntcp, Oatp1a1, and Oatp1b2 mRNA are down-regulated in ANIT-treated mice and rats and may aid in preventing uptake of bile acids into the liver (Ogawa et al., 2000; Liu et al., 2005; Cui et al., 2009b; Tanaka et al., 2009).

D. Lipopolysaccharide Cholestasis

One complication of systemic bacterial infections is intrahepatic cholestasis. Lipopolysaccharide (LPS), also termed endotoxin, is a component of the outer cell wall of Gram-negative bacteria that enters the liver through circulating portal blood. LPS exogenously administered to rodents impedes bile flow and biliary excretion of organic anions and leads to cholestatic liver injury. Dramatic reductions in bile flow can be observed within 6 to 12 h after LPS treatment. Because of the rapid decline in bile flow after LPS, it has been hypothesized that LPS exposure alters expression and/or function of transporters that participate in bile salt-dependent (Ntcp, Bsep) and bile salt-independent (Mrp2) bile flow. In line with this hypothesis, Ntcp mRNA is reduced in rodent livers 2 h after LPS administration (Green et al., 1996), and by 16 h, both Ntcp mRNA and protein levels are reduced to 10% of control rats (Trauner et al., 1998; Lee et al., 2000a; Geier et al., 2003b; Cherrington et al., 2004). The response of mice and humans to LPS is similar to that of rats. Down-regulation of Ntcp mRNA and protein occurs in the livers of LPS-treated mice and in human liver slices after incubation with LPS (Elferink et al., 2004; Lickteig et al., 2007b). Bile acid transport is compromised not only on the basolateral membrane, but also on the canalicular surface of rat livers. LPS down-regulates Bsep mRNA and protein in rodent livers (Vos et al., 1998; Lee et al., 2000a; Hojo et al., 2003; Cherrington et al., 2004; Lickteig et al., 2007b). As a consequence, the efflux of bile acids from canalicular plasma membrane vesicles is reduced in livers from LPS-treated rats (Moseley et al., 1996; Bolder et al., 1997).

Administration of LPS to rodents diminishes the biliary excretion of not only bile acids, but also non–bile-acid organic anions. Lower expression of Mrp2 mRNA and protein in livers of LPS-treated rodents corresponds with impaired biliary excretion of Mrp2 substrates (Bolder et al., 1997; Vos et al., 1998; Lee et al., 2000a; Geier et al., 2003b; Hojo et al., 2003; Cherrington et al., 2004; Lickteig et al., 2007b). A decline in biliary organic anion excretion in rats is observed as early as 3 h after LPS and is probably a result of rapid retrieval of Mrp2 protein from the canalicular membrane to subapical vesicles (Kubitz et al., 1999; Zinchuk et al., 2005). Using liver slices from rats, subapical staining of Mrp2 protein after in vitro LPS exposure has also been reported (Elferink et al., 2004). In contrast, MRP2 staining in human liver slices is reduced in response to LPS, but remains localized to the canaliculus with no observable redistribution to other membrane sites (Elferink et al., 2004). From these in vitro findings, it is thought that the mechanisms responsible for protein regulation and trafficking in response to LPS occur in a species-specific manner.

Impaired uptake of chemicals across the basolateral hepatocyte membrane during endotoxemia probably contributes to the compromised excretion of organic anions into bile. Likewise, reduced mRNA expression of mouse and rat Oatp1a1, -1a4, and -1b2 are observed in livers after LPS (Hartmann et al., 2002; Geier et al., 2003b; Cherrington et al., 2004; Li and Klaassen, 2004; Lickteig et al., 2007b). Likewise, mouse Oat2 and rat Oat3 mRNA are decreased after LPS (Cherrington et al., 2004; Lickteig et al., 2007b). Reduced mRNA expression of organic anion transporters is reflected functionally in lower uptake of organic anions into basolateral plasma membrane vesicles from LPS-treated rats (Bolder et al., 1997).

E. Bile-Duct Ligation

Extrahepatic cholestasis is typically observed in patients with gallstones or tumors in the common biliary tract, and it is often recapitulated in rodents by ligating the common bile duct (BDL). BDL prevents bile flow, leading to a backflow of biliary constituents, such as bile acids into hepatocytes, as early as 1 day after surgery (Slitt et al., 2007). The liver adapts to the higher burden of biliary constituents in part by altering the expression of hepatobiliary transporters. In general, BDL decreases mRNA and protein levels of uptake transporters such as Ntcp, Oatp1a1, Oatp1b2, and Oct1 (Gartung et al., 1996; Dumont et al., 1997; Denk et al., 2004a; Donner et al., 2007). Increased serum and urinary bile acid concentrations observed in rodents after BDL are due, to some extent, to decreased Ntcp and Oatp expression (Lee et al., 2001a; Zollner et al., 2002; Kamisako and Ogawa, 2005). Apart from these findings, there are a number of mouse Oatp isoforms (2b1, 4a1, 1c1) for which the mRNA expression does not change 3 days after BDL (Lickteig et al., 2007b). Two Oatp genes (1a4 and 3a1) are induced in mouse livers 3 to 7 days after BDL (Lickteig et al., 2007b; Slitt et al., 2007). Differential mRNA regulation of Oatp isoforms (decreased, increased, and unchanged) during extrahepatic cholestasis may alter the uptake of some organic anions into the liver in a selective manner.

Investigations of the regulation of canalicular transporters after BDL have yielded conflicting findings. Bsep mRNA and protein are unchanged or up-regulated in rodents after BDL (Hyogo et al., 2001; Wagner et al., 2003; Kamisako and Ogawa, 2005; Lickteig et al., 2007a; Slitt et al., 2007). Differing reports suggest that canalicular Mrp2 mRNA and protein can be increased or decreased after BDL, depending on the species (Trauner et al., 1997; Kagawa et al., 1998; Paulusma et al., 2000; Hyogo et al., 2001; Lee et al., 2001a; Wagner et al., 2003; Kamisako and Ogawa, 2005; Donner et al., 2007; Slitt et al., 2007). Mrp2 mRNA and protein are reduced in rats after BDL (Trauner et al., 1997; Kagawa et al., 1998; Paulusma et al., 2000; Donner and Keppler, 2001; Hyogo et al., 2001; Lee et al., 2001a; Denk et al., 2004b; Kamisako and Ogawa, 2005), but remain preserved or slightly increased in mouse livers (Wagner et al., 2003; Slitt et al., 2007). Additional canalicular transporters are differentially expressed after BDL. Mdr mRNA (namely, Mdr1b and Mdr2) and Pgp protein are increased in rodent livers after BDL (Accatino et al., 1996; Kagawa et al., 1998; Hyogo et al., 2001). In contrast, BDL reduces gene expression of the sterol half-transporters (Abcg5 and Abcg8) within 1 day after surgery in rats (Kamisako and Ogawa, 2005). Because BDL causes the complete interruption of bile flow and cannot be overcome, there is probably little functional consequence of compensatory up-regulation of canalicular transporters. Instead, transporter changes probably reflect a general adaptation to liver injury.

Similar to chemical-induced liver injury, basolateral efflux transporters are up-regulated after BDL and probably function as an alternate excretion pathway to prevent intracellular accumulation of bile constituents within hepatocytes and cholangiocytes. Numerous reports have demonstrated elevated mRNA and protein levels of Mrp1, -3, -4, -5, Ostα (protein only), and Ostβ (mRNA only) between 3 to 14 days after BDL (Ogawa et al., 2000; Donner and Keppler, 2001; Soroka et al., 2001; Wagner et al., 2003; Denk et al., 2004b; Kamisako and Ogawa, 2005; Boyer et al., 2006; Slitt et al., 2007). Mrp4-null mice have enhanced liver injury after BDL compared with wild-type mice (Mennone et al., 2006), suggesting that Mrp4 up-regulation is an important compensatory mechanism of the liver (Denk et al., 2004b). The adaptive up-regulation of basolateral efflux transporters entails some isoform selectivity, because Mrp6, -7, and -9 mRNA are unchanged in rodent livers after BDL.

Mrp3 is normally expressed in centrilobular hepatocytes (Aleksunes et al., 2006). In response to BDL, Mrp3

staining is enhanced in centrilobular hepatocytes and extends to periportal cells (Donner and Keppler, 2001; Soroka et al., 2001). Although Asbt mRNA and protein levels are increased approximately 3-fold in livers from rats after BDL, the intensity of Asbt protein staining on proliferating cholangiocytes is reduced (Lee et al., 2001a). One explanation for this discrepancy may be the dramatic increase in cholangiocyte proliferation (greater than 10-fold) after BDL, in effect diluting Asbt protein among a larger number of cells. Coordinated regulation of the efflux transporters Mrp3, Mrp4, Asbt, Ostα, and Ostβ in hepatocytes and cholangiocytes probably reduces the bile acid burden of the liver during extrahepatic cholestasis.

F. Partial Hepatectomy

One of the unique features of the liver is its ability to regenerate. In response to cellular loss, a number of stimuli activate normally quiescent hepatocytes to undergo cell division. Administration of nonlethal doses of toxicants, such as APAP and CCl_4, triggers parenchymal cells to undergo mitosis to repopulate the liver lobule. During severe liver injury or when hepatocyte proliferation is inhibited (using 2-acetyl-aminofluorene), a resident population of progenitor cells is activated to replace hepatocytes and cholangiocytes. In addition to toxicant exposure, hepatic regeneration can be modeled in rodents using surgical removal of 66% of the liver (partial hepatectomy; PHx). Appropriate controls for these studies are sham-operated rodents that undergo the same surgical procedure without ligation of lobes and without removal of two thirds of the liver. Within 24 to 36 h of removing three liver lobes, parenchymal cells undergo synchronized DNA synthesis and cell division. By 1 to 2 weeks, the original liver cell mass is restored and hepatocytes return to quiescence.

Within 24 h after PHx, bile flow and biliary secretion of bile acids, cholesterol (mice only), and phospholipids (mice only) in rodents are increased (Vos et al., 1999; Csanaky et al., 2009). In contrast, the secretion of glutathione into bile is reduced. It should be noted that these parameters are expressed as secretion into bile per gram of liver, rather than normalized to total body weight. Likewise, bile acid and total bilirubin levels are elevated in the plasma of rats and mice 24 h after PHx (Vos et al., 1999; Chang et al., 2004; Csanaky et al., 2009). Phenotypic changes in bile flow and the disposition of bile constituents suggest that hepatocytes adapt to cell loss by differentially regulating bile acid transporters (and possibly bile acid synthesis) to limit accumulation of toxic bile acids in remnant hepatocytes.

Compared with sham-operated control rats, remnant livers from PHx rats exhibit early reductions (3–24 h) in the mRNA expression of Oatp1a1, Oatp1a4, and Ntcp that are restored to normal levels by 2 to 4 days (Gerloff et al., 1999; Vos et al., 1999). Similar declines in Ntcp and Oatp1a4 proteins are observed at 24 h in PHx-rats (Vos et al., 1999). In contrast, Oatp1a4 mRNA and protein are elevated in mice 24 to 48 h after PHx (Csanaky et al., 2009). Regulation of Oatp1a1 protein in remnant rodent livers is either unchanged or reduced 1 to 4 days after PHx (Gerloff et al., 1999; Vos et al., 1999; Csanaky et al., 2009). Microarray analysis has confirmed lower mRNA levels of Oatp1a4, Oatp1b2, and Ntcp in rat livers between 12 and 48 h after PHx (Dransfeld et al., 2005). It is noteworthy that Oatp1a6 mRNA is increased by 3 h and remains elevated over a 48-h period (Dransfeld et al., 2005). Lower expression of Ntcp and Oatp isoforms corresponds with reduced taurocholate uptake in basolateral plasma membrane vesicles obtained from rat livers after PHx (Green et al., 1997; Gerloff et al., 1999; Vos et al., 1999).

Canalicular Bsep and Mrp2 transport proteins are either unchanged or elevated after PHx, depending on the species and strain. In Wistar rats, expression of Bsep and Mrp2 mRNA and protein is fairly stable 24 h after PHx (Vos et al., 1999; Ros et al., 2003; Dransfeld et al., 2005). Furthermore, the subcellular localization of Bsep and Mrp2 to the canalicular membrane is not affected by PHx (Dransfeld et al., 2005). In contrast, Sprague-Dawley rats have increased Bsep and Mrp2 protein expression from 12 h to 2 days after PHx (Gerloff et al., 1999). It is noteworthy that increased Bsep and Mrp2 mRNA levels are not observed until 2 to 4 days, suggesting that early protein changes occur through post-transcriptional processes (Gerloff et al., 1999). As in rats, transporter profiling of mouse livers after PHx demonstrates either increased or unchanged Bsep mRNA (Huang et al., 2006b; Csanaky et al., 2009). Normal or enhanced Bsep and Mrp2 expression after PHx is consistent with functional bile flow and bile acid excretion by the remnant liver, as well as the requirement of an animal with a smaller liver mass to transport the same amount of bile acids and endobiotics as animals with a regular liver mass.

Rat Mdr1b mRNA (but not mouse) dramatically increases shortly after PHx and remains elevated through 48 h (Vos et al., 1999; Csanaky et al., 2009). Levels of Mdr1b increase approximately 40-fold in rat liver after PHx, with no change in Mdr1a (Vos et al., 1999; Ros et al., 2003). In mice, PHx stimulates expression of Mdr2 at 24 and 48 h after surgery, which corresponds with increased excretion of phospholipids into bile (Csanaky et al., 2009).

Consistent with toxicant-induced hepatocyte loss, expression of basolateral Mrp1, Mrp3, Mrp4, and Ostβ transporters is increased in rodents after PHx. Within 3 h after PHx, Mrp1 mRNA expression is enhanced and persists at high levels through 48 h (Vos et al., 1999). Mrp3 protein is dramatically up-regulated in remnant livers from rats and mice after 70 and 90% PHx (Chang et al., 2004; Csanaky et al., 2009). PHx enhances the immunostaining of Mrp3 on the basolateral membranes of hepatocytes throughout the liver (Csanaky et al.,

2009). Mrp3 protein is increased most notably in hepatocytes surrounding the central and portal veins (Csanaky et al., 2009). The mRNA analysis has also revealed a 2-fold increase in Mrp4 in rat hepatocytes 24 h after PHx (Ros et al., 2003). It has more recently been shown that mRNA expression of Ostβ is elevated in remnant mouse livers at 24 and 48 h (Csanaky et al., 2009). Because Mrp3, Mrp4, and Ostβ transport bile acids, up-regulation of these transporters in response to PHx probably contributes to enhanced basolateral egress and elevated plasma bile acid levels.

As noted above, progenitor cells contribute to the repopulation of the liver after hepatocyte loss. Pretreatment of rats with 2-acetyl-aminofluorene before PHx prevents hepatocytes from dividing, leading to the activation of progenitor oval cells in the liver. By 9 days after PHx, expression of Mdr1b, Mdr2, Mrp1, and Mrp4 mRNA in progenitor cells increases compared with appropriate control rats (Ros et al., 2003). Collectively, these data suggest that efflux transporter expression can be stimulated in hepatocytes and progenitor cells during liver regeneration, and the specific cell type engaged in proliferation and transporter expression is dependent upon the degree of tissue injury.

G. Ischemia-Reperfusion

Hepatic ischemia followed by tissue reperfusion is a complication of liver resection surgery, transplantation, hypovolemic shock, intra-arterial chemotherapy, and embolization. Ischemia with and without reperfusion can be recapitulated surgically in rodents. Prominent features of ischemia-mediated injury include hypoxia, activation of resident macrophages, and cholestasis. Within 6 to 24 h after hepatic ischemia in rats (with or without reperfusion), hypoxia and cytokine signaling are detected (Tanaka et al., 2006; Fouassier et al., 2007). During this period, there are declines in bile flow and biliary bile acid excretion in ischemic rats. Corresponding increases in markers of cholestasis, such as serum transaminases, bilirubin, and bile acids, are also observed.

Similar to other pathogenic conditions within the liver, hepatobiliary transporter expression is altered in rodents after ischemia reperfusion. Ischemia elevates hepatic Mdr1b mRNA and reduces Ntcp, Oatp1a1, Oatp1a4, Oatp1b2, Bsep, and Mrp2 mRNA in rats (Tanaka et al., 2006, 2008; Fouassier et al., 2007). In addition, incubation of cultured hepatocytes under hypoxic conditions decreases mRNA and protein expression of Ntcp, Bsep, and Mrp2 (Fouassier et al., 2007). It is noteworthy that hepatic ischemia-reperfusion injury is accompanied by up-regulation of Mrp2 and Mrp4 mRNA and protein in the kidneys (Tanaka et al., 2008). These data suggest that there is a shift from biliary to renal excretion of chemicals generated by hepatic ischemia and reperfusion.

Collectively, the chemical and surgical models of liver injury presented in this section demonstrate similar changes in the regulation of hepatobiliary transporters. Although beyond the scope of this section, there are a number of other chemicals (bromobenzene and troglitazone) and conditions (fatty liver, nonalcoholic steatohepatitis, hepatocellular carcinoma, and viral hepatitis) that show analogous findings. In general, a diseased liver reduces expression of sinusoidal uptake transporters while increasing efflux transporters on both the basolateral and canalicular membranes (Fig. 24). It is noteworthy that the remarkable induction of basolateral efflux transporters represents an alternate route of excretion for hepatocytes during injury. Future studies are needed to determine whether differential transporter regulation is a beneficial event for the human liver to recover and regenerate. Likewise, the clinical consequences of altered transporter expression in patients with liver disease need to be addressed (i.e., drug disposition).

IX. Future Directions

Since the identification of drug transporters as mediators of multidrug resistance in cancer cells, researchers have demonstrated ubiquitous expression of not only efflux but also uptake carriers in a variety of tissues. In this review, we have attempted to thoroughly describe the expression patterns of rodent and human bile acid and drug transporters throughout the body. It is noteworthy that some transporters are expressed across many tissues, whereas others have very restrictive expression patterns. Although the exact endogenous roles of only some of these transporters are known, initial insights have been gained from the development of knockout mice and the identification of human polymorphic variants.

There are a number of areas for future investigation that will aid in our understanding of the physiological and pharmacological functions of transporters:

A. Transporter Localization

The development of specific antibodies to transporters has aided in the identification of subcellular and tissue distribution. However, there are differences in transporter isoform localization for which a mechanism is not clear. For example, some transporters localize to the apical surface in certain epithelia and to the basolateral membrane in others. Additional work is needed to understand tissue-specific targeting in polarized cells.

B. In Vitro-In Vivo Extrapolation

Extrapolation of in vitro determined transport properties (using recombinantly expressed transporters) needs to be judicious. For example, uptake of fluvastatin by OATP1B1, -1B3, and -2B1 is inhibited by gemfibrozil between 60 and 90% in overexpressed systems, whereas

uptake into primary hepatocytes is blocked to a lesser extent (27% inhibition) (Noe et al., 2007). In vivo studies are needed to confirm the functional activity of transporters for the various in vitro substrates.

C. Transport Driving Forces

A better understanding of transport mechanisms and driving forces for transport (cosubstrates, countertransport) may be facilitated by structural modeling and determination of transporter crystal structures.

D. Substrate Binding Domains

Depending on the transporter, there may be more than one substrate binding domain. Chemicals that are transported by a particular pump may not compete for transport if they bind to different domains. Therefore, work is needed to thoroughly characterize the inhibitory potency and cooperativity of cosubstrates in vitro and in vivo to guide clinical decision-making (Noe et al., 2007).

E. Racial Differences

There are limited comparisons of transporter expression and regulation in various ethnic groups. More comprehensive screening of drug transporters in human tissues should aid in predicting whether particular transporters are more influential in drug disposition in different populations. Databases such as HapMap and PharmGKB are particularly useful in estimating the frequency of race-specific polymorphism allelic variants.

F. Pharmacokinetics

The existence of efflux transporters in various cell types necessitates reconsideration of how transporters influence pharmacokinetic drug profiles. Plasma clearance of drugs has traditionally been used to evaluate pharmacokinetics. Although this clinical parameter probably reflects the influence of uptake transporters, plasma drug concentrations do not address tissue accumulation and the function of efflux transporters on opposing domains of the plasma membrane. The expression and/or function of these transporters will influence intracellular concentrations and, consequently, the activation of cytosolic and/or nuclear drug targets. In addition, the intracellular concentrations of drugs will affect susceptibility of cells to toxicity.

G. Redundancy and Cooperativity

Mutations in the expression of some transporters clearly underlie genetic disorders and thereby point to critical roles for these proteins in normal physiology. However, other transporters exhibit overlapping substrate specificity resulting in functional redundancy. As a result, the development of single isoform null mice demonstrated little effect on the pharmacokinetics of some substrates identified from in vitro screens. It was not until double- and triple-knockout mice were generated that the in vivo redundancy of transporters was more clearly elucidated. This has been most evident for shared substrates of Bcrp and Mdr1a/1b. Because of these findings, polymorphisms in redundant transporters may not yield a clinical phenotype. Instead, it may become important to look at combinations of variants in functionally related transport systems to assess variations in drug pharmacokinetics.

H. Novel Polymorphisms

Because transporters are highly expressed in excretory organs, it can be hypothesized that clinically observed variations in drug kinetics and pharmacodynamics involve transporters. Up until now, research has primarily been limited to nonsynonymous polymorphisms in the coding region of transporters. However, future work should aim to characterize the functional consequence of intronic and promoter variants in drug pharmacokinetics and response.

I. Ontogeny

The expression profile of hepatic transporters before and after birth has been well characterized in mice. Additional work is necessary to extend this work to human livers (as well as other tissues) and to identify the "triggers" that turn on or off the expression of transporters during different developmental periods. This work will be particularly important in adjusting dosing regimens for newborns and premature infants to ensure proper efficacy and minimize drug toxicity.

J. Novel Drug Delivery Routes

Drug transporters may be exploited for delivery of therapeutics into the body. For example, Oat6 in the nasal epithelium may be a novel route of administration of drugs to the central nervous system (Nigam et al., 2007). Likewise, the mRNA expression of a number of OATP isoforms (1A2, 2B1, 3A1, and 4A1) is elevated in human breast carcinoma compared with nonmalignant specimens (Miki et al., 2006; Wlcek et al., 2008). The relative expression of OATPs in cancer cells needs to be compared with that of other normal tissues such as liver. Up-regulation of uptake transporters in cancer cells may be used in drug development to improve targeting of chemotherapeutic agents and minimize cytotoxicity to normal cells.

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