Review Article

Theme: Transporters and Cancer Therapy
Guest Editor: Rajgopal Govindarajan

Role of Organic Anion-Transporting Polypeptides (OATPs) in Cancer Therapy

Nilay Thakkar,¹ A. Craig Lockhart,² and Woojin Lee^{1,3,4}

Received 28 September 2014; accepted 11 February 2015; published online 4 March 2015

Abstract. The superfamily of organic anion-transporting polypeptides (OATPs, gene symbol *SLCO*) includes important transporters handling a variety of endogenous and xenobiotic substrates. Currently, 11 human OATPs are known and their substrates include endogenous hormones and their conjugates, anticancer drugs, and imaging agents. The contribution of OATPs to the *in vivo* disposition of these substrates has been extensively investigated. An accumulating body of evidence also indicates that the expression of some OATPs may be up- or downregulated in several types of cancers, suggesting potential pathogenic roles during the development and progression of cancer. Given that the role of OATPs in handling cancer therapeutics has been already covered by several excellent reviews, this review will focus on the recent progresses on the topic, in particular the role of OATPs in the disposition of anticancer drugs, the impact of OATP genetic variations on the function of OATPs, and the OATPs differentially expressed in cancer and their potential roles in cancer development, progression, and treatment.

KEY WORDS: cancer therapy; organic anion-transporting polypeptides; transporters.

INTRODUCTION

The organic anion-transporting polypeptides (OATPs) represent an important superfamily of solute carriers expressed in various tissues throughout the body. The OATPs can mediate the bidirectional transport of a diverse array of endogenous and xenobiotic compounds, including organic dyes, bile acids, prostaglandins, cyclic nucleotides, steroid hormones and their conjugates, thyroid hormones, drugs, and environmental toxins. The majority of OATP substrates are large amphipathic organic anions (molecular weights greater than 300), but OATPs can also transport cationic and neutral compounds. OATPs are known to transport their substrates in a sodium-independent manner. Common structural features of the OATP superfamily include 12 transmembrane domains with intracellular amino and carboxy termini as well as a large extracellular loop between the ninth and tenth transmembrane regions.

The OATP superfamily belongs to the *SLCO* gene family and is divided into six families based on sequence similarities (1). Currently, 11 human OATPs are known with the OATP1 family being most well characterized. The OATP1 family includes four members, OATP1A2,

OATP1B1, OATP1B3, and OATP1C1, which display broad and overlapping substrate specificity. The OATP2 family includes two members, OATP2A1 and OATP2B1, both of which display relatively narrow substrate specificity compared to other OATPs. The OATP4 family includes OATP4A1 and OATP4C1. The OATP3, OATP5, and OATP6 families include OATP3A1, OATP5A1, and OATP6A1, respectively. Orthologs of human OATPs are reported in other species, but there are cases that no straightforward ortholog is shared between humans and animals. For example, humans have only one OATP1A family member (OATP1A2), but mice have at least four known Oatp1a family members (Oatp1a1, Oatp1a4, Oatp1a5, and Oatp1a6). On the other hand, humans have two OATP1B transporters (OATP1B1 and OATP1B3), whereas mice have a single rodent ortholog of Oatp1b2 (1).

Early investigations primarily focused on the identification and characterization of OATPs expressed in various organs throughout the body and the roles of OATPs in determining the disposition of substrates *in vitro* and *in vivo*. Subsequent reports revealed that the expression of OATPs may be altered in different disease conditions including cancer and may play a potential role in the development and progression of cancer as well as the disposition of anticancer drugs (2–6). Given that the role of OATPs in handling cancer therapeutics has been already covered by several excellent reviews (7–10), this review will focus on the recent findings in the field. We will first provide a brief summary of the current understanding of the roles of OATPs on the disposition of anticancer drugs and the impact of their genetic polymorphisms on the expression and function of OATPs, as well as the use of animal models to study the role of OATPs in anticancer drug disposition. In a later section,

¹Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, Kentucky, USA.

²Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA.

³College of Pharmacy, Seoul National University, Seoul, South Korea.

⁴To whom correspondence should be addressed. (e-mail: woojin.lee@uky.edu)

we will provide an update on the current knowledge about OATPs expressed in cancer and their potential roles in cancer development, progression, and treatment.

ROLE OF OATPS IN THE DISPOSITION OF SUBSTRATES IMPLICATED IN CANCER THERAPY

OATPs can mediate the transport of a wide range of endogenous and xenobiotic substrates in various tissues. The endogenous substrates of OATPs include cyclic and linear peptides, prostaglandins, bile acids, steroid hormone and their conjugates, and thyroid hormones. Diverse classes of drugs, including anticancer drugs, are also substrates of OATPs (1,11). In particular, the transporters of the OATP1 family have a number of substrates relevant in cancer therapy (Table I). In this section, we will briefly summarize the current knowledge regarding the role of OATPs in handling the most well-studied substrates in cancer therapy since several extensive reviews are already available on this topic (7,8,12).

Endogenous steroid hormones have been implicated in enhancing the survival and proliferation of cancer cells. Estrone-3-sulfate (E3S) is a major form of circulating estrogens and serves as an important source of estrogenic activity in postmenopausal women, the population with a high incidence rate of hormone-dependent breast and ovarian cancers. Due to its hydrophilic and charged nature, E3S is not readily permeable across the plasma membrane and it often relies on a transporter-mediated mechanism to enter the cells. Among the 11 human OATP members, seven (OATP1A2,

OATP1B1, OATP1B3, OATP1C1, OATP2B1, OATP3A1, and OATP4A1) are shown to transport E3S (7,13). These OATPs may facilitate the uptake of E3S not only in major organs such as the liver, kidney, intestine, and brain but also in hormone-dependent cancers (13–15). Similar to E3S, dehydroepiandrosterone sulfate (DHEA-S) is transported by multiple OATPs (OATP1A2, OATP1B1, OATP1B3, and OATP2B1) and may gain entry to cells *via* these transporters (7). On the other hand, testosterone appears to be transported only by OATP1B3 (16,17). Many of these investigations, however, focused on the uptake of steroid hormones and their conjugates into cancer cells and the subsequent impact on cancer cell proliferation and related cellular pathways, rather than the disposition of hormonal substrates in the whole body.

In the case of anticancer drugs handled by OATPs, a number of investigations have examined whether the expression/function of OATPs can influence the pharmacokinetic profiles of anticancer drugs, and consequently therapeutic effects and toxicities. The most well-studied substrates include methotrexate, doxorubicin, and taxanes (paclitaxel and docetaxel). For these drugs, multiple reports indicated that these agents are handled by OATP1A2, OATP1B1, and OATP1B3 (3,18–20). The results were obtained from various models, ranging from *in vitro* heterologous expression systems, *in vivo* preclinical knockout and humanized mouse models, and clinical studies. Docetaxel is reported to be a substrate of human OATP1B1 and OATP1B3 and rat and mouse Oatp1b2 *in vitro* (21,22). However, the pharmacokinetic profiles of docetaxel were not substantially altered in a cohort of patients harboring genetic variations associated with decreased OATP1B1 or OATP1B3 activity (23). These results might be related to the presence of other uptake transporters with overlapping functions in the human liver. Indeed, a recent study using humanized transgenic mice indicated that elevated plasma levels of docetaxel observed in the knockout mice lacking Oatp1a/1b can be rescued by liver-specific expression of human OATP1B1, OATP1B3, or OATP1A2, confirming the relevance and overlapping nature of these OATP transporters in determining *in vivo* disposition of docetaxel (19). When the involvement of OATPs in the handling of taxanes is considered, there was also a report indicating that taxanes are not handled by OATP1B3 (21). These apparent discrepancies may be due to differences in the expression systems (*Xenopus laevis* oocytes vs HEK293) (21). Other well-studied anticancer drugs handled by OATP1B1 and OATP1B3 are rapamycin (sirolimus) and SN-38 (7-ethyl-10-hydroxycamptothecin, an active metabolite of irinotecan) (21,24–27). Additionally, OATP1B1 transports CP-724,714 (a Her2 tyrosine kinase inhibitor), *cis*-diammine-chloro-cholyglycinate-platinum(II) (a bile-acid cisplatin derivative), and gimatecan (a camptothecin analog) (28–30). Imatinib, used for leukemia therapy, is reported to be transported by OATP1A2 and OATP1B3 (31,32). Further investigations will be necessary to elucidate the clinical relevance of these transporters in influencing the *in vivo* disposition and therapeutic effects of these substrate drugs.

The magnetic resonance imaging agent gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is also shown to be transported by OATP1B1 and OATP1B3 (33–35). In a retrospective study involving 22

Table I. Selected Endogenous Substrates, Anticancer Drugs, and Imaging Agents Transported by OATPs

OATPs	Substrates
OATP1A2	Endogenous hormones and conjugates Estrone-3-sulfate, DHEA-S Anticancer drugs Imatinib, methotrexate, paclitaxel, doxorubicin, docetaxel
OATP1B1	Endogenous hormones and conjugates Estrone-3-sulfate, DHEA-S Anticancer drugs Methotrexate, paclitaxel, rapamycin, flavopiridol, SN-38, gimatecan, doxorubicin, docetaxel, CP-724,714, <i>cis</i> -diammine-chloro-cholyglycinate-platinum(II) Imaging agents Gd-EOB-DTPA
OATP1B3	Endogenous hormones and conjugates Estrone-3-sulfate, DHEA-S, testosterone Anticancer drugs Rapamycin, methotrexate, paclitaxel, doxorubicin, docetaxel, imatinib, SN-38 Imaging agents Gd-EOB-DTPA

Due to the limited number of references that can be cited in this review, Table I does not include original references, but details can be found in the recent reviews (7,8) and references therein. OATP organic anion-transporting polypeptide, DHEA-S dehydroepiandrosterone sulfate, Gd-EOB-DTPA gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid

patients with hepatic cancer, high OATP1B3 expression levels were significantly correlated with increased uptake of Gd-EOB-DTPA (33). In individuals carrying certain genetic variations associated with decreased OATP1B1 activity, the liver enhancement by the gadolinium-based imaging agent was substantially attenuated (35). These findings suggest that the activity of OATPs and genetic variations may be potential confounders leading to a reduced signal intensity in liver magnetic resonance imaging. A recent retrospective study took advantage of this relationship and attempted to use the signal intensity of Gd-EOB-DTPA as a marker for hepatic vascularity and OATP-related activity and potentially as a prognostic factor for patients with early-stage hepatic cancer (36). It should be noted that these investigations did not include the control group with no cancer, so the results do not provide evidence on differential expression of OATP1B1 or OATP1B3 in hepatic cancer tissues relative to the nonmalignant liver tissues. Other reports indicate that the expression of OATP1B1 and OATP1B3 is reduced in hepatic cancer tissues compared to nonmalignant liver cells (37–41).

IMPACT OF OATP POLYMORPHISMS ON THE PHARMACOKINETICS OF ANTICANCER DRUGS

A number of naturally occurring single nucleotide polymorphisms (SNPs) in the genes encoding OATPs have been reported and extensively investigated for their impact on the expression and function of the corresponding OATPs and consequently on the disposition and efficacy of anticancer drugs. In particular, polymorphic variants of genes encoding OATP1A2, OATP1B1, and OATP1B3 have been reported to be clinically relevant. Comprehensive reviews on this topic are already available elsewhere (7,8). Thus, only a brief summary and an update involving the disposition of anticancer drugs are provided below.

For OATP1A2, the initial investigation was carried out using *X. laevis* oocytes expressing genetic variants of OATP1A2 and methotrexate (18). Four out of the 12 OATP1A2 variants examined displayed altered transport of E3S and methotrexate; the p.I13T (rs10841795) variant displayed enhanced transport activity, the p.R168C (rs11568564) and p.E172D (rs11568563) variants demonstrated decreased transport activity, and the p.N278DEL (rs11568555) variant produced a nonfunctional protein. However, the impact of these OATP1A2 variants on the pharmacokinetics of methotrexate in patients remains to be determined. More recently, a similar line of clinical investigation was carried out with imatinib and genetic variations present in the coding and promoter regions of the gene encoding OATP1A2 (32). The authors were able to identify polymorphic variations in the promoter region of OATP1A2 (–1105G>A (rs4148977) in linkage disequilibrium with –1032G>A (rs4148978), and –361G>A (rs3764043)) which correlated with the clearance of imatinib in patients with chronic myeloid leukemia (32). Further clinical studies are required to confirm these findings in a larger group of patients and to verify whether the identified OATP1A2 variations correlate with therapeutic effects or toxicities of imatinib.

For OATP1B1, there are several commonly occurring SNPs or diplotypes. In particular, the OATP1B1*15 (harboring variations causing two amino acid substitutions, p.N130D

(rs2306283) and p.V174A (rs4149056)) variant has been most extensively investigated. Compared to the wild-type OATP1B1 (OATP1B1*1a), the OATP1B1*15 displayed reduced uptake of SN-38 (an active metabolite of irinotecan), when tested in *in vitro* cell line models stably expressing OATP1B1 variant proteins (25). The clinical relevance of these findings was subsequently validated by comparing the pharmacokinetics and toxicity profiles in patients receiving irinotecan therapy (42,43). Patients with the OATP1B1*15 genotype showed increased systemic exposure and toxicities of SN-38 compared to those with the wild-type OATP1B1 (42,43). Similar findings have been reported with patients treated with methotrexate. In particular, recent reports validating the relevance of the OATP1B1*15 genotype in determining the pharmacokinetics and toxicities of methotrexate were from genome-wide association studies or studies involving a large number of patients and cohorts from different institutions (44–46). Continued investigations examining the prospective utility of the OATP1B1 genotypes in improving therapeutic effects and safety profiles of these anticancer drugs are warranted.

As a closely related member to OATP1B1, OATP1B3 displays substantial overlapping substrate specificity, yet harbors fewer genetic variations. Initially, the functional impact of three nonsynonymous SNPs of OATP1B3 (p.S112A (rs4149117), p.M233I (rs7311358), and p.G522C (rs72559743)) was examined using *in vitro* models (47). However, none of these three SNPs were found to have a significant impact on the clearance and other pharmacokinetic parameters of paclitaxel in cancer patients (48). For docetaxel, a potential association between OATP1B3 genotypes and toxicity (leukopenia/neutropenia) has been recently reported in patients (49,50). Additional investigations will be required to validate the clinical relevance of these findings.

ANIMAL MODELS TO INVESTIGATE THE ROLE OF OATPS IN THE DISPOSITION OF ANTICANCER DRUGS

Given the increasingly recognized roles that OATPs play in determining the disposition of many drugs, it has become important to assess the potential of OATPs and their genetic variations as a source for variable drug disposition and response *in vivo*. In recent years, a number of transgenic mouse models have been reported, including the knockout mouse models lacking the orthologs of human OATP1A and OATP1B subfamily members and the humanized mouse models where human OATPs are introduced after deleting the genes for mouse orthologs.

In rodents, there is only one member of the Oatp1b subfamily and it is considered to be the closest ortholog for both human OATP1B1 and OATP1B3. The knockout mouse models lacking Oatp1b2 have been developed by three independent groups and have served as useful tools to delineate and extrapolate the *in vivo* relevance of both human OATP1B1 and OATP1B3 to the disposition of relevant substrates (51–53). Given the large overlap in tissue distribution and substrate specificity within the OATP1 family, another transgenic mouse model deficient for all five established *Slco1a* and *Slco1b* genes (*Slco1a1b*^{–/–} mice) has also been developed (54). These mice lacking Oatp1a1,

Oatp1a4, Oatp1a5, Oatp1a6, and Oatp1b2 displayed drastically reduced hepatic uptake of methotrexate, fexofenadine, and paclitaxel and subsequently increased systemic exposure for all of these drugs (54,55).

In addition, humanized transgenic mouse models expressing OATP1A2, OATP1B1, and OATP1B3, in the absence of the background expression of the mouse orthologs, have been developed and used to account for possible species-dependent differences between the mouse and human OATP orthologs (56). For example, a humanized OATP1B1 mouse model with liver-specific expression of OATP1B1 was generated and the disposition of methotrexate was investigated. The plasma concentrations of intravenously administered methotrexate in the humanized OATP1B1 transgenic mice were substantially lower than in the control animals (56). In addition, the humanized OATP1B1 transgenic mice displayed a greater amount of methotrexate in the liver as well as a higher liver to plasma ratio of methotrexate than the control animals (56). Similarly, transgenic humanized OATP1A/1B mouse models were generated with liver-specific expression of OATP1B1, OATP1B3, and OATP1A2 in an Oatp1a/1b knockout background. This model was utilized to show that paclitaxel, methotrexate, SN-38, docetaxel, and doxorubicin are transported by OATP1A/1B *in vivo* (19,20,57,58).

These findings have provided further insights regarding the contribution of OATP1A/1B transporters to the disposition, response, and toxicity of anticancer drugs. Importantly, those investigations have provided the impetus for additional studies to elucidate the role of other OATPs and commonly observed polymorphisms in the pharmacokinetics and pharmacodynamics of anticancer drugs. Together, these tools will continue to provide a useful guide for drug development and optimization of anticancer drug therapy.

OATPS EXPRESSED IN CANCER

There is a substantial body of evidence indicating that the expression of OATPs can be altered in various types of cancers. In this section, we will summarize the current literature about different OATPs expressed in cancer tissues and their proposed functions and cancer-specific mechanisms of regulation.

OATP1A2 (Gene Symbol, *SLCO1A2*)

OATP1A2 expression has been confirmed in several normal tissues and cell types including the blood-brain barrier, enterocytes, cholangiocytes, and kidneys (59,60). Given that OATP1A2 can mediate the transport of endogenous hormonal substrates and several anticancer drugs (Table I), several investigations have examined the expression and functional impact of OATP1A2 in cancer. OATP1A2 expression was first reported in breast cancer and subsequently in additional types of cancer including colon, prostate, and bone (Table II) (6,61–63,65). To date, the potential functional significance of OATP1A2 has been reported in breast cancer, but not in other types of cancer.

The expression of OATP1A2 messenger RNA (mRNA) and protein in breast cancer was first reported by Miki *et al.* (61). The results from reverse transcriptase-polymerase chain

reaction (RT-PCR) analyses indicated that OATP1A2 is expressed in human breast cancer tissues, but not in noncancerous breast tissues, adipose tissues, or stromal cells (61). These findings are consistent with the reports showing that OATP1A2 mRNA was barely detectable in nonmalignant mammary epithelial cells (below the level of quantification) (95). Interestingly, Miki *et al.* also reported a significant correlation between the expression of OATP1A2 and the nuclear receptor PXR (pregnane X receptor), providing possible insights into the regulation of OATP1A2 expression (61). These findings were further validated in breast cancer cell line models (62) where treatment of T47-D cells with rifampicin (a well-known PXR activator) increased the expression of OATP1A2 and cellular uptake of E3S and promoted breast cancer cell proliferation *in vitro*. In line with these findings, a more recent study using mouse xenograft models reported that OATP1A2 may play a role in regulating *in vivo* tissue distribution of E3S and the growth of hormone-dependent breast cancer (14). In the clinical setting, the expression of OATP1A2 combined with another transporter OCT6 in patients with triple-negative breast cancer (which displays no detectable expression for estrogen receptor, progesterone receptor, and Her2/neu and has very poor prognosis) was predictive of response to anthracycline/taxane-based neoadjuvant chemotherapy (96). Further investigations will be required to evaluate the clinical relevance of these findings in patients with hormone-dependent or triple-negative breast cancers.

Although detailed functional investigations have not been reported, the expression of OATP1A2 has been observed in other cancers. Arakawa *et al.* reported that OATP1A2 is expressed in human prostate cancer cell lines (LNCaP and 22Rv1) and facilitates the uptake of DHEA-S and enhances cancer cell growth under androgen-depleted conditions (6). The levels of OATP1A2 mRNA were reported to be elevated in human osteosarcoma cell lines (HOS and MG-63) and human kidney cancer cells metastasized to bone tissue (65). On the other hand, colon polyps and colon cancer tissues were reported to have reduced OATP1A2 mRNA levels compared to healthy colon tissue (63).

As noted above, the nuclear receptor PXR may play a role in regulating OATP1A2 expression in cancer (62). A PXR response element present in the human OATP1A2 promoter was confirmed to have physical interactions with PXR and to play a role in the transactivation of OATP1A2 in breast cancer cells (62). If OATP1A2 is eventually identified to have an important role in cancer development, progression, or therapy, its regulation through PXR may be a key relationship to investigate.

OATP1B1 (Gene Symbol, *SLCO1B1*)

OATP1B1 is abundantly expressed in the normal liver and was initially considered to be liver specific (2,66). Several investigations have been carried out to assess the expression levels and functions of OATP1B1 in cancer. To date, OATP1B1 is reported to be expressed in colon cancer and ovarian cancer and variably expressed in hepatocellular carcinoma (HCC).

A number of reports indicate that the expression of OATP1B1 is decreased in HCC compared to nonmalignant

liver. Since the first report on the decreased OATP1B1 protein levels in HCC cell lines (67), many subsequent investigations have reported similar findings using HCC tissue samples and cell lines (37–40). However, there is also a report noting no significant reduction of OATP1B1 in HCC tissues compared to nonmalignant liver tissues (41). These apparent discrepancies may be related to different detection methods as well as tumor heterogeneity (37,41).

In contrast to the variable expression of OATP1B1 in HCC, OATP1B1 expression was reported to be elevated in cancers derived from nonhepatic tissues which normally do not express OATP1B1. For instance, OATP1B1 expression has been reported in colon polyps and colon cancer tissue (63) as well as ovarian cancer tissue samples and cell lines (SK-OV-3) (69). In regard to its transport functions in cancer, OATP1B1 is implicated to play a role in paclitaxel uptake in ovarian cancer cells (69). Overall, further investigations will be necessary to examine the clinical significance of altered expression of OATP1B1 in cancers.

OATP1B3 (Gene Symbol, *SLCO1B3*)

When OATP1B3 was cloned for the first time, it was found to be abundantly expressed in the normal liver, but not in any other nonmalignant tissues (3). This initial report noted that OATP1B3 is also expressed in multiple types of cancer, which was confirmed by a number of subsequent investigations. Currently, OATP1B3 is arguably the most extensively investigated OATP member with regard to cancer-related alterations in expression. In recent years, there has been substantial progress in our understanding of cancer-specific expression of OATP1B3 including the identification of cancer-specific variants.

OATP1B3 mediates the transport of several endogenous substrates including hormones (E3S, DHEA-S, testosterone), cancer drugs (methotrexate, imatinib, paclitaxel, SN-38, rapamycin, docetaxel, doxorubicin), microcystins, and MRI contrast agents (gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)) (33,97). Similar to the decreased expression of the closely related member OATP1B1 in HCC, OATP1B3 expression was shown to be decreased in primary and metastatic liver cancers (39,41,98). It has been suggested that the decreased expression of OATP1B3 and OATP1B1 in hepatic cancer tissues may be related to poor differentiation status and defective membrane protein maturation process often observed in the malignant tissues. On the other hand, OATP1B3 is frequently expressed in several cancerous tissues derived from the gastrointestinal tract, pancreas, lung, breast, prostate, and testes, all of which do not express any detectable level of OATP1B3 in noncancerous settings.

The expression of OATP1B3 in multiple types of cancer was first reported by Abe *et al.* (3). Specifically, northern blot analyses showed the expression of OATP1B3 in various established cancer cell lines (derived from the colon, stomach, pancreas, gall bladder, and lung) and clinical samples (from gastric, colon, and pancreatic cancers) (3). This finding was subsequently corroborated by multiple studies which utilized RT-PCR and immunohistochemical detection methods (Table II). In human breast cancer, OATP1B3 was detected in approximately 50% of

the clinical tissue samples examined by immunohistochemistry and OATP1B3 immunoreactivity was associated with a decreased risk of recurrence and improved prognosis (75). The authors speculated that OATP1B3 overexpression may be associated with hormone-dependent growth mechanisms considering that OATP1B3 transports E3S. In line with these findings, subsequent studies have also suggested that OATP1B3 contributes to the growth of estrogen-dependent breast cancer (13,15). OATP1B3 is also reported to be expressed in prostate and colorectal cancers (16,17,99). In reference to colorectal cancer, OATP1B3 is found to be expressed in the majority (56%) of clinical tissue specimens examined and possibly associated with improved clinical outcomes (99). During these investigations, it was also noted that the immunohistochemical staining for OATP1B3 showed predominantly a cytoplasmic pattern, clearly different from the membranous pattern in normal hepatocytes (4,99).

The efforts to probe possible reasons underlying the cytoplasmic localization pattern of OATP1B3 expressed in cancer cells led to the identification of a cancer-specific OATP1B3 variant (csOATP1B3 or OATP1B3 V1) which utilizes an alternative transcription initiation site from wild-type (WT) OATP1B3 expressed in normal liver (71). The protein translated from the longest open reading frame (ORF) of csOATP1B3 lacks 28 amino acids at the N-terminus compared to WT OATP1B3. Further investigations indicated that in comparison to OATP1B3 WT, csOATP1B3 has defective plasma membrane trafficking, resulting in reduced transport activity of cholecystokinin-8 (a prototype OATP1B3 substrate) (71). Similarly, Nagai *et al.* reported that lung, colon, and pancreatic cancer tissues and cell lines express an alternative OATP1B3 transcript (72). However, this study proposed the four potential ORFs resulting in much shorter amino acid sequences than the ORF reported by our laboratory and another subsequent report (71,100). Currently, csOATP1B3 is found to be the major isoform expressed only in cancer cells, but not in normal tissues. Further studies are required to delineate the biological significance of csOATP1B3 in cancer, specifically whether csOATP1B3 confers any survival advantage or chemotherapy resistance to cancer cells.

With regard to the regulatory mechanisms for OATP1B3 expression, several investigations implicated the involvement of the liver-enriched transcription factor, hepatocyte nuclear factor 3 β (HNF3 β), as well as epigenetic and hypoxia-mediated mechanisms (41,100–102). The contribution of these reported mechanisms may vary depending on the tissue types and disease states. In an earlier report, Vavricka *et al.* showed that HNF3 β is responsible for the transcriptional repression of OATP1B3 expression in HCC (41). A later study showed that epigenetic mechanisms by DNA methylation-dependent gene silencing are involved in the regulation of OATP1B3 in different cancer cell lines (101). A more recent study showed that DNA methylation-dependent gene silencing involving methyl-DNA binding protein 2 (MBD2) regulates the expression of csOATP1B3 (100). A study by Han *et al.* showed that csOATP1B3, but not OATP1B3 WT, is transcriptionally activated by hypoxia (102). Briefly, a functional hypoxia response element (HRE) within the promoter regions of csOATP1B3 was shown to

physically interact with hypoxia-inducible factor-1 α (HIF-1 α) in colon and pancreatic cancer cells (102). We postulated that hypoxia-induced regulation of csOATP1B3 may be operating in line with epigenetic regulation. This hypothesis is based on the observation that the HRE site proposed in our recent study (102) is located in close proximity to the potential methylation site (100). Thus, we examined the effect of *in vitro* methylation on the transactivation of a reporter construct of the csOATP1B3 promoter containing the proposed HRE and methylation sites. Our results showed no substantial changes by *in vitro* methylation, suggesting that hypoxia and epigenetic mechanisms likely work independently in regulating the csOATP1B3 (Thakkar and Lee, unpublished data).

OATP1C1 (Gene Symbol, *SLCO1C1*)

OATP1C1 was identified as a high-affinity transporter for thyroid hormones in brain, Leydig cells of the testis (76), and ciliary bodies (77). Thus far, no cancer drugs have been identified to be substrates of OATP1C1. A study by Liedauer *et al.* showed that OATP1C1 mRNA expression was detected in clinical samples from human osteosarcomas and metastasized kidney cancers, with the highest expression observed in aneurysmal bone cysts (65). This is the only study to report the expression of OATP1C1 in cancer, and the functional role of OATP1C1 in bone cancers is currently unknown.

OATP2A1 (Gene Symbol, *SLCO2A1*)

OATP2A1 was initially cloned and identified as a prostaglandin transporter (103). Currently, no cancer drugs have been reported to be substrates of OATP2A1. In noncancerous tissues, OATP2A1 is expressed ubiquitously. Altered expression of OATP2A1 is reported in various types of cancers (Table II). OATP2A1 expression is reported to be increased in breast cancer, HCC, cholangiocarcinoma, and liver metastases from colon cancer (17,79). On the other hand, reduced OATP2A1 levels are reported in other types of cancer from colon, stomach, ovary, lung, and kidneys (81). Interestingly, the reduced expression of OATP2A1 was linked with increased extracellular levels of proinflammatory prostaglandin E2 (PGE2) in colorectal cancer (81). Higher extracellular levels of PGE2 may activate various signaling cascades in colorectal cancer by interacting with G protein-coupled receptors on the surface. Further investigations are required to better understand the impact of altered OATP2A1 expression in cancer.

OATP2B1 (Gene Symbol, *SLCO2B1*)

OATP2B1 is a ubiquitously expressed uptake transporter that was initially cloned by Tamai *et al.* (90) (Table II). OATP2B1 transports various substrates including steroid hormone conjugates, thyroid hormones, prostaglandins, and other drugs. Although no cancer drugs are currently known to be substrates of OATP2B1, its altered expression is reported in different cancers (Table II). In breast cancer, increased OATP2B1 expression was reported in clinical samples as well as cell lines and was correlated with high tumor grades, but not with altered clinical outcomes (84).

OATP2B1 expression was also shown to be higher in bone cysts compared to that in osteosarcoma tissues (65). Alternatively, Pressler *et al.* showed that OATP2B1 mRNA expression was lower in liver and pancreatic cancers compared to that in nonmalignant tissues (68). However, these findings have not been validated at the protein level. Currently, the role of OATP2B1 in cancer cells is not well understood.

OATP3A1 (Gene Symbol, *SLCO3A1*)

In nonmalignant tissues, OATP3A1 is expressed ubiquitously where it transports various hormones, prostaglandins, and drugs (7). Altered expression of OATP3A1 is reported in various types of cancers (Table II). Increased expression of OATP3A1 transcripts has been reported in multiple cancer cell lines (7,90). Higher OATP3A1 mRNA was detected in aneurysmal bone cysts as compared to osteosarcomas (65). In breast cancer, OATP3A1 is localized both on the plasma membrane and in the cytoplasm (89). Wleck *et al.* showed that OATP3A1 levels were increased in primary and metastatic liver cancers (80).

OATP4A1 (Gene Symbol, *SLCO4A1*)

OATP4A1 is expressed ubiquitously and plays a role in the transport of several endogenous (hormones, prostaglandins, and bile acids) and drug substrates (reviewed in (7)). Similar to OATP3A1, OATP4A1 is also overexpressed in multiple cancer cell lines, aneurysmal bone cysts, liver cancers, and breast cancers (65,79,80,90). In colorectal neoplasia specimens, OATP4A1 mRNA levels were reported to be elevated (91). Additionally, the authors suggested that increased expression of PGE2-transporting OATP2B1 and OATP4A1 may lead to decreased sensitivity to cyclic nucleotides in colorectal neoplasia.

OATP4C1 (Gene Symbol, *SLCO4C1*)

OATP4C1 expression in noncancerous tissues is mainly limited to the kidney where it mediates the uptake of thyroid hormone, cAMP, cardiac glycosides, and methotrexate (92). In breast cancer tissues and cell lines, Wleck *et al.* showed that elevated OATP4C1 mRNA levels were present (79).

OATP5A1 (Gene Symbol, *SLCO5A1*)

OATP5A1 is reported to be expressed in the epithelial cells lining the mammary ducts (89). To date, the tissue distribution and substrates of OATP5A1 are poorly understood. Different studies report the expression of OATP5A1 in cancers (Table II). Immunohistochemical analyses confirmed that OATP5A1 is expressed on the membrane and in the cytoplasm of breast cancer cells (89). OATP5A1 at both the mRNA and protein levels was found to be upregulated in liver cancer (80) and small cell lung cancer (SCLC) (5). As a potential marker of chemotherapy resistance, HEK-293 cells transfected with OATP5A1 showed resistance to satraplatin treatment (5). Further studies may be warranted to elucidate the impact of OATP5A1 on tumor resistance and better understand the role OATP5A1 in cancer.

Table II. Expression of OATPs in Non-malignant and Malignant Tissues

OATPs	Non-malignant tissues	Malignant tissues and cells	
		Alterations	Detection method
OATP1A2	Blood-brain barrier (59)	↑ in breast cancer (61,62)	RT-PCR, IF
	Enterocytes (60)	↓ in colon polyps and colon cancer (63)	RT-PCR
	Cholangiocytes (60)	↑ in prostate cancer cells (6)	qRT-PCR
	Kidney (64)	↑ in bone cancer (65)	RT-PCR
OATP1B1	Liver (2,66)	↓ in liver cancer (37–39,67,68)	RT-PCR, IF, IB
		↑ in colon polyps and colon cancer (63)	RT-PCR
		↑ in ovarian cancer (69)	RT-PCR
OATP1B3	Liver (3,70)	↓ in liver cancer (41)	qRT-PCR, IB
		↑ in colon cancer (4,71,72)	RT-PCR, qRT-PCR, IB, IHC
		↑ in pancreatic cancer (71–73)	RT-PCR, qRT-PCR, IB, IHC
		↑ in lung cancer (38)	RT-PCR, qRT-PCR, IF
		↑ in prostate cancer (16,17,68,74)	qRT-PCR, IF
		↑ in breast cancer (75)	qRT-PCR, IHC
		↑ in testicular cancer (68)	qRT-PCR, IF
		↑ in ovarian cancer (69)	RT-PCR
OATP1C1	Brain (76)	↑ in bone cancers (65)	RT-PCR
	Testes (76)		
	Ciliary body (77)		
OATP2A1	Ubiquitous (78)	↑ in breast cancer (79)	qRT-PCR
		↑ in liver cancer (80)	qRT-PCR, IF
		↑ in bone metastases from kidney cancer (65)	qRT-PCR, IB
		↓ in cancers of bowel, stomach, ovary, lung, and kidney (81)	RT-PCR
OATP2B1	Blood-brain barrier (82)	↑ in bone cancer (65)	RT-PCR
	Heart (83)	↑ in breast cancers (79,84)	qRT-PCR, IF, IB
	Enterocytes (85)	↓ in liver and pancreatic cancers (68)	qRT-PCR
	Liver (86)		
	Placenta (87)		
OATP3A1	Ubiquitous (88)	↑ in bone cysts (65)	RT-PCR
		↑ in breast cancer tissues and cell lines (89)	qRT-PCR, IF, IHC
		↑ in primary and metastatic liver cancer (80)	qRT-PCR, IF
		↑ in cancer cell lines of multiple tissues (90)	RT-PCR
OATP4A1	Ubiquitous (90)	↑ in bone cysts (65)	RT-PCR
		Detected in breast cancer (79)	RT-PCR
		↑ in primary and metastatic liver cancer (80)	qRT-PCR, IF
		Detected in cancer cell lines of multiple tissues (90)	RT-PCR
		↑ in colon cancer (91)	qRT-PCR
OATP4C1	Kidney (92)	Detected in breast cancer cell lines (79)	RT-PCR
OATP5A1	Lactiferous ducts of breast (89)	↑ in breast cancer (89)	qRT-PCR, IF, IHC
		↑ in primary and metastatic liver cancers (80)	qRT-PCR, IF
		↑ in small cell lung cancer (5)	qRT-PCR, IF
OATP6A1	Testes (93)	Detected in lung, bladder, and esophageal cancers (94)	RT-PCR

↑ increased, ↓ decreased, RT-PCR reverse transcriptase-polymerase chain reaction, qRT-PCR quantitative RT-PCR, IF immunofluorescence, IB immunoblotting, IHC immunohistochemistry

OATP6A1 (Gene Symbol, *SLCO6A1*)

OATP6A1 was initially identified as a gonad-specific transporter expressed predominantly in the testes (93,94). Its expression is also reported in cancer tissues (lung, esophageal, and bladder) and lung cancer cell lines (94).

As noted in this section, further investigations are needed to better understand the expression and roles of the OATP2, OATP3, OATP4, OATP5, and OATP6 family members.

CONCLUSIONS AND OUTLOOK

OATPs are expressed in multiple tissues and organs and mediate the transport of a wide range of substrates in a

sodium-independent manner. It is increasingly recognized that OATPs play an important role in the disposition of substrates implicated in cancer therapy. In particular, the variable expression/activity of OATP1 family members and their genetic variations have been extensively investigated as a possible source for altered pharmacokinetics and pharmacodynamics of anticancer drugs. There is a long list of anticancer drugs recognized as OATP substrates, but further research is required to elucidate the *in vivo* relevance of these interactions. In recent years, the increasing availability of transgenic mouse models is moving the field forward, yet further clinical validation in terms of disposition, response, and toxicity to anticancer drugs will be crucial.

It is now well recognized that certain OATPs are differentially regulated in normal and cancer tissues. Certain

OATPs differentially regulated in cancer may have pathogenic roles during cancer development and progression and potentially serve as therapeutic targets. Further studies are necessary to obtain more comprehensive profiles of OATPs differentially regulated in cancer cells, along with a better understanding of molecular mechanisms underlying altered expression of OATPs in cancer. So far, many of the reports focused on the altered expression of certain OATPs and it will be important to clarify the functional implications of OATPs during the development and progression of cancers. Moreover, many of the current studies utilize mRNA-based methods to determine the OATPs in cancer. It is important to carefully examine the OATP protein levels in cancer to aid the investigations of their functional importance and clinical relevance. Recently, there has been progress in our understanding of the OATP1 family in terms of their expression, regulation, and potential functions in cancer cells. With the wealth of provocative data generated, further studies are warranted to investigate the potential roles of other OATP family members expressed in cancer.

REFERENCES

- Hagenbuch B, Meier PJ. Organic anion transporting polypeptides of the OATP/SLC21 family: phylogenetic classification as OATP/SLCO superfamily, new nomenclature and molecular/functional properties. *Pflugers Arch*. 2004;447(5):653–65. doi:10.1007/s00424-003-1168-y.
- Abe T, Kakyo M, Tokui T, Nakagomi R, Nishio T, Nakai D, *et al.* Identification of a novel gene family encoding human liver-specific organic anion transporter LST-1. *J Biol Chem*. 1999;274(24):17159–63.
- Abe T, Unno M, Onogawa T, Tokui T, Kondo TN, Nakagomi R, *et al.* LST-2, a human liver-specific organic anion transporter, determines methotrexate sensitivity in gastrointestinal cancers. *Gastroenterology*. 2001;120(7):1689–99.
- Lee W, Belkhir A, Lockhart AC, Merchant N, Glaeser H, Harris EI, *et al.* Overexpression of OATP1B3 confers apoptotic resistance in colon cancer. *Cancer Res*. 2008;68(24):10315–23. doi:10.1158/0008-5472.can-08-1984.
- Olszewski-Hamilton U, Svoboda M, Thalhammer T, Buxhofer-Ausch V, Geissler K, Hamilton G. Organic anion transporting polypeptide 5A1 (OATP5A1) in small cell lung cancer (SCLC) cells: possible involvement in chemoresistance to satraplatin. *Biomark Cancer*. 2011;3:31–40. doi:10.4137/bic.s7151.
- Arakawa H, Nakanishi T, Yanagihara C, Nishimoto T, Wakayama T, Mizokami A, *et al.* Enhanced expression of organic anion transporting polypeptides (OATPs) in androgen receptor-positive prostate cancer cells: possible role of OATP1A2 in adaptive cell growth under androgen-depleted conditions. *Biochem Pharmacol*. 2012;84(8):1070–7. doi:10.1016/j.bcp.2012.07.026.
- Obaidat A, Roth M, Hagenbuch B. The expression and function of organic anion transporting polypeptides in normal tissues and in cancer. *Annu Rev Pharmacol Toxicol*. 2012;52:135–51. doi:10.1146/annurev-pharmtox-010510-100556.
- Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol*. 2009;158(3):693–705. doi:10.1111/j.1476-5381.2009.00430.x.
- Buxhofer-Ausch V, Seckly L, Wlecek K, Svoboda M, Kounnis V, Briasoulis E, *et al.* Tumor-specific expression of organic anion-transporting polypeptides: transporters as novel targets for cancer therapy. *J Drug Deliv*. 2013;2013:863539. doi:10.1155/2013/863539.
- Liu T, Li Q. Organic anion-transporting polypeptides: a novel approach for cancer therapy. *J Drug Target*. 2014;22(1):14–22. doi:10.3109/1061186x.2013.832767.
- Hagenbuch B, Gui C. Xenobiotic transporters of the human organic anion transporting polypeptides (OATP) family. *Xenobiotica*. 2008;38(7–8):778–801. doi:10.1080/00498250801986951.
- Roth M, Obaidat A, Hagenbuch B. OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. *Br J Pharmacol*. 2012;165(5):1260–87. doi:10.1111/j.1476-5381.2011.01724.x.
- Banerjee N, Allen C, Bendayan R. Differential role of organic anion-transporting polypeptides in estrone-3-sulphate uptake by breast epithelial cells and breast cancer cells. *J Pharmacol Exp Ther*. 2012;342(2):510–9. doi:10.1124/jpet.112.192344.
- Banerjee N, Fonge H, Mikhail A, Reilly RM, Bendayan R, Allen C. Estrone-3-sulphate, a potential novel ligand for targeting breast cancers. *PLoS One*. 2013;8(5):e64069. doi:10.1371/journal.pone.0064069.
- Maeda T, Irokawa M, Arakawa H, Kuraoka E, Nozawa T, Tateoka R, *et al.* Uptake transporter organic anion transporting polypeptide 1B3 contributes to the growth of estrogen-dependent breast cancer. *J Steroid Biochem Mol Biol*. 2010;122(4):180–5. doi:10.1016/j.jsmb.2010.06.014.
- Hamada A, Sissung T, Price DK, Danesi R, Chau CH, Sharifi N, *et al.* Effect of SLCO1B3 haplotype on testosterone transport and clinical outcome in Caucasian patients with androgen-independent prostatic cancer. *Clin Cancer Res*. 2008;14(11):3312–8. doi:10.1158/1078-0432.CCR-07-4118.
- Wright JL, Kwon EM, Ostrander EA, Montgomery RB, Lin DW, Vessella R, *et al.* Expression of SLCO transport genes in castration-resistant prostate cancer and impact of genetic variation in SLCO1B3 and SLCO2B1 on prostate cancer outcomes. *Cancer Epidemiol Biomarkers Prev*. 2011;20(4):619–27. doi:10.1158/1055-9965.epi-10-1023.
- Badagnani I, Castro RA, Taylor TR, Brett CM, Huang CC, Stryke D, *et al.* Interaction of methotrexate with organic-anion transporting polypeptide 1A2 and its genetic variants. *J Pharmacol Exp Ther*. 2006;318(2):521–9. doi:10.1124/jpet.106.104364.
- Iusuf D, Hendriks JJ, van Esch A, van de Steeg E, Wagenaar E, Rosing H, *et al.* Human OATP1B1, OATP1B3 and OATP1A2 can mediate the in vivo uptake and clearance of docetaxel. *Int J Cancer*. 2014. doi:10.1002/ijc.28970.
- van de Steeg E, van Esch A, Wagenaar E, Kenworthy KE, Schinkel AH. Influence of human OATP1B1, OATP1B3, and OATP1A2 on the pharmacokinetics of methotrexate and paclitaxel in humanized transgenic mice. *Clin Cancer Res*. 2013;19(4):821–32. doi:10.1158/1078-0432.ccr-12-2080.
- Yamaguchi H, Kobayashi M, Okada M, Takeuchi T, Unno M, Abe T, *et al.* Rapid screening of antineoplastic candidates for the human organic anion transporter OATP1B3 substrates using fluorescent probes. *Cancer Lett*. 2008;260(1–2):163–9. doi:10.1016/j.canlet.2007.10.040.
- Smith NF, Acharya MR, Desai N, Figg WD, Sparreboom A. Identification of OATP1B3 as a high-affinity hepatocellular transporter of paclitaxel. *Cancer Biol Ther*. 2005;4(8):815–8.
- de Graan AJ, Lancaster CS, Obaidat A, Hagenbuch B, Elens L, Friberg LE, *et al.* Influence of polymorphic OATP1B-type carriers on the disposition of docetaxel. *Clin Cancer Res*. 2012;18(16):4433–40. doi:10.1158/1078-0432.CCR-12-0761.
- Oswald S, Nassif A, Modest C, Keiser M, Hanke U, Engel A, *et al.* Pharmacokinetic and pharmacodynamic interactions between the immunosuppressant sirolimus and the lipid-lowering drug ezetimibe in healthy volunteers. *Clin Pharmacol Ther*. 2010;87(6):663–7. doi:10.1038/clpt.2009.266.
- Nozawa T, Minami H, Sugiura S, Tsuji A, Tamai I. Role of organic anion transporter OATP1B1 (OATP-C) in hepatic uptake of irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin: in vitro evidence and effect of single nucleotide polymorphisms. *Drug Metab Dispos*. 2005;33(3):434–9. doi:10.1124/dmd.104.001909.
- Fujita K, Sugiura T, Okumura H, Umeda S, Nakamichi N, Watanabe Y, *et al.* Direct inhibition and down-regulation by uremic plasma components of hepatic uptake transporter for SN-38, an active metabolite of irinotecan, in humans. *Pharm Res*. 2014;31(1):204–15. doi:10.1007/s11095-013-1153-x.
- Picard N, Levoir L, Lamoureux F, Yee SW, Giacomini KM, Marquet P. Interaction of sirolimus and everolimus with hepatic and intestinal organic anion-transporting polypeptide

- transporters. *Xenobiotica*. 2011;41(9):752–7. doi:10.3109/00498254.2011.573882.
28. Feng B, Xu JJ, Bi YA, Mireles R, Davidson R, Duignan DB, *et al*. Role of hepatic transporters in the disposition and hepatotoxicity of a HER2 tyrosine kinase inhibitor CP-724,714. *Toxicol Sci*. 2009;108(2):492–500. doi:10.1093/toxsci/kfp033.
29. Briz O, Serrano MA, Rebollo N, Hagenbuch B, Meier PJ, Koepsell H, *et al*. Carriers involved in targeting the cytostatic bile acid-cisplatin derivatives cis-diammine-chloro-cholylglycinate-platinum(II) and cis-diammine-bisursodeoxycholate-platinum(II) toward liver cells. *Mol Pharmacol*. 2002;61(4):853–60.
30. Oostendorp RL, van de Steeg E, van der Kruijssen CM, Beijnen JH, Kenworthy KE, Schinkel AH, *et al*. Organic anion-transporting polypeptide 1B1 mediates transport of Gimitecan and BNP1350 and can be inhibited by several classic ATP-binding cassette (ABC) B1 and/or ABCG2 inhibitors. *Drug Metab Dispos*. 2009;37(4):917–23. doi:10.1124/dmd.108.024901.
31. Hu S, Franke RM, Filipinski KK, Hu C, Orwick SJ, de Bruijn EA, *et al*. Interaction of imatinib with human organic ion carriers. *Clin Cancer Res*. 2008;14(10):3141–8. doi:10.1158/1078-0432.ccr-07-4913.
32. Yamakawa Y, Hamada A, Shuto T, Yuki M, Uchida T, Kai H, *et al*. Pharmacokinetic impact of SLCO1A2 polymorphisms on imatinib disposition in patients with chronic myeloid leukemia. *Clin Pharmacol Ther*. 2011;90(1):157–63. doi:10.1038/clpt.2011.102.
33. Narita M, Hatano E, Arizono S, Miyagawa-Hayashino A, Isoda H, Kitamura K, *et al*. Expression of OATP1B3 determines uptake of Gd-EOB-DTPA in hepatocellular carcinoma. *J Gastroenterol*. 2009;44(7):793–8. doi:10.1007/s00535-009-0056-4.
34. Leonhardt M, Keiser M, Oswald S, Kuhn J, Jia J, Grube M, *et al*. Hepatic uptake of the magnetic resonance imaging contrast agent Gd-EOB-DTPA: role of human organic anion transporters. *Drug Metab Dispos*. 2010;38(7):1024–8. doi:10.1124/dmd.110.032862.
35. Nassif A, Jia J, Keiser M, Oswald S, Modess C, Nagel S, *et al*. Visualization of hepatic uptake transporter function in healthy subjects by using gadoxetic acid-enhanced MR imaging. *Radiology*. 2012;264(3):741–50. doi:10.1148/radiol.12112061.
36. Yamashita T, Kitao A, Matsui O, Hayashi T, Nio K, Kondo M, *et al*. Gd-EOB-DTPA-enhanced magnetic resonance imaging and alpha-fetoprotein predict prognosis of early-stage hepatocellular carcinoma. *Hepatology*. 2014. doi:10.1002/hep.27093.
37. Zollner G, Wagner M, Fickert P, Silbert D, Fuchsbichler A, Zatloukal K, *et al*. Hepatobiliary transporter expression in human hepatocellular carcinoma. *Liver Int*. 2005;25(2):367–79. doi:10.1111/j.1478-3231.2005.01033.x.
38. Monks NR, Liu S, Xu Y, Yu H, Bendelow AS, Moscow JA. Potent cytotoxicity of the phosphatase inhibitor microcystin LR and microcystin analogues in OATP1B1- and OATP1B3-expressing HeLa cells. *Mol Cancer Ther*. 2007;6(2):587–98. doi:10.1158/1535-7163.MCT-06-0500.
39. Libra A, Ferneti C, Lorusso V, Visigalli M, Anelli PL, Staud F, *et al*. Molecular determinants in the transport of a bile acid-derived diagnostic agent in tumoral and nontumoral cell lines of human liver. *J Pharmacol Exp Ther*. 2006;319(2):809–17. doi:10.1124/jpet.106.106591.
40. Vander Borgh T, Libbrecht L, Blokzijl H, Faber KN, Moshage H, Aerts R, *et al*. Diagnostic and pathogenetic implications of the expression of hepatic transporters in focal lesions occurring in normal liver. *J Pathol*. 2005;207(4):471–82. doi:10.1002/path.1852.
41. Vavricka SR, Jung D, Fried M, Grutzner U, Meier PJ, Kullak-Ublick GA. The human organic anion transporting polypeptide 8 (SLCO1B3) gene is transcriptionally repressed by hepatocyte nuclear factor 3beta in hepatocellular carcinoma. *J Hepatol*. 2004;40(2):212–8.
42. Takane H, Kawamoto K, Sasaki T, Moriki K, Moriki K, Kitano H, *et al*. Life-threatening toxicities in a patient with UGT1A1*6/*28 and SLCO1B1*15/*15 genotypes after irinotecan-based chemotherapy. *Cancer Chemother Pharmacol*. 2009;63(6):1165–9. doi:10.1007/s00280-008-0864-x.
43. Xiang X, Jada SR, Li HH, Fan L, Tham LS, Wong CI, *et al*. Pharmacogenetics of SLCO1B1 gene and the impact of *1b and *15 haplotypes on irinotecan disposition in Asian cancer patients. *Pharmacogenet Genomics*. 2006;16(9):683–91. doi:10.1097/01.fpc.0000230420.05221.71.
44. Trevino LR, Shimasaki N, Yang W, Panetta JC, Cheng C, Pei D, *et al*. Germline genetic variation in an organic anion transporter polypeptide associated with methotrexate pharmacokinetics and clinical effects. *J Clin Oncol*. 2009;27(35):5972–8. doi:10.1200/jco.2008.20.4156.
45. Ramsey LB, Panetta JC, Smith C, Yang W, Fan Y, Winick NJ, *et al*. Genome-wide study of methotrexate clearance replicates SLCO1B1. *Blood*. 2013;121(6):898–904. doi:10.1182/blood-2012-08-452839.
46. Radtke S, Zolk O, Renner B, Paulides M, Zimmermann M, Moricke A, *et al*. Germline genetic variations in methotrexate candidate genes are associated with pharmacokinetics, toxicity, and outcome in childhood acute lymphoblastic leukemia. *Blood*. 2013;121(26):5145–53. doi:10.1182/blood-2013-01-480335.
47. Letschert K, Keppler D, König J. Mutations in the SLCO1B3 gene affecting the substrate specificity of the hepatocellular uptake transporter OATP1B3 (OATP8). *Pharmacogenetics*. 2004;14(7):441–52.
48. Smith NF, Marsh S, Scott-Horton TJ, Hamada A, Mielke S, Moss K, *et al*. Variants in the SLCO1B3 gene: interethnic distribution and association with paclitaxel pharmacokinetics. *Clin Pharmacol Ther*. 2007;81(1):76–82. doi:10.1038/sj.clpt.6100011.
49. Kiyotani K, Mushiroda T, Kubo M, Zembutsu H, Sugiyama Y, Nakamura Y. Association of genetic polymorphisms in SLCO1B3 and ABCC2 with docetaxel-induced leukopenia. *Cancer Sci*. 2008;99(5):967–72. doi:10.1111/j.1349-7006.2008.00765.x.
50. Yamada A, Maeda K, Kiyotani K, Mushiroda T, Nakamura Y, Sugiyama Y. Kinetic interpretation of the importance of OATP1B3 and MRP2 in docetaxel-induced hematopoietic toxicity. *CPT Pharm Syst Pharmacol*. 2014;3:e126. doi:10.1038/psp.2014.23.
51. Chen C, Stock JL, Liu X, Shi J, Van Deusen JW, DiMattia DA, *et al*. Utility of a novel Oatp1b2 knockout mouse model for evaluating the role of Oatp1b2 in the hepatic uptake of model compounds. *Drug Metab Dispos*. 2008;36(9):1840–5. doi:10.1124/dmd.108.020594.
52. Lu H, Choudhuri S, Ogura K, Csanaky IL, Lei X, Cheng X, *et al*. Characterization of organic anion transporting polypeptide 1b2-null mice: essential role in hepatic uptake/toxicity of phalloidin and microcystin-LR. *Toxicol Sci*. 2008;103(1):35–45. doi:10.1093/toxsci/kfn038.
53. Zaher H, Meyer zu Schwabedissen HE, Tirona RG, Cox ML, Obert LA, Agrawal N, *et al*. Targeted disruption of murine organic anion-transporting polypeptide 1b2 (Oatp1b2/Slco1b2) significantly alters disposition of prototypical drug substrates pravastatin and rifampin. *Mol Pharmacol*. 2008;74(2):320–9. doi:10.1124/mol.108.046458.
54. van de Steeg E, Wagenaar E, van der Kruijssen CM, Burggraaff JE, de Waart DR, Elferink RP, *et al*. Organic anion transporting polypeptide 1a/1b-knockout mice provide insights into hepatic handling of bilirubin, bile acids, and drugs. *J Clin Invest*. 2010;120(8):2942–52. doi:10.1172/jci42168.
55. van de Steeg E, van Esch A, Wagenaar E, van der Kruijssen CM, van Tellingen O, Kenworthy KE, *et al*. High impact of Oatp1a/1b transporters on in vivo disposition of the hydrophobic anticancer drug paclitaxel. *Clin Cancer Res*. 2011;17(2):294–301. doi:10.1158/1078-0432.ccr-10-1980.
56. van de Steeg E, van der Kruijssen CM, Wagenaar E, Burggraaff JE, Mesman E, Kenworthy KE, *et al*. Methotrexate pharmacokinetics in transgenic mice with liver-specific expression of human organic anion-transporting polypeptide 1B1 (SLCO1B1). *Drug Metab Dispos*. 2009;37(2):277–81. doi:10.1124/dmd.108.024315.
57. Iusuf D, Ludwig M, Elbatsh A, van Esch A, van de Steeg E, Wagenaar E, *et al*. OATP1A/1B transporters affect irinotecan and SN-38 pharmacokinetics and carboxylesterase expression in knockout and humanized transgenic mice. *Mol Cancer Ther*. 2014;13(2):492–503. doi:10.1158/1535-7163.mct-13-0541.

58. Durmus S, Naik J, Buil L, Wagenaar E, van Tellingen O, Schinkel AH. In vivo disposition of doxorubicin is affected by mouse Oatp1a/1b and human OATP1A/1B transporters. *Int J Cancer*. 2014;135(7):1700–10. doi:10.1002/ijc.28797.
59. Gao B, Hagenbuch B, Kullak-Ublick GA, Benke D, Aguzzi A, Meier PJ. Organic anion-transporting polypeptides mediate transport of opioid peptides across blood-brain barrier. *J Pharmacol Exp Ther*. 2000;294(1):73–9.
60. Lee W, Glaeser H, Smith LH, Roberts RL, Moeckel GW, Gervasi G, *et al.* Polymorphisms in human organic anion-transporting polypeptide 1A2 (OATP1A2): implications for altered drug disposition and central nervous system drug entry. *J Biol Chem*. 2005;280(10):9610–7. doi:10.1074/jbc.M411092200.
61. Miki Y, Suzuki T, Kitada K, Yabuki N, Shibuya R, Moriya T, *et al.* Expression of the steroid and xenobiotic receptor and its possible target gene, organic anion transporting polypeptide-A, in human breast carcinoma. *Cancer Res*. 2006;66(1):535–42. doi:10.1158/0008-5472.can-05-1070.
62. Meyer zu Schwabedissen HE, Tirona RG, Yip CS, Ho RH, Kim RB. Interplay between the nuclear receptor pregnane X receptor and the uptake transporter organic anion transporter polypeptide 1A2 selectively enhances estrogen effects in breast cancer. *Cancer Res*. 2008;68(22):9338–47. doi:10.1158/0008-5472.can-08-0265.
63. Ballester MR, Monte MJ, Briz O, Jimenez F, Gonzalez-San Martin F, Marin JJ. Expression of transporters potentially involved in the targeting of cytostatic bile acid derivatives to colon cancer and polyps. *Biochem Pharmacol*. 2006;72(6):729–38. doi:10.1016/j.bcp.2006.06.007.
64. Glaeser H, Bailey DG, Dresser GK, Gregor JC, Schwarz UI, McGrath JS, *et al.* Intestinal drug transporter expression and the impact of grapefruit juice in humans. *Clin Pharmacol Ther*. 2007;81(3):362–70. doi:10.1038/sj.clpt.6100056.
65. Liedauer R, Svoboda M, Wlcek K, Arrich F, Ja W, Toma C, *et al.* Different expression patterns of organic anion transporting polypeptides in osteosarcomas, bone metastases and aneurysmal bone cysts. *Oncol Rep*. 2009;22(6):1485–92.
66. König J, Cui Y, Nies AT, Keppler D. A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane. *Am J Physiol Gastrointest Liver Physiol*. 2000;278(1):G156–64.
67. Cui Y, König J, Nies AT, Pfannschmidt M, Hergt M, Franke WW, *et al.* Detection of the human organic anion transporters SLC21A6 (OATP2) and SLC21A8 (OATP8) in liver and hepatocellular carcinoma. *Lab Invest*. 2003;83(4):527–38.
68. Pressler H, Sissung TM, Venzon D, Price DK, Figg WD. Expression of OATP family members in hormone-related cancers: potential markers of progression. *PLoS One*. 2011;6(5):e20372. doi:10.1371/journal.pone.0020372.
69. Svoboda M, Wlcek K, Taferner B, Hering S, Stieger B, Tong D, *et al.* Expression of organic anion-transporting polypeptides 1B1 and 1B3 in ovarian cancer cells: relevance for paclitaxel transport. *Biomed Pharma Biomed Pharmacot*. 2011;65(6):417–26. doi:10.1016/j.biopha.2011.04.031.
70. König J, Cui Y, Nies AT, Keppler D. Localization and genomic organization of a new hepatocellular organic anion transporting polypeptide. *J Biol Chem*. 2000;275(30):23161–8. doi:10.1074/jbc.M001448200.
71. Thakkar N, Kim K, Jang ER, Han S, Kim K, Kim D, *et al.* A cancer-specific variant of the SLC01B3 gene encodes a novel human organic anion transporting polypeptide 1B3 (OATP1B3) localized mainly in the cytoplasm of colon and pancreatic cancer cells. *Mol Pharm*. 2013;10(1):406–16. doi:10.1021/mp3005353.
72. Nagai M, Furihata T, Matsumoto S, Ishii S, Motohashi S, Yoshino I, *et al.* Identification of a new organic anion transporting polypeptide 1B3 mRNA isoform primarily expressed in human cancerous tissues and cells. *Biochem Biophys Res Commun*. 2012;418(4):818–23. doi:10.1016/j.bbrc.2012.01.115.
73. Hays A, Apte U, Hagenbuch B. Organic anion transporting polypeptides expressed in pancreatic cancer may serve as potential diagnostic markers and therapeutic targets for early stage adenocarcinomas. *Pharm Res*. 2013;30(9):2260–9. doi:10.1007/s11095-012-0962-7.
74. Pratt E, Sissung TM, Figg WD. Loss of OATP1B3 function causes Rotor syndrome: implications for potential use of inhibitors in cancer. *Cancer Biol Ther*. 2012;13(14):1374–5. doi:10.4161/cbt.22010.
75. Muto M, Onogawa T, Suzuki T, Ishida T, Rikiyama T, Katayose Y, *et al.* Human liver-specific organic anion transporter-2 is a potent prognostic factor for human breast carcinoma. *Cancer Sci*. 2007;98(10):1570–6. doi:10.1111/j.1349-7006.2007.00570.x.
76. Pizzagalli F, Hagenbuch B, Stieger B, Klenk U, Folkers G, Meier PJ. Identification of a novel human organic anion transporting polypeptide as a high affinity thyroxine transporter. *Mol Endocrinol*. 2002;16(10):2283–96. doi:10.1210/me.2001-0309.
77. Gao B, Huber RD, Wenzel A, Vavricka SR, Ismail MG, Reme C, *et al.* Localization of organic anion transporting polypeptides in the rat and human ciliary body epithelium. *Exp Eye Res*. 2005;80(1):61–72. doi:10.1016/j.exer.2004.08.013.
78. Schuster VL. Prostaglandin transport. *Prostaglandins Other Lipid Mediat*. 2002;68–69:633–47.
79. Wlcek K, Svoboda M, Thalhammer T, Sellner F, Krupitza G, Jaeger W. Altered expression of organic anion transporter polypeptide (OATP) genes in human breast carcinoma. *Cancer Biol Ther*. 2008;7(9):1450–5.
80. Wlcek K, Svoboda M, Riha J, Zakaria S, Olszewski U, Dvorak Z, *et al.* The analysis of organic anion transporting polypeptide (OATP) mRNA and protein patterns in primary and metastatic liver cancer. *Cancer Biol Ther*. 2011;11(9):801–11.
81. Holla VR, Backlund MG, Yang P, Newman RA, DuBois RN. Regulation of prostaglandin transporters in colorectal neoplasia. *Cancer Prev Res (Phila)*. 2008;1(2):93–9. doi:10.1158/1940-6207.capr-07-0009.
82. Bronger H, König J, Kopplow K, Steiner HH, Ahmadi R, Herold-Mende C, *et al.* ABC drug efflux pumps and organic anion uptake transporters in human gliomas and the blood-tumor barrier. *Cancer Res*. 2005;65(24):11419–28. doi:10.1158/0008-5472.can-05-1271.
83. Grube M, Kock K, Oswald S, Draber K, Meissner K, Eckel L, *et al.* Organic anion transporting polypeptide 2B1 is a high-affinity transporter for atorvastatin and is expressed in the human heart. *Clin Pharmacol Ther*. 2006;80(6):607–20. doi:10.1016/j.clpt.2006.09.010.
84. Al Sarakbi W, Mokbel R, Salhab M, Jiang WG, Reed MJ, Mokbel K. The role of STS and OATP-B mRNA expression in predicting the clinical outcome in human breast cancer. *Anticancer Res*. 2006;26(6C):4985–90.
85. Kobayashi D, Nozawa T, Imai K, Nezu J, Tsuji A, Tamai I. Involvement of human organic anion transporting polypeptide OATP-B (SLC21A9) in pH-dependent transport across intestinal apical membrane. *J Pharmacol Exp Ther*. 2003;306(2):703–8. doi:10.1124/jpet.103.051300.
86. Kullak-Ublick GA, Ismail MG, Stieger B, Landmann L, Huber R, Pizzagalli F, *et al.* Organic anion-transporting polypeptide B (OATP-B) and its functional comparison with three other OATPs of human liver. *Gastroenterology*. 2001;120(2):525–33.
87. St-Pierre MV, Hagenbuch B, Ugele B, Meier PJ, Stallmach T. Characterization of an organic anion-transporting polypeptide (OATP-B) in human placenta. *J Clin Endocrinol Metab*. 2002;87(4):1856–63.
88. Adachi H, Suzuki T, Abe M, Asano N, Mizutamari H, Tanemoto M, *et al.* Molecular characterization of human and rat organic anion transporter OATP-D. *Am J Physiol Renal Physiol*. 2003;285(6):F1188–97. doi:10.1152/ajprenal.00402.2002.
89. Kindla J, Rau TT, Jung R, Fasching PA, Strick R, Stoehr R, *et al.* Expression and localization of the uptake transporters OATP2B1, OATP3A1 and OATP5A1 in non-malignant and malignant breast tissue. *Cancer Biol Ther*. 2011;11(6):584–91.
90. Tamai I, Nezu J, Uchino H, Sai Y, Oku A, Shimane M, *et al.* Molecular identification and characterization of novel members of the human organic anion transporter (OATP) family. *Biochem Biophys Res Commun*. 2000;273(1):251–60. doi:10.1006/bbrc.2000.2922.
91. Kleberg K, Jensen GM, Christensen DP, Lundh M, Grunnet LG, Knuhtsen S, *et al.* Transporter function and cyclic AMP turnover in normal colonic mucosa from patients with and

- without colorectal neoplasia. *BMC Gastroenterol.* 2012;12:78. doi:10.1186/1471-230x-12-78.
92. Mikkaichi T, Suzuki T, Onogawa T, Tanemoto M, Mizutamari H, Okada M, *et al.* Isolation and characterization of a digoxin transporter and its rat homologue expressed in the kidney. *Proc Natl Acad Sci U S A.* 2004;101(10):3569–74. doi:10.1073/pnas.0304987101.
 93. Suzuki T, Onogawa T, Asano N, Mizutamari H, Mikkaichi T, Tanemoto M, *et al.* Identification and characterization of novel rat and human gonad-specific organic anion transporters. *Mol Endocrinol.* 2003;17(7):1203–15. doi:10.1210/me.2002-0304.
 94. Lee SY, Williamson B, Caballero OL, Chen YT, Scanlan MJ, Ritter G, *et al.* Identification of the gonad-specific anion transporter SLCO6A1 as a cancer/testis (CT) antigen expressed in human lung cancer. *Cancer Immun.* 2004;4:13.
 95. Alcorn J, Lu X, Moscow JA, McNamara PJ. Transporter gene expression in lactating and nonlactating human mammary epithelial cells using real-time reverse transcription-polymerase chain reaction. *J Pharmacol Exp Ther.* 2002;303(2):487–96. doi:10.1124/jpet.102.038315.
 96. Hashimoto Y, Tatsumi S, Takeda R, Naka A, Ogane N, Kameda Y, *et al.* Expression of organic anion-transporting polypeptide 1A2 and organic cation transporter 6 as a predictor of pathologic response to neoadjuvant chemotherapy in triple negative breast cancer. *Breast Cancer Res Treat.* 2014;145(1):101–11. doi:10.1007/s10549-014-2913-y.
 97. Niedermeyer TH, Daily A, Swiatecka-Hagenbruch M, Moscow JA. Selectivity and potency of microcystin congeners against OATP1B1 and OATP1B3 expressing cancer cells. *PLoS One.* 2014;9(3):e91476. doi:10.1371/journal.pone.0091476.
 98. Tsuboyama T, Onishi H, Kim T, Akita H, Hori M, Tatsumi M, *et al.* Hepatocellular carcinoma: hepatocyte-selective enhancement at gadoteric acid-enhanced MR imaging—correlation with expression of sinusoidal and canalicular transporters and bile accumulation. *Radiology.* 2010;255(3):824–33. doi:10.1148/radiol.10091557.
 99. Lockhart AC, Harris E, Lafleur BJ, Merchant NB, Washington MK, Resnick MB, *et al.* Organic anion transporting polypeptide 1B3 (OATP1B3) is overexpressed in colorectal tumors and is a predictor of clinical outcome. *Clin Exper Gastro.* 2008;1:1–7.
 100. Imai S, Kikuchi R, Tsuruya Y, Naoi S, Nishida S, Kusuhara H, *et al.* Epigenetic regulation of organic anion transporting polypeptide 1B3 in cancer cell lines. *Pharm Res.* 2013;30(11):2880–90. doi:10.1007/s11095-013-1117-1.
 101. Ichihara S, Kikuchi R, Kusuhara H, Imai S, Maeda K, Sugiyama Y. DNA methylation profiles of organic anion transporting polypeptide 1B3 in cancer cell lines. *Pharm Res.* 2010;27(3):510–6. doi:10.1007/s11095-010-0064-3.
 102. Han S, Kim K, Thakkar N, Kim D, Lee W. Role of hypoxia inducible factor-1alpha in the regulation of the cancer-specific variant of organic anion transporting polypeptide 1B3 (OATP1B3), in colon and pancreatic cancer. *Biochem Pharmacol.* 2013;86(6):816–23. doi:10.1016/j.bcp.2013.07.020.
 103. Lu R, Kanai N, Bao Y, Schuster VL. Cloning, in vitro expression, and tissue distribution of a human prostaglandin transporter cDNA(hPGT). *J Clin Invest.* 1996;98(5):1142–9. doi:10.1172/jci118897.