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Effect of Liver Disease on Hepatic Transporter Expression and Function

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Abstract

Liver disease can alter the disposition of xenobiotics and endogenous substances. Regulatory agencies such as the Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) recommend, if possible, studying the effect of liver disease on drugs under development to guide specific dose recommendations in these patients. While extensive research has been conducted to characterize the effect of liver disease on drug-metabolizing enzymes, emerging data have implicated that the expression and/or function of hepatobiliary transport proteins also are altered in liver disease. This review summarizes recent developments in the field, which may have implications for understanding altered disposition, safety, and of efficacy of new and existing drugs. A brief review of liver physiology and hepatic transporter localization/function is provided. Then, the expression and function of hepatic transporters in cholestasis, hepatitis C infection, hepatocellular carcinoma (HCC), human immunodeficiency virus (HIV) infection, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), and primary biliary cirrhosis (PBC) are reviewed. In the absence of clinical data, nonclinical information in animal models is presented. This review aims to advance the understanding of altered expression and function of hepatic transporters in liver disease and the implications of such changes on drug disposition.

INTRODUCTION

The liver is an important organ in the biotransformation, disposition, and elimination of endogenous (*e.g.,* macromolecules, bile acids) and exogenous molecules (*e.g.,* drugs). Drug metabolizing enzymes play a central role in hepatic drug elimination; however, efforts over the past decade have revealed that transport proteins are also important determinants of hepatic clearance. Hepatic transporters are transmembrane proteins anchored in polarized hepatocytes, the primary parenchymal cell type of the liver, that facilitate the transport of molecules to and from sinusoidal blood and hepatocytes (basolateral transporters) or from

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hepatocytes into the biliary canaliculus (canalicular transporters). These transporters are classified into two superfamilies: the solute carrier (SLC) protein family and the adenosine triphosphate (ATP)-binding cassette (ABC) protein family.

The expression and function of transporters are subject to complex regulatory mechanisms and are contributing factors to interindividual variability. Characterizing sources that contribute to individual variability in hepatic transporter expression/function will improve the efficient development of new and safer pharmacological interventions and advance our mechanistic understanding of the genesis/progression of some diseases. The identification of drug-drug interactions (DDIs) and genetic polymorphisms that influence the expression and/or function of drug transporters have been under extensive investigation in recent years. However, DDIs and genetic polymorphisms represent only a portion of the total contribution to interindividual variability.

Liver disease may influence the expression and function of hepatic transporters. Chronic liver disease is a significant source of morbidity and mortality in both industrialized and developing nations. It is estimated that one million deaths worldwide were attributed to liver cirrhosis alone in 2010, while many more were due to liver cancer and hepatitis. [1] The etiologies of liver disease are diverse and can include chronic alcohol abuse, viral/bacterial infection, fatty liver disease, and drug-induced injury – all of which may have genetic components that can influence the development, manifestation, and severity of disease. The purpose of this article is to review the literature characterizing and quantifying the effects of liver disease on the expression and function of hepatic transporters in humans. First, a brief overview of hepatic transporters will be provided. Then, the effects of cholestasis, hepatitis C (HCV) infection, hepatocellular carcinoma (HCC), human immunodeficiency virus (HIV) infection, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), and primary biliary cholangitis (PBC) on hepatic transporter expression and function will be summarized. In addition to highlighting current knowledge regarding the effect of liver disease on hepatic transporters, this review will identify knowledge gaps in our understanding of the contribution of liver disease to human variability in drug disposition and elimination. [2]

Basolateral Uptake Transporters

Sodium-Taurocholate Co-transporting Polypeptide (NTCP)—The *SLC10A1* gene encodes NTCP, a key transport protein involved in the enterohepatic recirculation of bile acids.[3] NTCP is homogenously expressed throughout the liver acinus and specifically coordinates the sodium-dependent uptake of bile acids from the sinusoidal blood to hepatocytes by co-transporting two sodium ions and one bile acid molecule.[4,5] NTCP transports a variety of bile acids but appears to have higher affinity for glycine- and taurine-conjugated bile acids compared to their unconjugated counterparts, and a higher affinity for dihydroxy bile acids (*e.g.,* chenodeoxycholate and deoxycholate conjugates) than trihydroxy bile acids (*e.g.,* cholate conjugates). Although little emphasis is placed on NTCP-mediated interactions during drug development, NTCP has been shown to transport drugs. For example, drug-conjugated bile acids have been proposed as a potential strategy for drug delivery.[6] Approximately 35% of total rosuvastatin uptake into hepatocytes was accounted

for by NTCP [7]; however, it is not clear whether this contribution is relevant in the presence of systemic bile acids, which may selectively outcompete rosuvastatin *in vivo*. Interestingly, NTCP was shown to be a functional receptor for the hepatitis B virus and thus, may serve as a novel therapeutic target to inhibit the viral entry mechanism.[8,9]

Organic Anion Transporters (OATs)—OATs, members of the *SLC22A* superfamily, are a ubiquitously expressed group of organic anion transporters that have broad distribution in the kidney, liver, brain, pancreas, salivary glands, and skeletal muscle.[10] These proteins generally mediate the transport of negatively charged endogenous and exogenous molecules in a bidirectional manner in exchange for dicarboxylate ions [11–13], although uncharged and even cationic molecules have been reported as substrates.[14,15] OATs also transport endogenous substances including cGMP, bile acids, and hormone derivatives.[16–18] Prostaglandins and glutamate are examples of endogenous substrates of OAT2, whereas methotrexate, valproic acid, and allopurinol are examples of drug substrates.[17–20] OAT7 is another liver-specific OAT that appears to have similar and overlapping substrate specificity with other OATs.[18,20] Despite the expression and function of OATs in the liver, there is little evidence demonstrating the clinical relevance of these transporters in the context of DDIs and/or genetic polymorphisms, although pravastatin recently was identified as a novel OAT7 substrate.[21,22]

Organic Anion-Transporting Polypeptides (OATPs)—OATPs are a class of proteins that belong to the *SLCO* superfamily with 12-transmembrane spanning domains that are localized on the basolateral membrane of many epithelial cells. OATPs are highly expressed in the liver (predominantly OATP1B1, OATP1B3, and OATP2B1).[23–26] OATPs transport a wide variety of amphipathic and anionic substances in a bidirectional manner through counter transport with either bicarbonate or reduced glutathione.[27–29] OATP substrates include endogenous compounds such as bile acids, bilirubin, thyroid hormones, and steroid conjugates. Several drug classes have been characterized, or even specifically designed, as substrates for OATPs including 3-hydroxy-3-methylglutaryl coenzyme A HMG-Co-A reductase inhibitors (*i.e.,* statins), angiotensin II receptor antagonists, angiotensin converting enzyme inhibitors, and cardiac glycosides.[29,30] The liver-specific OATP1B1, OATP1B3, and to a lesser extent, OATP2B1, are considered clinically relevant drug transporters by the Food and Drug Administration (FDA) and are routinely evaluated during drug development.[30]

Organic Cation Transporters (OCTs)—The first OCT (*i.e.,* OCT1) was isolated and cloned from rat kidney by Gründemann et al. in 1994 and was later shown to display a 12-transmembrane structure that mediates the bidirectional transport of various small molecules (~60–350 Da) in an electrogenic manner.[31,32] Similar to other transporters of the SLC family, OCTs display broad tissue distribution in such organs as the kidney, liver, and intestine. Three OCT isoforms have been identified in humans. OCT1 exhibits greatest expression in the liver. OCTs generally mediate the transport of small hydrophilic compounds with at least one positive charged amine moiety, although uncharged or anionic substrates have been reported.[32] Classic substrates include tetraethylammonium (TEA) and the parkinsonian neurotoxin 1-methyl-4-phenylpyridinium (MPP^+); clinically relevant drug substrates include famotidine, ranitidine, and metformin.[33–35]

Canalicular Efflux Transporters

Breast Cancer Resistance Protein (BCRP)—BCRP (*ABCG2*) was first cloned by Doyle et al. (2003) and although its name suggests otherwise, BCRP is expressed in a variety of tissues and cell types (*e.g.,* intestine, brain, liver, cardiac muscle).[36] BCRP is a half transporter hypothesized to function as a homodimer or potentially a tetramer.[37,38] In the liver, BCRP is localized to the canalicular membrane with broad substrate specificity, which includes organic ions, sulfate conjugates, and both negatively and positively charged molecules. BCRP substrates have been characterized primarily in the context of oncology due to the resistance of certain cancer types against chemotherapeutic agents. Some examples include mitoxantrone, SN-38, topotecan, and doxorubicin.[39–41] However, BCRP can transport sulfate and glucuronide bile acid conjugates and may play a compensatory role when the function of other transporters (*e.g.,* MRP2) is impaired.[42,43]

Bile Salt Export Pump (BSEP)—*ABCB11* encodes BSEP, a member of the ABC transporter family, which is the primary hepatocellular transporter responsible for secretion of bile acids into the bile canaliculus. BSEP is predominantly expressed throughout the human liver acinus. Bile acid transport requires the hydrolysis of ATP, which drives the conformational change in the transmembrane domain of BSEP, thereby translocating bile acids from hepatocytes to the canalicular space. In addition to bile acids, BSEP has been reported to transport pravastatin.[44] Mono-anionic and conjugated bile acids represent the majority of BSEP substrates; unconjugated bile acids do not appear to be substrates as evidenced by *in vitro* and *in vivo* human data.[45,46] Differences in substrate specificity between species have been reported; for example, human BSEP is able to transport taurolithocholate-3-sulfate although this is not true for the rodent orthologue.[47] The affinity (*i.e.,* K_m) for bile acids is generally in the low micromolar range across species, but differences in rank-order and specificity have been noted. For example, human BSEP has a higher affinity for taurocholate than mouse BSEP (human K_m: 4.25 μM compared to mouse K_m: 15–30 μM).[47]

Multidrug and Toxin Extrusion Protein 1 (MATE1)—MATE1 (*SLC47A1*) is an H^+/organic cation transporter first identified in 2005 that mediates the electrogenic transport of organic cations independent of a sodium gradient.[48] It is primarily expressed on the canalicular membrane of hepatocytes and the luminal membrane of the proximal tubules and is thought to play a physiological role in the excretion of toxic endogenous substances, although several drugs have been identified as substrates (*e.g.,* metformin, cimetidine, and acyclovir).[49]

Multidrug Resistance-Associated Protein 2 (MRP2)—MRP2 is a member of the *ABCC* family and one of nine recognized MRPs. First identified in the canalicular membrane of hepatocytes, MRP2 has been characterized in the kidney, small intestine, gallbladder, and placenta.[50–53] MRP2 is a major driving force for bile-acid independent bile flow through the secretion of reduced glutathione, although it transports divalent and glucuronide- and sulfate-conjugated bile acids into the bile canaliculus. MRP2 is responsible for the biliary transport of many anionic drugs/metabolites including methotrexate, acetaminophen-glucuronide, and etoposide.[54,55] MRP2 plays an important physiological

role in the biliary excretion of bilirubin (specifically, the conjugated species); patients with Dubin-Johnson Syndrome, who harbor polymorphisms in the *ABCC2* gene, exhibit impaired secretion of conjugated bilirubin into bile.[56,57] Naturally occurring Mrp2-deficient rats (*i.e.,* Eisai hyperbilirubinemic and CY/TR$^-$ mutant rat strains) have been a valuable *in vivo* model for understanding the role of Mrp2 in drug disposition.[55,58]

Multidrug Resistance Protein 1 (MDR1)—MDR1, commonly known as P-glycoprotein (P-gp), was one of the first ABC proteins identified due to its important role in drug resistance in chemotherapy. Like other ABC transporters, P-gp is comprised of two membrane-bound domains each consisting of six transmembrane helices.[59] Expression has been quantified in many tissues such as the liver, brain, testis, gut, and colon.[60] Although the physiological role of P-gp has been debated, it likely plays a general role in the protection from xenobiotics and disposition of endogenous substances, as evidenced by its ability to transport a variety of amphipathic drugs, natural products, and peptides. P-gp transports immunosuppressants, hormones, calcium channel blockers, and cardiac glycosides, but P-gp expression and function have been studied the most in the context of cancer chemotherapy. Apart from being expressed in major organs governing drug disposition (*e.g.,* the liver, gut), P-gp is overexpressed in many cancer cell types, which limits the distribution/exposure of chemotherapeutics to the site of action.[61–63]

Basolateral Efflux Transporters

Multidrug Resistance-Associated Protein 1 (MRP1)—The clinical relevance of MRP1, encoded by the *ABCC1* gene, was first recognized in the transport of hydrophobic and hydrophilic anticancer agents such as vincristine and etoposide.[64–66] Under normal conditions, the expression of MRP1 in the liver is low.[67,68] *In vitro* studies have established that MRP1 can transport a variety of physiological organic anions including drugs and their conjugated metabolites. For example, MRP1 can transport endogenous substances such as 17β-estradiol glucuronide, glutathione, leukotriene C4, folic acid, and vitamin B12, which may indicate a physiological role in cellular defense and oxidative stress.[67,68]

Multidrug Resistance-Associated Protein 3 (MRP3)—MRP3, encoded by the *ABCC3* gene, actively transports organic ions using energy generated by the hydrolysis of ATP. MRP3 is localized on the basolateral membrane of hepatocytes and is expressed in other tissues such as the gut, kidney, and adrenal cortex.[69] In the context of the liver, MRP3 is thought to play an adaptive role in response to hepatocellular stress as evidenced by the upregulation of MRP3 in cholestatic conditions.[70,71] MRP3 transports bulky organic anions from the hepatocyte to the systemic circulation and preferentially mediates the transport of glucuronide and, to a lesser extent, sulfate conjugates (*e.g.,* bilirubin glucuronide, bile acid conjugates).[72,73] Although MRP3 has been studied in the context of bile acid transport, several drugs and/or metabolites have been identified as MRP3 substrates including acetaminophen glucuronide, methotrexate, and sorafenib.[74–77]

Multidrug Resistance-Associated Protein 4 (MRP4)—In contrast to MRP3, MRP4 (*ABCC4*) transports a dynamic range of endogenous molecules such as folate, bile acids, uric acid, eicosanoids, steroid hormones, and cyclic nucleotides. [72,78] Although MRP4 was

first characterized as a transporter that confers resistance to cytotoxic agents, MRP4 has since shown broad substrate specificity to drugs from many classes including antibiotics, antivirals, and cardiovascular agents. MRP4 is generally expressed in tissues with a barrier function such as the liver, brain, and intestine. In the liver, MRP4 is localized on the basolateral membrane and translocates molecules from the hepatocyte to the systemic circulation. Similar to MRP3, it is thought that the physiological role of MRP4 is to protect the liver from toxic accumulation of bile acids as evidenced by marked increases in MRP4 expression in cholestasis.[79] This hypothesis is further supported by the finding that Mrp4-knockout mice exhibited more severe liver injury due to obstructive cholestasis than wild-type mice with functional Mrp4.[80]

Liver Disease—The effects of liver disease on hepatic transporter expression and function in humans are summarized in the following section. Table 1 highlights reports of altered hepatic transporter expression in liver diseases where data in diseased and healthy subjects were compared. Table 2 summarizes published reports of altered transporter-mediated drug disposition in liver disease resulting in changes in pharmacokinetics and/or efficacy.

Cholestasis—Cholestasis is the impairment of bile formation (hepatocellular) and/or flow (obstructive) that can arise from a number of intrinsic and extrinsic factors. In response to accumulating bile constituents, adaptive mechanisms induce hepato-protective systems (*e.g.,* bile acid transporter expression) aimed at reducing intracellular accumulation of bile acids, which can be hepatotoxic due to their detergent-like properties.

The functional role of transporters in cholestasis is highlighted in patients harboring mutations in the *ABC11* (BSEP) gene known as progressive familial intrahepatic cholestasis 2 (PFIC2). First described by Clayton et al. (1969), the PFIC-2 phenotype includes pruritus, jaundice, and clinical signs of cholestasis (discolored stools, dark urine), which often leads to fulminant liver failure and death early in life.[81,82] Hepatic bile acid uptake transporters (*e.g.,* NTCP, OATP1B1, OATP1B3) were downregulated compared to control samples, whereas OATP2B1 was unaffected based on mRNA and protein analysis.[83] Interestingly, MRP4, but not MRP3 was strongly upregulated in PFIC-2 livers, consistent with an adaptive response to increased hepatocellular bile acid concentrations. Although it is not clear why the authors did not observe increased MRP3, as would be expected in cholestasis, it must be noted that the sample size was small (n=4 PFIC-2 and n=3 control samples). MRP2 was localized to the canalicular membrane and appeared to be downregulated in PFIC-2; however, this result did not reach statistical significance.[83]

Because the etiologies of cholestasis can be diverse, altered transporter function may be causal or an adaptive response to cholestasis, or both. For example, intrahepatic cholestasis of pregnancy (ICP) is an acute form of cholestasis that typically presents in the third trimester of pregnancy and is associated with premature delivery, respiratory distress, and intrauterine death.[84] *In vivo* studies revealed that the transcriptional dynamics of BSEP were inversely correlated with serum 17β-estradiol (E2) levels, implicating E2 levels in the repression of BSEP, which may increase susceptibility to ICP.[85,86] In the same study, repression of BSEP expression also was demonstrated in human primary hepatocytes.[85] The procholestatic effects of estrogens and progesterone may also alter Mrp2; E2 administration

causes endocytic internalization, as well as decreased expression and function of Mrp2 in rodents.[87,88] Downregulation of hepatic sinusoidal transporters (*i.e.,* Oatp1a1, Oatp1a4, and Oatp1b2) are likely an adaptive response to increased bile acid concentrations and cholestasis.[89,90] Although ethical considerations may preclude the quantification of hepatic transporter expression in ICP, the expression of OATP1B3 in placenta was decreased in pregnant women diagnosed with ICP, consistent with altered transporter expression revealed in animal studies.[91] Zollner et al. (2001) reported that NTCP mRNA correlated with serum bile acids in patients with inflammatory cholestasis.[92] Similar observations were reported for OATP1B1 and BSEP, but MRP2 mRNA was unchanged. [92]

Given the limited availability of human samples, the application of animal models has provided information about the mechanisms underlying transporter expression/function in cholestasis. For example, ligation of the common bile duct in rodents leading to cholestasis decreased Mrp2 protein levels without a corresponding change in mRNA expression, suggestive of an impaired posttranslational modification effect.[93] Immunofluorescent staining revealed intracellular localization of Mrp2, which may indicate that Mrp2 trafficking to the canalicular membrane is compromised resulting in the endocytic retention of Mrp2 and possible lysosomal degradation. Indeed, retrieval of MRP2 from the canalicular membrane into the cytoplasm of hepatocytes has been reported in patients with cholestasis.[94] Although the exact mechanism underlying this observation has yet to be fully elucidated, altered binding and subsequent improper anchoring in the canalicular membrane via radixin and/or other actin filament interactions appears to play a role.[94–97]

Few studies have investigated the effect of cholestasis on the pharmacokinetics and hepatobiliary disposition of drugs. Bile duct ligation in rats significantly increased the systemic concentrations of morphine-3-glucuronide, the active metabolite of the analgesic morphine due, in part, to increased expression of hepatic Mrp3.[98] mRNA and protein expression of MRP3 were significantly increased by ~3-fold in patients with obstructive cholestasis[70]; hence, it is conceivable that increased systemic exposure of morphine glucuronide(s) could impact pharmacodynamic activity and/or toxicity in this patient population. In experimental intrahepatic cholestasis induced by 17α-ethynylestradiol in rats, the antidiabetic effect of metformin was reduced due to impaired hepatic uptake of Oct1.[99] Although clinical data are needed, these observations suggest that metformin efficacy (*e.g.,* in gestational diabetes) may be impaired in diabetic patients with estrogen-associated ICP. In the same rodent model, systemic concentrations of doxorubicin were increased by ~60%, which was partially attributed to a ~67% reduction in Mrp2-mediated biliary excretion.[100] Lastly, the apparent half-life and systemic exposure of digoxin were decreased in a rodent model of cholestasis, presumably through impaired P-gp-mediated enterohepatic recirculation.[101]

Hepatitis C Infection—Hepatitis C virus (HCV) is a prevalent form of viral hepatitis. The risk of developing cirrhosis, liver cancers, or both is increased in HCV-infected patients.[102] HCV induces hepatoprotective response pathways in response to fibrosis and hepatocellular injury that can affect normal gene expression patterns.[103] The World Health Organization estimates that more than 150 million individuals are chronically infected with HCV.[104] Thus, understanding altered expression and/or function of proteins involved in absorption,

distribution, metabolism, and excretion (ADME) is crucial to pharmacotherapeutic intervention in this population.

Due to inflammation associated with viral infection, prevailing evidence implicates the coordinate downregulation of ADME genes by nuclear transcription factors [*e.g.,* PXR, CAR, aryl hydrocarbon receptor (AHR), RXR], although interaction(s) with the HCV virus and the transcriptional factor RXR have be reported.[105–107] Therefore, the pathophysiological role of HCV in altered ADME expression cannot be dismissed. Relative mRNA expression of OATP1B1 and OATP2B1 was reduced in the livers of patients with chronic HCV infection, although the mechanistic link between inflammatory cytokines and OATP downregulation is not clear.[108,109] Downregulation of NTCP, OAT2, and OCT1 correlated with fibrosis state, but another study observed no difference compared to control samples.[108,109] In the presence of HCV-induced cirrhosis, expression of NTCP, OATP1B3, and OCT1 are decreased compared to control samples using proteomic analysis.[110]

Hepatic basolateral efflux transporters MRP3 and MRP4 are elevated compared to the livers of non-infected controls using mRNA analysis. These data are consistent with Ogasawara et al. (2010) who identified MRP4 mRNA as a potential marker for liver disease.[103,111,112] Under normal physiological conditions, MRP3 and MRP4 protein are expressed at low levels but are significantly increased in cholestatic and inflammatory conditions, possibly due to the activation of AHR and/or Nrf2 observed in end-stage liver disease.[71,80,112–114] In contrast, the canalicular transporters BCRP and BSEP appeared to be downregulated whereas MRP1 and P-gp were upregulated. Some observations report that MRP2 is unaffected, although one study found a negative correlation between fibrosis stage and MRP2 mRNA expression.[103,109,111] The impact of altered mRNA expression on protein expression has yet to be quantified, although immunohistochemistry shows increased MRP1 and P-gp staining in HCV liver biopsies.[112] In HCV-induced cirrhosis, protein expression of BSEP, MRP2, and P-gp are downregulated whereas BCRP and MATE1 are unchanged.[110] To date, the clinical relevance of these findings in HCV-infected patients is unclear. The systemic clearance of nelfinavir, a P-gp substrate, was reduced in HIV/HCV-co-infected patients compared to HIV-infected patients without HCV.[115] However, P-gp is expressed in other tissues (*e.g.,* gut, blood brain barrier) and this must be considered as a contributing factor to altered pharmacokinetics due to HCV-associated changes in P-gp function. Hepatic uptake and excretion of ^{99m}Tc-mebrofenin was decreased in HCV-infected patients, suggestive of altered OATP-, MRP2-, and MRP3-mediated function.[116]

Hepatocellular carcinoma—Hepatocellular carcinoma (HCC) is a malignancy of the liver cells that often occurs in patients with hepatic diseases such as cirrhosis or chronic hepatitis associated with HCV. There is a substantial body of evidence indicating that the expression of hepatic uptake and efflux transporters is altered in HCC. NTCP and OATP1B1 are the key transporters responsible for the uptake of drugs linked to bile acids as carrier molecules.[117–119] Studies have shown that the expression of NTCP and OATP1B1 is significantly reduced in patients with HCC.[117] This is consistent with previous *in vitro* studies that demonstrated reduced bile acid uptake in hepatoma cell lines. These studies highlight the risk of liver toxicity in nonmalignant cells with preserved expression levels of NTCP and OATP1B1 that would be overloaded with bile salt-coupled chemotherapy

whereas the carcinoma cells, with reduced expression of NTCP and OATP1B1, would have impaired accumulation of bile salt-coupled drugs.[117] OATP1B1 and OATP1B3 have been studied extensively in different types of cancers including HCC.[120–122] Although initially considered to be liver specific, subsequent studies have shown that OATP1B1 and OATP1B3 are frequently expressed in multiple types of cancer tissues.[120,123–128] After the initial study reporting the reduced expression of OATP1B1 protein in HCC cell lines, many other *in vitro* studies reported similar findings.[117,129–132] However, one study reported no significant change in expression of OATP1B1 compared to normal liver.[121] These apparent differences may be attributed to different detection methods.[117,121] Similarly, OATP1B3 mRNA and protein are also reduced in HCC.[121,131,133] Although studies in other cancer types have implied a potential association between OATP1B3 expression and clinical outcomes, the functional role of OATP1B3 in HCC remains to be investigated.[124,134]

Interestingly, mRNA and protein expression of some other OATPs (*e.g.,* OATP2A1, OATP3A1, OATP4A1 and OATP5A1) are reported to be upregulated in primary and metastatic liver cancer suggesting the potential role of these OATPs in supplying nutrients and hormones to tumor cells.[135,136] OCT1 is downregulated by epigenetic mechanisms in HCC compared to nonmalignant tissues.[137] The downregulation of OCT1 expression is clinically associated with tumor progression and poor outcomes in patients with HCC.[137,138]

Several studies indicate that the expression of canalicular and basolateral efflux transporters can be altered in HCC. Although BCRP mRNA was unchanged in a study by Borel et al.[139], other studies showed a significant elevation of BCRP mRNA and protein expression in HCC compared to normal hepatocyte tissues.[140,141] Interestingly, BCRP expression increased following chemotherapy in hepatoblastoma patients highlighting its potential role in drug resistance in HCC.[140,142] On the other hand, BSEP expression was reported to be reduced secondary to inflammation-induced decreases in Farnesoid X receptor (FXR) [143]. Although the role of BSEP in resistance to chemotherapy is unclear, many studies have shown that high bile acid levels in the liver contribute to HCC pathogenesis.[143–148] In fact, children with BSEP deficiency demonstrated a higher risk of cholestasis and HCC.[144,145] Collectively, these findings highlight the potential role of BSEP and altered bile acid homeostasis in HCC progression.[143]

P-gp expression in HCC showed divergent results at mRNA and protein levels in some *in vitro* and *in vivo* studies, which may be related to different detection methods as well as the tumor heterogeneity.[139,149–153] P-gp protein expression appeared to be reduced or expressed less extensively in HCC tissues compared to normal hepatocytes.[151–153] In regard to its function, P-gp expression was inversely correlated with chemotherapeutic response in patients with inoperable HCC. [152,154] MRP2 expression in HCC was unchanged compared to normal hepatocyte tissues.[117,155,156] MRP1, which is not expressed in normal hepatocytes, is overexpressed at both the mRNA and protein levels in HCC.[112,157,158] One study showed that a MRP1 promoter (-1666GG) polymorphism was a predictor of poor survival in patients with HCC from Southeast China [158]. MRP3 and MRP4 mRNA levels were reported to be upregulated in HCC.[112,139,159] Although several studies have noted the altered expression of drug transporters in HCC, further investigations are necessary to examine their clinical significance in HCC.

Human Immunodeficiency Virus (HIV) Infection—Similar to viral hepatitis, HIV is associated with chronic inflammation as evidenced by the presence of elevated proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α.[160] The mRNA and protein expression of major sinusoidal uptake transporters (*i.e.,* OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, and NTCP) were downregulated in human hepatocytes when incubated with TNF-α, which resulted in reduced functional activity.[161] mRNA and protein levels of MRP2 were increased by IL-6 or IL-1β exposure in sandwich-cultured human hepatocytes whereas BSEP protein expression appeared to decrease.[162] In another study, MRP2 and BCRP were reported to be downregulated in primary human hepatocytes after exposure to IL-6 or IL-1β; therefore, additional mechanistic studies are required to definitively conclude that canalicular transporters are upregulated or downregulated.[161] Based on these data, it is conceivable that liver transporter expression and/or function may be impacted in HIV-infected patients because such signaling molecules can modulate transporters *in vitro*. It also must be noted that the administration of antiretroviral therapy is associated with a reduction in cytokine levels that may contribute to interindividual variability in hepatic transporter expression in HIV-infected patients.[163]

Despite the aforementioned data, the effect of HIV infection on the expression of transporters has not been evaluated systematically. In addition, coinfection (*e.g.,* bacterial infection) could contribute to altered transporter regulation. For example, gene expression of hepatic Mrp2, Bcrp, and Oatps was downregulated in HIV-1 transgenic rats co-infected with endotoxin.[164] P-gp and MRP2 protein levels in the rectal-sigmoid colon were lower in antiretroviral-naïve patients compared to non-infected subjects; whether similar expression patterns occur in the liver remains to be evaluated.[165,166] Data quantifying hepatic transporter protein expression followed by subsequent functional studies are needed. Altered ADME processes in clearance organs (*i.e.,* intestine, liver, and kidney) in combination with the potential for induction by co-medications (*e.g.,* protease inhibitors) highlights the complexity of predicting transporter-mediated drug disposition in HIV-infected patients.[167,168]

Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH)—NAFLD consists of liver pathology ranging from simple steatosis to NASH, an advanced inflammatory state of liver disease. NAFLD has become the most common form of liver disease in Western and industrialized nations driven by the prevailing obesity epidemic; it is estimated that ~20–30% of the general population is affected, although some reports are as high as 50%.[169–172] For reasons not fully known, some patients with NAFLD develop NASH, which may lead to HCC, cirrhosis, and/or fulminant liver failure. Due to the increasing prevalence of NAFLD and NASH, considerable research has been dedicated to quantifying how NASH affects ADME enzymes/transporters. These findings may have important implications in the treatment and disposition of drugs in this patient population.

Global gene expression analysis first implicated a coordinated downregulation of hepatic uptake transporters (*e.g.,* OATPs) in patients with NASH.[173] Further reports by Cherrington and colleagues revealed a significant increase in OATP1B1, but a decrease in OATP1B3, and no change in OATP2B1 in human liver biopsies using immunoblot techniques. Interestingly, no differences were observed in these transporters based on mRNA analysis.[174] These

findings are in contrast to data obtained from a commonly used diet-induced rodent model of NASH; mRNA and protein analyses were in agreement that rodent orthologues of human OATPs were decreased.[175,176] These results support increased systemic concentrations of simvastatin acid, an OATP/Oatp substrate, in the rodent model of NASH compared to wild-type rats.[175] NTCP, the primary hepatic bile acid transporter, is decreased in patients with NASH compared to patients with simple steatosis based on real-time reverse transcription polymerase chain reaction and immunoblot techniques; these data are consistent with a recent publication reporting that serum bile acids are increased in patients with NASH.[177,178] Rat Ntcp and Oat2 also were shown to decrease in an experimental rodent model of NASH, presumably mediated through pro-inflammatory cytokines known to decrease hepatic transporter expression. Pharmacokinetic studies that quantify the functional impact of altered uptake transporter expression are limited in humans. However, our group recently reported increased systemic concentrations of ^{99m}Tc-mebrofenin, a hepatobiliary diagnostic agent and OATP, MRP2 and MRP3 substrate, in patients with biopsy-confirmed NASH.[2]

In what appears to be an adaptation to prevent further damage by toxicants, hepatic efflux transporters are increased in NASH. For example, MRP3-6 are induced in liver biopsies from NASH patients, similar to findings in a rodent model of NASH.[176,180–182] Similarly, Mrp1 mRNA is increased ~5-fold compared to control animals.[176] Functional drug disposition studies corroborate these reports as evidenced by increased plasma acetaminophen glucuronide concentrations in diet-induced NASH animals attributable to increased Mrp3 expression.[181] Administration of morphine and acetaminophen to patients with NASH resulted in increased systemic concentrations of the glucuronide conjugates, consistent with increased function of MRP3 in this patient population.[74,183] Although MRP2 is increased, a growing body of evidence supports a functional decrease in MRP2-mediated biliary excretion due to disruption of cellular trafficking and/or improper localization away from the canalicular membrane.[74,180] This is supported by reports of reduced biliary excretion of acetaminophen glucuronide and pemetrexed in rats, consistent with impaired Mrp2 function.[181,184] These findings corroborate enhanced hepatic retention and a prolonged half-life of the liver contrast agent gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) in NASH-induced rats.[184] In contrast to Hardwick et al., who reported an increase in total MRP2 in human liver biopsies, a recent study reported decreased MRP2 protein in livers from NASH patients, which correlated inversely with progression of NAFLD.[185,180] However, much of the increased MRP2 in this study was only partially glycosylated; complete glycosylation of MRP2 is required for plasma membrane trafficking.[186] Decreased Mrp2 mRNA and protein expression were reported in a diet-induced rodent model of hypercholesterolemia.[187] These apparent discrepancies may be due to species differences in composition of the bile acid pool, cytotoxicity of the predominant bile acid species, differences in regulation of Mrp2, or to the heterogeneous population of NASH patients and interindividual variability in MRP2 expression. Regardless, functional studies in humans are needed to evaluate the impact of altered MRP2 expression and/or localization. Although pharmacokinetic studies are limited, our group recently reported increased hepatic exposure of ^{99m}Tc-mebrofenin in patients with biopsy-confirmed NASH, which lends credence to the hypothesis that altered trafficking and localization of MRP2

result in a functional decrease in MRP2-mediated efflux.[2] BCRP mRNA and protein expression were increased in NASH liver biopsies, but this finding was not observed in rodent models of NASH.[180,188] Finally, rodent P-gp expression appears to be increased in NASH but protein expression has not been quantified.[177,185,188]

Primary Biliary Cholangitis—Primary biliary cholangitis (PBC) is a disease that causes bile duct inflammation and chronic damage over time. This leads to accumulation of bile acids and toxins that can cause cholestasis, fibrosis and cirrhosis. Hepatic transporters play an important role in the movement of solutes from the blood to the bile, and PBC may lead to alterations in these transport processes. The following section summarizes the literature studies that have examined the altered transporter expression in PBC. Several studies have reported that the mRNA and protein expression of NTCP, OATP1B1, and OATP1B3 are downregulated in PBC as compared to normal liver.[189–192] These findings suggest the potential adaptation by hepatocytes to limit the accumulation of toxic bile acids.[189]

Studies performed using *in vitro* systems and human tissues confirmed that expression of efflux transporters was either maintained or tended to increase in PBC as compared to normal liver.[189–191] One study reported that BSEP and MRP2 expression were unchanged whereas P-gp and MRP3 expression were upregulated in PBC.[189] Interestingly, it was reported that these alterations may be related to the adaptation of transporters, and that expression patterns may change from early to late stage PBC.[190,193] In addition to the changes in expression, the localization of MRP2 was altered in PBC stage III.[191] MRP1 and OST α/β, which are not expressed or expressed at low levels in normal hepatocytes, are upregulated in patients with PBC.[149,190,193,194] Consistent with the literature findings, data from our laboratory indicated that MRP1 protein was expressed in liver tissue from a patient with PBC (Figure 1). Interestingly, our findings suggest that MRP1 was expressed primarily in the inflamed tissues in macrophages around the hepatocytes in PBC. These findings are consistent with previous reports of MRP1 expression in macrophages.[195] Further studies are required to better understand the functional role of MRP1 and OST α/β in PBC.

Summary and Perspective—Understanding the impact of liver disease on hepatic transporter function and the disposition of clinically-relevant drugs is one of the major challenges in treating liver disease. Genetic factors (*e.g.*, single nucleotide polymorphisms, Dubin-Johnson syndrome, PFIC diseases, Rotor syndrome), bile acid accumulation, epigenetic and environmental factors (*e.g.,* xenobiotics, toxins) also may play an important role in the etiology of liver diseases thereby affecting the expression of drug transporters. These features must be considered in order to accurately predict drug disposition and develop optimal drug dosage regimens. [196,197]

Inflammation is prevalent among different forms of liver disease discussed in this review and appears to be a key regulator in liver disease-mediated alterations in drug transporter expression and function. Hence, evaluating the activation of Toll-like receptor signaling pathways in viral infections, for example, and other downstream proinflammatory cytokines (*e.g.,* IL-1β, IL-6 and TNF-α) will be critical to understanding altered drug disposition in patients with various types of liver disease.[198–200] The effects of inflammation on drug transporter function are likely to be disease specific and will require extensive knowledge

regarding the mechanisms of immuno-stimulation, the varying degrees of inflammatory challenge, as well as patient-specific clinical factors.

The field of drug transport continues to evolve as more transporter-specific substrates and inhibitors are identified. However, clinically relevant probes are lacking due, in part, to the multiplicity of drug transporters (*i.e.,* overlapping substrate specificity between transporters), the dynamic interplay between uptake, efflux, and metabolism processes, and the inability to quantify tissue-specific drug concentrations. Advances in magnetic resonance imaging (MRI) and positron emission tomography (PET), coupled with development of imaging probes that are substrates for specific transporters, will continue to facilitate the quantification of hepatic transporter function, particularly canalicular efflux transporters. These tools will improve our ability to assess transporter function in diseases afflicting the liver. Finally, the amalgamation of such functional data can serve as input for the development of pharmacokinetic modeling and systems pharmacology approaches to better understand and predict the disposition of drugs and endogenous substrates of hepatic transporters in patients with liver disease. This will improve our ability to select safe and effective drugs and design optimal dosage regimens for patients with liver disease.

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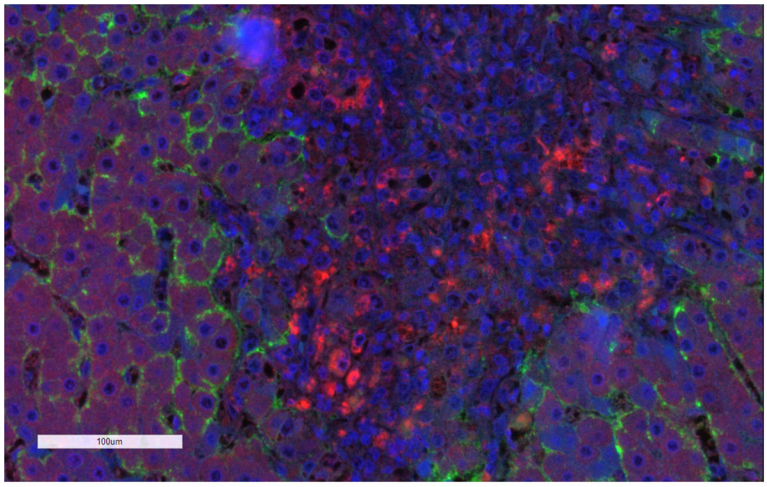

Figure 1. Immunofluorescence staining of MRP1 in a liver tissue section from a patient with primary biliary cirrhosis

Dual staining of MRP1 (red) and Na^+/K^+ ATPase (green), which was used as a basolateral membrane marker. The nuclei are stained in blue. The general methods are described in Pomozi et al.[201] MRP1 and Na^+/K^+ ATPase antibodies were purchased from Abcam and SantaCruz Biotechnology, respectively.

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Table 1

Altered Expression of Hepatic Transporters in Liver Disease

Transporter	Liver Disease	Alterations (mRNA)	Alterations (protein)	Technique	References
NTCP/Ntcp	Cholestasis	↓ (~2-fold, human); ↓ (~3-fold, rodent)	↓ (~3-fold, human); ↓ (~3-fold, rodent)	RT-qPCR; NB; WB	70,89,92,202
	HCV	↓ (human) or ↔ (human); ↔ (rodent)	-	RT-qPCR	108,109,203
	HCC	↓ (~2-fold, human)	↓ (human)	RT-qPCR; NB	151,204
	HIV	-	-	-	-
	NASH	↑ (~1.5-fold, human) or ↓ (~2–5-fold, human); ↓ (~2-fold, rodent)	↓ (~5-fold, human)	ISH; RT-qPCR WB	176,177,179,185
	PBC/cirrhosis	↓ (~1.5–3-fold, human)	↓ (~2-fold, human)	RT-qPCR; WB; IF	189,191
OATP1B1/Oatp1b2	Cholestasis	↓ (~2-fold, human); ↓ (~2-fold, rodent)	↔ (rodent)	NB; RT-qPCR; WB	89,92,202
	HCV	↓ (~1.5-fold human); ↔ (rodent)	-	RT-qPCR	108,109,205
	HCC	↓ (~2–3-fold, human) or ↔ (human)	↓ (human)	RT-qPCR; IF; IHC; WB	121,129–132,204
	HIV	-	-	-	-
	NASH	↔ (human); ↑ (~10-fold, rodent) or ↔ (rodent) or ↓ (~2-fold, rodent)	↑ (~5-fold, human); ↑ (~10-fold, rodent) or ↔ (rodent)	ISH; RT-qPCR; WB	169,174,179,188
	PBC/cirrhosis	↔ (human) or ↓ (~2–3-fold, human)	↔ (human) or ↓ (~2-fold, human)	RT-qPCR; IF; WB	189–191,205
OATP1B3	Cholestasis	↓ (~2-fold, human); ↓ (~2-fold, rodent)	↔ (rodent)	NB; RT-qPCR; WB	89,202
	HCV	-	-	-	-
	HCC	↓ (~5–50-fold, human)	↓ (human)	NB; RT-qPCR; WB; IHC; IF	121,131,133
	HIV	-	-	-	-
	NASH	↔ (human)	↓ (~10-fold, human)	ISH; WB	175
	PBC/cirrhosis	↔ (human) or ↓ (~2-fold, human)	↔ (human) or ↓ (~2–3-fold, human)	RT-qPCR; IF; WB	189–191

Transporter	Liver Disease	Alterations (mRNA)	Alterations (protein)	Technique	References
OATP2B1/Oatp2b1	Cholestasis	-	-	-	-
	HCV	↓ (, human); ↑ (~2-fold rodent)	-	RT-qPCR	109,203
	HCC	-	-	-	-
	HIV	↔ (rodent)	-	RT-qPCR	164
	NASH	↔ (human); ↔ (rodent)	↔ (human); ↓ (~2-fold, rodent)	ISH; WB	174,188
	PBC/cirrhosis	↑ (human)	↑ (human)	RT-qPCR; WB	205
OAT2/Oat2	Cholestasis	-	-	-	-
	HCV	↓ (human); ↔ (rodent)	-	RT-qPCR	109,203
	HCC	-	-	-	-
	HIV	-	-	-	-
	NASH	↓ (~2-fold, rodent)		RT-qPCR	179
	PBC/cirrhosis	-	-	-	-
OCT1/Oct1	Cholestasis	↓ (~3-fold rodent)	↓ (~2-fold rodent)	RT-qPCR; WB	88
	HCV	↔ (human) or ↓ (human); ↓ (~2-fold rodent)	-	RT-qPCR	108,109,203
	HCC	↓ (~2–3-fold, human)	↓ (human)	RT-qPCR; WB; IF	137,138
	HIV	-	-	-	-
	NASH	-	-	-	-
	PBC/cirrhosis	-	-	-	-
MRP1/Mrp1	Cholestasis	-	-	-	-
	HCV	↑ (10-fold human)	↑ (human)	RT-qPCR; IHC	112

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Transporter	Liver Disease	Alterations (mRNA)	Alterations (protein)	Technique	References
	HCC	↑ (human)	↑ (human)	RT-qPCR; WB	112,158,206
	HIV	↔ (rodent)	-	RT-qPCR	164
	NASH	↑ (~2-fold, human); ↑ (~2-fold, rodent)	↑ (~2-fold, human)	ISH; RT-qPCR; WB	74,176,180
	PBC/cirrhosis	↑ (human)	↑ (human)	RT-qPCR; IHC	112,205
MRP3/Mrp3	Cholestasis	↑ (~3-fold, human)	↑ (~3-fold, human)	RT-qPCR; IHC	70
	HCV	↑ (~10-fold, human); ↔ (rodent)	↑ (~2–20-fold, human)	RT-qPCR; WB	111,112,203
	HCC	↑ (~2-fold, human); ↔ (human)	-	RT-qPCR	112,139,158,206
	HIV	↑ (~3-fold, rodent)	-	RT-qPCR	164
	NASH	↑ (~2-fold, human); ↓ (~2-fold, rodent) or ↑ (~5-fold, rodent)	↑ (~2-fold, human); ↓ (~2-fold, rodent) or ↑ (~3-fold, rodent)	ISH; WB	74,174,180
	PBC/cirrhosis	↑ (~10-fold, human) or ↓ (human, diabetic cirrhosis); ↔ (human, alcohol cirrhosis)	↑ (human) and ↑ (human, diabetic and alcohol cirrhosis)	RT-qPCR; IHC	112,189,191,205
MRP4/Mrp4	Cholestasis	↑ (~1.5-fold, human)		RT-qPCR	70,188,202
	HCV	↑ (~2-fold, human); ↑ (~2-fold, rodent)	↑ (~3-fold, human)	RT-qPCR; WB	103,111,203
	HCC	↑ (~ 2-fold, human)	-	RT-qPCR	139
	HIV	↔ (rodent)	-	RT-qPCR	164
	NASH	↑ (~3-fold, human); ↑ (~3–40-fold, rodent)	↑ (~3-fold, human); ↑ (~3-fold, rodent)	ISH; RT-qPCR; WB	74,174,176,180
	PBC/cirrhosis	↔ (human) or ↑ (human)	↑ (human)	RT-qPCR; IHC; WB	190,205
BCRP/Bcrp	Cholestasis	-	-	-	-
	HCV	↓ (~2-fold, human); ↓ (~2-fold, rodent)	-	RT-qPCR	103,203
	HCC	↑ (human); ↔ (human)	↑ (human)	RT-qPCR; IHC	139–141

Transporter	Liver Disease	Alterations (mRNA)	Alterations (protein)	Technique	References
	HIV	↔ (rodent)	-	RT-qPCR	164
	NASH	↑ (~2-fold, human); ↑ (~5-fold, rodent)	↑ (~2-fold, human); ↔ (rodent)	RT-qPCR; WB	74,180
	PBC/cirrhosis	↑ (~ 2-fold, human)	↑ (human)	RT-qPCR; WB; IHC	205,207
BSEP/Bsep	Cholestasis	↔ (human) or ↓ (~2-fold, human); ↓ (~2-fold, rodent)	↔ (human); ↓ (~2-fold, rodent)	RT-qPCR; WB; IHC	70,85,188,202
	HCV	↑ (~2-fold human) or ↓ (human); ↔ (rodent)	↔ (human)	RT-qPCR; IHC	109,111,112,203
	HCC	↓ (human)	↓ (human)	RT-qPCR; WB	143,144
	HIV	-	-	-	-
	NASH	↑ (~5-fold, human) or ↓ (~2-fold, human); ↔ (rodent)	-	RT-qPCR	176,177,185
	PBC/cirrhosis	↔ (human) or ↓ (human)	↔ (human) or ↓ (human)	IHC; RT-qPCR; WB	190,191
MRP2/Mrp2	Cholestasis	↔ (human) or ↓ (~2-fold, human)	↓ (human)	RT-qPCR; IHC	70,92,188,202
	HCV	↔ (human) or ↓ (~2-fold human); ↔ (rodent)	↔ (human)	RT-qPCR; IHC	103,109,111,112,203
	HCC	↔ (human)	↔ (human)	RT-qPCR; IHC	109,155
	HIV	↑ (~2-fold, rodent)	↑ (~1.5-fold, rodent)	qPCR; WB	164
	NASH	↔ (human) or ↓ (~2-fold, human); ↔ (rodent) or ↑ (~2-fold, rodent)	↑ (~3-fold, human); ↑ (~2-fold, rodent) or ↔ (rodent)	ISH; RT-qPCR; WB	74,174,176,179,180,185
	PBC/cirrhosis	↔ (human)	↔ (human)	RT-qPCR; WB; IHC	189–191
P-gp	Cholestasis	-	↔ (human)	IHC	188
	HCV	↑ (~2–5-fold, human); ↔ (rodent)	↑ (~20-fold, human)	RT-qPCR; IHC	103,111,112,203
	HCC	↓ (human)	↑ (human)	RT-qPCR; WB	150–153
	HIV	-	↑ (~1.5-fold, rodent)	WB	164
	NASH	↑ (~2-fold, rodent)	↑ (~2-fold, rodent)	ISH; WB	188

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Transporter	Liver Disease	Alterations (mRNA)	Alterations (protein)	Technique	References
	PBC/cirrhosis	↑ (human)	↑ (5-fold, human)	RT-qPCR; WB; IHC	[112,189]

Abbreviations: no data available (-); hepatocellular carcinoma (HCC); hepatitis C virus (HCV); human immunodeficiency virus (HIV); immunofluorescence microscopy (IF); immunohistochemistry (IHC); *in situ* hybridization (ISH); nonalcoholic steatohepatitis (NASH); northern blot (NB); primary biliary cholangitis (PBC); quantitative reverse transcription polymerase chain reaction (RT-qPCR); western blot (WB); ↑ increased expression compared to normal tissues, ↓ decreased expression compared to normal tissues, ↔ no change in expression compared to normal tissues. Although humans have two different OATP1B transporters (OATP1B1 and OATP1B3), mice have a single Oatp1b2 ortholog, which was grouped with OATP1B1 in this table for simplicity.

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Table 2

Altered Transporter-Mediated Drug Disposition in Liver Disease Resulting in Changes in Pharmacokinetics and/or Efficacy

Liver Disease	Drug	Drug Class	Altered Drug Disposition	Implicated Transport Protein	References
Cholestasis	Doxorubicin	Chemotherapeutic	↑ systemic concentrations	Mrp2 (rodent)	100
	Metformin	Antidiabetic	↓ systemic clearance and hepatic uptake; ↓ suppression of glucose production	Oct1 (rodent)	99
HCV	Nelfinavir	Antiretroviral	↑ systemic concentrations	P-gp (human)	115
	^{99m}Tc-mebrofenin	Hepatobiliary imaging agent	↓ hepatic uptake, ↑ T_{max}, ↓ hepatic excretion	OATP, MRP2(human)	116
HCC	Gd-EOB-DTPA	Hepatobiliary contrast agent	↑ or ↓ signal intensity	OATP1B1 (human) OATP1B3(human) MRP2 (human)	19,20
	Methotrexate	Antimetabolite	↑ or ↓ systemic concentrations	OATP1B1 (transgenic mice)	208
HIV	Indinavir, Nelfinavir, Saquinavir	Protease inhibitors	↑ or ↓ systemic concentrations	Mdr1a (rodent)	209
NASH	APAP/APAP-glucuronide	Analgesic	↑ systemic concentrations; ↓ biliary excretion	MRP3 (human); Mrp2/Mrp3 (rodent)	74
	Morphine/morphine-glucuronide	Analgesic	↑ systemic concentrations	MRP3 (human)	183
	^{99m}Tc-mebrofenin	Hepatobiliary imaging agent	↑ systemic concentrations; ↑ hepatic exposure	OATP, MRP2, MRP3 (human)	2
	Gd-EOB-DTPA	Hepatobiliary contrast agent	↑ hepatic exposure	Mrp2 (rodent)	184
	Methotrexate	Chemotherapeutic	↑ liver and ↑ GI toxicity	Mrp1–4, Mdr1 P-gp, Bcrp (rodent)	207
	Pemetrexed	Chemotherapeutic	↑ systemic concentrations; ↓ biliary excretion	Mrp2 (rodent)	210
	Simvastatin	Cholesterol-lowering	↑ systemic concentrations	Oatp (rodent)	175
PBC/cirrhosis	Gd-EOB-DTPA	Hepatobiliary contrast agent	↓ hepatic signal intensity	OATP (human)	192

Abbreviations: data not available (-); hepatocellular carcinoma (HCC); hepatitis C virus (HCV); human immunodeficiency virus (HIV); nonalcoholic steatohepatitis (NASH); primary biliary cholangitis (PBC), ↑ increased, ↓ decrease