The Expression and Function of Organic Anion Transporting Polypeptides in Normal Tissues and in Cancer

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Abstract

Organic anion transporting polypeptides (OATPs) are members of the *SLCO* gene superfamily of proteins. The 11 human OATPs are classified into 6 families and subfamilies on the basis of their amino acid sequence similarities. OATPs are expressed in several epithelial tissues throughout the body and transport mainly amphipathic molecules with molecular weights of more than 300 kDa. Members of the OATP1 and OATP2 families are functionally the best-characterized OATPs. Among these are the multispecific OATP1A2, OATP1B1, OATP1B3, and OATP2B1. They transport various endo- and xenobiotics, including hormones and their conjugates as well as numerous drugs such as several anticancer agents. Recent reports demonstrate that some OATPs are up- or downregulated in several cancers and that OATP expression might affect cancer development. On the basis of the findings summarized in this review, we propose that OATPs could be valuable targets for anticancer therapy.

INTRODUCTION

OATP: organic anion transporting polypeptide

SLCO: solute carrier of the OATPs

Transport proteins are important for the absorption, distribution, and excretion of drugs and other xenobiotics that cannot freely diffuse through cellular membranes. Among these transporters is the superfamily of organic anion transporting polypeptides, abbreviated OATPs (1, 2). OATPs are multispecific transport proteins, which means that they can transport a wide range of structurally unrelated compounds. They are expressed in a wide range of tissues in the body and are responsible for the Na^+-independent uptake of large amphipathic organic anions into cells. Generally, OATP substrates are anions with molecular weights greater than 300 kDa. However, OATP substrates are not limited to anions; they transport cationic and neutral compounds as well.

OATPs belong to the superfamily of solute carrier transporters and are classified within the solute carrier of the OATPs (*SLCO*) gene family (2). There are 11 known human OATPs that are divided into six families, on the basis of a 40% amino acid sequence identity. Families are further divided into subfamilies, on the basis of a 60% amino acid sequence identity. Thus far, the OATP1 family is the best characterized among the OATP families. This family includes the multispecific transporters OATP1A2, OATP1B1, OATP1B3, and OATP1C1. The OATP2 family contains two members, OATP2A1 and OATP2B1, both of which have a narrow substrate specificity compared with other OATPs. OATP3A1, OATP5A1, and OATP6A1 are the only members in the OATP3, OATP5, and OATP6 families, respectively. The OATP4 family is composed of both OATP4A1 and OATP4C1. Orthologs of human OATPs are present in other species; however, owing to species divergence and gene duplication events, more than one rodent ortholog can correspond to a single human OATP or vice versa (2).

The OATP protein structure is predicted to have 12 transmembrane domains with intracellular amino and carboxy termini (**Figure 1**). Several structural features seem important for membrane localization and transport function. For instance, many OATPs contain a PDZ consensus sequence that is thought to be important for membrane anchoring (3). The fifth extracellular loop contains numerous conserved cysteines, which are thought to form S-H bonds that may be important for surface expression (4). Recent structure-function studies have highlighted amino acids within transmembrane domain 10 of OATP1B1 and OATP1B3 that are believed to be important in initial substrate recognition and translocation across the membrane (5–7).

OATPs function in the uptake of compounds into cells and can be either tissue-specific or expressed in multiple tissues throughout the body. Aside from OATP expression in normal tissues, recent studies have shown that OATP expression is up- or downregulated in certain cancers. This has led to an increased interest in the roles these uptake transporters play in cancer. This review focuses on the tissue distribution of OATPs in normal and cancer tissue; the substrate specificity of OATPs, including their ability to transport anticancer drugs; and their potential role in cancer development and treatment.

NORMAL TISSUE DISTRIBUTION OF OATPs

Some OATPs are expressed in multiple tissues, whereas the expression of other OATPs is restricted to a single tissue. In the OATP1 family, expression of OATP1A2 mRNA is highest in the brain, followed by expression in the kidney, liver, lung, testis, and placenta, according to Northern blot analysis (8, 9). OATP1A2 expression was confirmed at the protein level in the blood-brain barrier (10, 11); at the apical membrane of distal nephrons (11); at the apical membrane of enterocytes, where it is thought to be critical in the absorption of numerous xenobiotics (12); and at the apical membrane of cholangiocytes, which make up the bile duct epithelium (11). OATP1B1 and OATP1B3 are examples of tissue-specific OATPs. Expression of OATP1B1 was shown in adult and fetal liver by Northern blot analysis. This expression was confirmed at the protein level

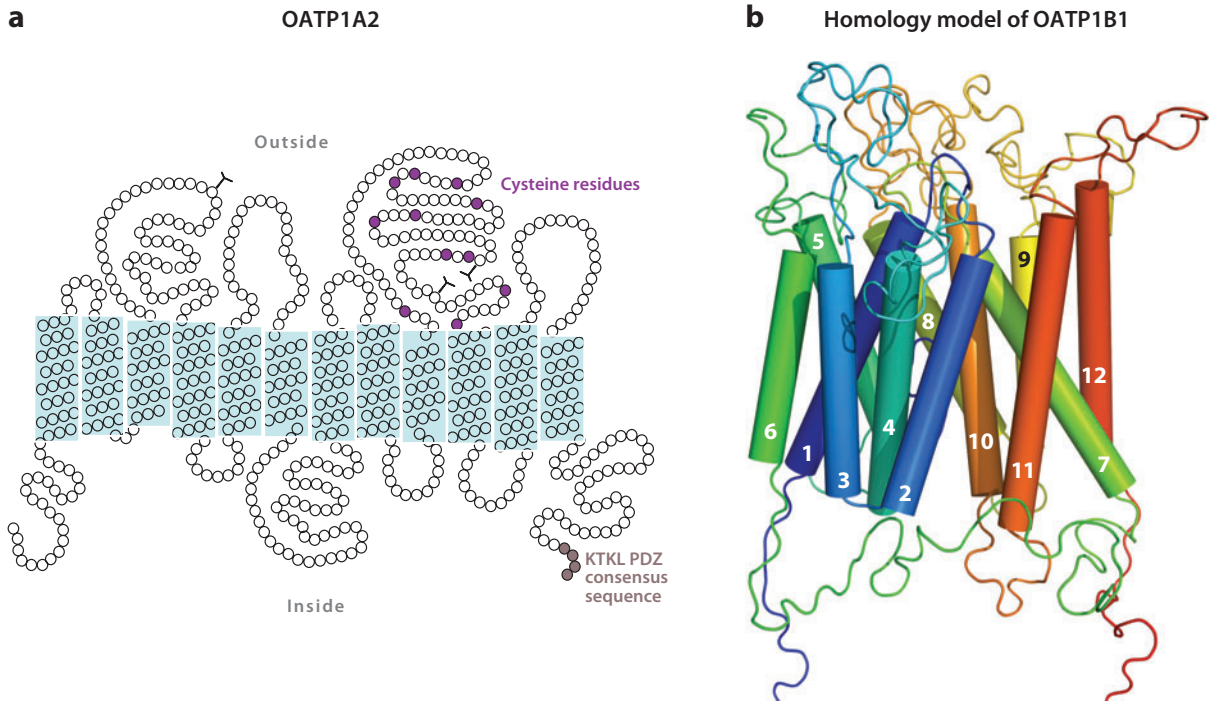

Figure 1

Predicted 12 transmembrane domain (*a*) secondary structure model of OATP1A2 and (*b*) homology model of OATP1B1. (*a*) Putative transmembrane domains were predicted on the basis of amino acid hydrophobicity. The highly conserved cysteine residues in the loop between transmembrane domains 9 and 10 are indicated by purple circles. At the C-terminal end, OATP1A2 has the "KTKL" PDZ consensus sequence, indicated by brown circles. (*b*) The homology model for OATP1B1 was calculated on the basis of the crystal structure of the bacterial multidrug transporter EmrD.

and localized to the basolateral membrane of hepatocytes throughout the liver lobule. Similarly, OATP1B3 is expressed exclusively in the liver at the basolateral membrane of hepatocytes; however, expression was much stronger in the pericentral region compared with the periportal region (13, 14, 15, 16, 17). A recent study based on real-time polymerase chain reaction (RT-PCR) analysis described OATP1B3 mRNA expression in the retina; however, protein expression has not been confirmed (18). OATP1C1 mRNA expression is highest in the brain and testis, and, because of its high affinity for T_4 and reverse T_3 (in the nanomolar range), OATP1C1 is thought to be a crucial thyroid hormone transporter (19–21). In addition, OATP1C1 protein was localized to the basolateral membrane of the choroid plexus epithelium (22), to the basolateral membrane of the pigmented ciliary body epithelium (23), and in Leydig cells of the testis (19).

OATP2A1, which is also known as the prostaglandin transporter, is thought to be ubiquitously expressed. OATP2A1 mRNA was detected in brain, colon, heart, liver, kidney, ovary, lung, pancreas, prostate, skeletal muscle, spleen, and small intestine (24). Thus far, expression of OATP2A1 at the protein level has been demonstrated in neurons in the frontal gyrus of the brain (25), in the pyloric glands of the antrum and parietal cells in the gastrointestinal tract (26), and in the luminal and glandular epithelium of the endometrium (27). OATP2B1, the second member of the OATP2 family, is expressed in several different tissues in the body, with the highest transcript levels in the liver (28, 29). OATP2B1 protein expression was confirmed at the basolateral membrane of hepatocytes (29), at the apical membrane of enterocytes (30), at the endothelium of the blood-brain

RT-PCR: real-time polymerase chain reaction

barrier (31), at the endothelial cells of the heart (32), at the myoepithelium of mammary ducts (33), and in the placenta (34).

OATP3A1 is the most highly conserved OATP among all species and has two different splice variants in humans (35). In general, OATP3A1 is considered to be widely expressed and was shown to be expressed at the mRNA level in testis, brain, heart, lung, spleen, peripheral blood leukocytes, and thyroid (35, 36). At the protein level, the two splice variants were localized to different cell types or cellular membranes in various tissues. OATP3A1_v1 was localized to the germ cells of the testes, to the neuroglial cells of the frontal cortex, and to the basolateral membrane of the choroid plexus. In contrast, expression of OATP3A1_v2 was shown in Sertoli cells in the testes, at the apical membrane of the choroid plexus, and in cell bodies of the frontal cortex neurons (35). Recently, OATP3A1 protein expression was demonstrated in epithelial cells of the lactiferous ducts in normal breast tissue (37).

OATP4A1 is another ubiquitously expressed OATP, with highest mRNA levels in the heart and placenta, followed by levels in the lung, liver, skeletal muscle, kidney, and pancreas (28, 38). Thus far, OATP4A1 protein expression has been confirmed only at the apical membrane of syncytiotrophoblasts in the placenta (39). The other OATP4 family member, OATP4C1, is expressed only in the kidney, as shown by Northern blot analysis (40), and thus is considered a kidney-specific OATP.

Little is known about OATP5A1 and OATP6A1. OATP5A1 protein was recently reported to be expressed at the plasma membrane of the epithelial cells that line the lactiferous ducts in normal breast tissue (37), whereas OATP6A1 mRNA expression has been detected in the testes, with low levels in the spleen, brain, fetal brain, and placenta (41, 42).

ALTERED TISSUE DISTRIBUTION OF OATPs IN CANCERS

Many different types of cancers have altered expression of OATPs. Altered OATP1A2 expression has been identified in gliomas, colon polyps and tumors, and cancers of the breast and bone. A study of human gliomas by RT-PCR showed OATP1A2 expression in different histological subtypes. Through the use of immunofluorescence microscopy, OATP1A2 was localized in the luminal membrane of the blood-brain barrier endothelium and in the blood-tumor barrier but not in the glioma cells (31). Through the use of RT-PCR, OATP1A2 expression was detected in healthy colon tissue; however, expression was decreased in polyps and in colon cancer tissue (43). In breast cancer cell lines, RT-PCR analysis showed that expression of OATP1A2 was highest in T47-D and ZR-75-1 cells and low in MCF-7, MDA-MB-231, and MDA-MB-468 cells. OATP1A2 expression was confirmed in tissue obtained from patients with breast cancer and was localized to the cell membrane and cytoplasm of breast carcinoma cells. However, OATP1A2 expression was not observed in non-neoplastic epithelium, stroma, and adipose tissue surrounding the carcinoma (44). These results were confirmed through the use of RT-PCR (45). OATP1A2 transcript levels were significantly higher in malignant breast tissue than they were in adjacent nonmalignant breast tissue, and transcripts of OATP1A2 were highest in stage I and stage IIA breast cancers (45). Immunofluorescence analysis confirmed OATP1A2 protein expression and demonstrated that it was restricted to the malignant cells of the breast tissue samples (45). In contrast, Wlcek et al. (46) were unable to detect significant mRNA levels of OATP1A2 in the four breast cancer cell lines MCF-7, MDA-MB-231, ZR-75-1, and MCF-10A, or in breast cancer tissue. These discrepancies might arise from differences found in cell lines cultured in different laboratories (47); therefore, such results must be interpreted cautiously if the exact experimental conditions are not known. OATP1A2 transcripts were detected both in bone metastases from primary kidney cancer and in the malignant osteosarcoma cell lines HOS and MG-63 (48).

In general, the expression of OATP1B1 and OATP1B3, both specific to the liver, tends to be reduced in hepatocellular carcinomas (HCCs). OATP1B1 and OATP1B3 mRNA was undetectable or reduced in the Hep3B and HepG2 cell lines (49, 50), confirming the previously reported reduced expression in HepG2 and PLC cell lines as well as in HCC tissue samples at the protein level (51, 52). Vavricka et al. (53) also reported reduced expression of OATP1B3 in 60% of HCC tissues compared with normal surrounding tissue. However, OATP1B1 levels were not significantly different in HCC samples compared with normal liver samples in their study. The expression of OATP1B1 and OATP1B3 in different benign liver tumors was investigated by Vander Borght and colleagues (54). They showed reduced expression of both OATPs in hepatocellular adenomas and a strong diffuse expression of both OATPs in focal nodular hyperplasia. Recently, Tsuboyama et al. (55) supported the general trend of reduced OATP1B1 and OATP1B3 expression in HCC tissue samples. In conclusion, the downregulation of OATP1B1 and OATP1B3 in HCC resembles the downregulation observed in primary cultured hepatocytes (56) and could be the result of dedifferentiation of the HCC cells.

HCC: hepatocellular carcinoma

Expression of the normally liver-specific OATP1B1 and OATP1B3 has also been identified in cancers of many different tissues (17). Overall, OATP1B3 is upregulated in a wide range of cancer types. Northern blot analysis showed that OATP1B3 is expressed in different gastrointestinal cancer cell lines and cancers, including the gastric cancer cell line KatoIII; the colon cancer cell lines DLD-1, MIP-101, Clone A, and CX-1; the pancreatic cancer cell lines MIA-Paca2, BXPC-1, PK-8, PK-9, and PK-45P; and the gallbladder cancer cell lines HuCCT-1, OcuchLM1, and TFK-1. Weak expression levels were also seen in the lung cancer cell line A549 and the glioblastoma cell line A172. Moreover, immunohistochemical staining of OATP1B3 was detected in gastric cancer tissue, pancreatic cancer tissue, colon cancer tissue, and a colon cancer metastatic to a lymph node (17). OATP1B1 was increased in colon polyps and in colon cancer tissue at the mRNA level as compared with normal colon tissue (43). However, the same study could not demonstrate significant differences in OATP1B3 mRNA expression between healthy and colon cancer tissue (43). OATP1B3 expression was markedly increased in colorectal adenocarcinoma tissues with obvious staining in the cytoplasm as opposed to membranous expression in normal liver (57). Analysis of OATP1B3 expression across different colorectal tumor stages showed that it was highest in earlier-stage and lower-grade tumors, suggesting that OATP1B3 expression might be indicative of clinical outcome (58). In non-small-cell lung cancer, OATP1B3 mRNA expression was significantly increased as compared with the nonmalignant surrounding tissue (49). OATP1B3 transcript levels were observed in prostate cancer tissue through the use of RT-PCR (59). Additionally, OATP1B3 expression was confirmed at the protein level in prostate tumor tissue but not confirmed in normal prostate or benign prostatic hyperplasia (60). Muto et al. (61) detected OATP1B3 by using immunohistochemistry in cells of invasive ductal breast carcinoma and suggested that OATP1B3 expression could be used as a prognostic factor in breast cancer.

Thus far, the only report to show expression of OATP1C1 in cancer demonstrated OATP1C1 mRNA in several samples from osteosarcomas, in a sample from a kidney cancer metastasis, and in several specimens from aneurysmal bone cysts, which had the highest levels (48).

OATP2A1 mRNA was detected at high levels in bone metastases from kidney cancer (48); in breast cancer; and in the breast cancer cell lines MCF-7, MDA-MB-231, and ZR-75-1 (46). OATP2A1 mRNA expression was generally higher in malignant breast tissue compared with adjacent nonmalignant breast tissue, but the difference did not reach statistical significance (46). Holla and colleagues (62) showed a trend for decreased OATP2A1 expression in colorectal tumor specimens as well as in stomach, ovary, lung, and kidney tumors. They were not able to detect OATP2A1 in several colorectal cancer cell lines, including LS-174T, HCT-116, HT-29, SW-620, SW-480, HCT-15, and HCA-7, although the colorectal cancer cell line LoVo showed high

expression levels of OATP2A1 mRNA and protein (62). OATP2A1 was also detected at the protein level in hepatocellular carcinoma, in cholangiocellular carcinoma, and in liver metastases from colon tumors (63).

OATP2B1 mRNA expression was identified in the colon adenocarcinoma cell line CX-1 (28) and was higher in bone cysts than in osteosarcoma tissues (48). With respect to breast cancer, OATP2B1 expression was shown in both normal and breast tumor specimens, and expression increased with increased tumor grade (64). This has also been studied by Wlcek et al. (46), who detected higher expression levels of OATP2B1 in nonmalignant specimens than in malignant breast tumors. OATP2B1 expression was also identified in human gliomas, where it was localized to endothelial cells at the blood-brain barrier and blood-tumor barrier (31).

RT-PCR analysis showed that OATP3A1 expression was significantly higher in aneurysmal bone cysts than in osteosarcomas. OATP3A1 transcripts were found (*a*) in the nonmalignant human osteoblast-like cells and bone marrow stromal cells derived from normal bone marrow and (*b*) in the osteosarcoma cell lines HOS and MG-63 (48). OATP3A1 expression was identified in a variety of additional cancer cell lines, including breast carcinoma (GI-101), lung carcinoma (LX-1 and GI-117), colon adenocarcinoma (CX-1 and GI-112), ovarian carcinoma (GI-102), and pancreatic adenocarcinoma (GI-103) (28). Through RT-PCR, two independent groups showed OATP3A1 expression in the breast cancer cell line T-47D (33, 65). OATP3A1 expression was also detected in the breast cancer cell line MCF-7 (66), and recently it was detected in the membrane and cytoplasm of malignant breast tumor specimens (37).

OATP4A1 has an expression pattern similar to that of OATP3A1 in various breast carcinoma, lung carcinoma, colon adenocarcinoma, ovarian carcinoma, and pancreatic carcinoma cell lines (28), as well as in the breast cancer cell lines T-47D and MCF-7 (33, 65). OATP4A1 expression is higher in bone cysts than in osteosarcoma tissues, with significantly higher expression in the malignant osteosarcoma cell lines HOS and MG-63 as compared with the nonmalignant human osteoblast-like cells and bone marrow stromal cells (48). The expression of OATP4A1 was detected in normal and tumorous breast tissue (46). In the same study, expression of OATP4C1 and the poorly characterized OATP5A1 was also revealed in normal and cancerous breast tissue (46). Recently, the expression of OATP5A1 was confirmed at the membrane and in the cytoplasm of malignant breast tumor specimens (37). Expression of the presumably gonad-specific OATP6A1 was shown in lung cancer cell lines, lung cancer, bladder cancer, and esophageal cancer tissues (41). The tissue expression profile of all 11 human OATPs is summarized in **Table 1**.

A few studies have suggested that OATP expression in cancer could be predictive of patient survival or the success of hormone therapy (58, 60, 61). However, because of the many inconsistent reports, it is too early to propose that the presence or absence of a certain OATP in a given cancer is predictive. Additional, larger population-based studies are required to confirm the predictive value of OATPs in different cancer types.

SUBSTRATE SPECIFICITY OF OATPs

OATPs transport a wide range of amphipathic compounds, including numerous endo- and xenobiotics (67, 68). Their substrates are generally organic anions, but OATPs also transport cations and neutral compounds (69). Among the endogenous substrates are bile acids, conjugated steroid hormones, thyroid hormones, and cyclic and linear peptides. We have previously demonstrated that uptake mediated by OATP1B3 can be allosterically stimulated by small molecules such as clotrimazole (70) and epigallocatechin gallate (71). This stimulation is dependent on the transported substrate, but once the underlying mechanism has been elucidated, such allosteric stimulation could be used to selectively increase drug uptake by OATP1B3 and potentially by other OATPs

Table 1 Tissue expression of all 11 human organic anion transporting polypeptides (OATPs) in normal and cancer tissues

OATP	Normal tissue expression	Reference(s)	Cancer tissue expression	Reference(s)
OATP1A2	Blood-brain barrier	10, 11	Expressed in bone cancer tissues and cell lines	48
	Kidney	11	Reduced in colon polyps and cancer	43
	Cholangiocytes	11	Increased in breast carcinoma cells and malignant breast tissue	44, 45
	Enterocytes	12		
OATP1B1	Liver	13, 14, 16	Reduced in hepatocellular carcinoma	49–52, 54, 55
OATP1B3	Liver	15, 17	Reduced in hepatocellular carcinoma	53
			Expressed in: Colorectal adenocarcinoma tissues	57
			Non-small-cell lung tumors	49
			Prostate cancer tissue	59, 60
			Invasive ductal carcinoma breast cells	61
			Cell lines of stomach, colon, pancreatic, and gallbladder cancers	17
OATP1C1	Brain	22	Expressed in bone cancers	48
	Testes	19		
	Ciliary body	23		
OATP2A1	Ubiquitous	24–27	Increased in malignant breast tissue and liver cancers	46, 63
			Reduced in tumors of bowel, stomach, ovary, lung, and kidney	62
OATP2B1	Liver	29	Increased in bone cysts	48
	Blood-brain barrier	31	Altered in breast cancers	46, 64
	Enterocytes	30		
	Placenta	34		
	Heart	32		
OATP3A1	Ubiquitous	35–37	Expressed in bone cancer and cancer cell lines of multiple tissues	48 28, 33, 37, 65, 66
OATP4A1	Ubiquitous	28, 38, 39	Expressed in bone cancer and cancer cell lines of multiple tissues	48 28, 33, 46, 65
OATP4C1	Kidney	40		
OATP5A1	Lactiferous ducts in breast	37	Expressed in malignant breast tumors	37
OATP6A1	Testes	41, 42	Expressed in tumors of the lung, bladder, and esophagus	41

into cells that express these OATPs. OATPs are important for drug disposition because their exogenous substrates include antibiotics, antidiabetic drugs, anti-inflammatory drugs, antifungals, antivirals, antihistamines, antihypertensives, fibrates, statins, cardiac glycosides, immunosuppressants, and anticancer drugs (67, 68). For a list of clinically relevant OATP substrates, including anticancer drugs, refer to **Table 2**. This review focuses on the transport of anticancer drugs in more detail.

The discovery of the altered expression of OATPs in cancer tissue has led to the recent interest in the transport of anticancer drugs, mainly by the well-characterized OATP transporters OATP1A2, OATP1B1, and OATP1B3. The multispecific OATP1A2 can transport a wide variety of compounds, including the bile acids cholate and taurocholate; the conjugated steroid hormones estrone-3-sulfate and estradiol-17β-glucuronide; and the thyroid hormones T_3 and T_4. Recently, OATP1A2 has been shown to transport imatinib, a drug used to treat certain types of leukemias (72), and to transport the folate antimetabolite methotrexate (73). OATP1B1 and

Table 2 Substrates transported by the different human OATPs

OATP1A2	OATP1B1	OATP1B3	OATP1C1
Hormones and conjugates	**Hormones and conjugates**	**Hormones and conjugates**	**Hormones and conjugates**
Estradiol-17 β-glucuronide	Estradiol-17 β-glucuronide	Estradiol-17 β-glucuronide	Estradiol-17 β-glucuronide
Estrone-3-sulfate	Estrone-3-sulfate	Estrone-3-sulfate	Estrone-3-sulfate
DHEA-S	Thyroxine (T_4)	DHEA-S	Thyroxine (T_4)
Reverse triiodothyronine (rT_3)	Triiodothyronine (T_3)	Testosterone	Triiodothyronine (T_3)
Thyroxine (T_4)	DHEA-S	**Drugs**	Reverse triiodothyronine (rT_3)
Triiodothyronine (T_3)	**Prostaglandins**	Atrasentan, Bosentan, Cefadroxil, Cefazolin, Cephalexin, Digoxin, Enalapril, Fexofenadine, Fluvastatin, Lopinavir, Methotrexate, Demethylphalloin, Paclitaxel, Docetaxel, Methotrexate, Imatinib, Olmesartan, Phalloidin, Pitavastatin, Telmisartan, Rapamycin, Rifampicin, Rosuvastatin, Valsartan, SN-38	Thyroxine sulfate (T_4S)
Prostaglandins	Prostaglandin E_2		**Others**
Prostaglandin E_2	**Bile acids**		BSP
Bile acids	Cholate		
Cholate	Taurocholate		
Taurocholate	Tauroursodeoxycholate		
Glycocholate	**Drugs**		
Taurochenodeoxycholate	Atorvastatin, Olmesartan, Bosentan, Phalloidin, Caspofungin, Pitavastatin, Cefazolin, Pravastatin, Cerivastatin, Rapamycin, Darunavir, Rifampicin, Enalapril, Rosuvastatin, Ezetimibe, Saquinavir, Flavopiridol, SN-38, Fluvastatin, Temocapril, Gimatecan, Troglitazone, Lopinavir, Valsartan, Methotrexate		
Tauroursodeoxycholate			
Others			
DPDPE			
Drugs			
Acebutolol, Rosuvastatin, Atenolol, Pitavastatin, Sotalol, Ouabain, Labetalol, Deltorphin II, Nadolol, Ciprofloxacin, Talinolol, Fexofenadine, Saquinavir, Gatifloxacin, Darunavir, Levofloxacin, Imatinib, Methotrexate			

OATP2A1	OATP2B1	OATP3A1	OATP4A1
Prostaglandins	**Hormones and conjugates**	**Hormones and conjugates**	**Hormones and conjugates**
Prostaglandin E_1	Estrone-3-sulfate	Thyroxine (T_4)	Estradiol-17 β-glucuronide
Prostaglandin E_2	DHEA-S	Estrone-3-sulfate	Estrone-3-sulfate
Prostaglandin $F_{2\alpha}$	Thyroxine (T_4)	**Prostaglandins**	Thyroxine (T_4)
Prostaglandin H_2	**Prostaglandins**	Prostaglandin E_1	Triiodothyronine (T_3)
Prostaglandin D_2	Prostaglandin E_2	Prostaglandin E_2	Reverse triiodothyronine (rT_3)
8-iso-prostaglandin $F_{2\alpha}$	**Drugs**	Prostaglandin $F_{2\alpha}$	**Bile acids**
Others	Atorvastatin	**Drugs**	Taurocholate
Thromboxane B_2	Bosentan	Deltorphin BQ-123	**Prostaglandins**
Drugs	Ezetimibe	Benzylpenicillin	Prostaglandin E_2
Latanoprost	Fluvastatin	**Others**	**Drugs**
	Glibenclamide	Vasopressin	Benzylpenicillin
	Pitavastatin	Arachidonic acid	Unoprostone metabolite
	Pitavastatin		
	Montelukast		
	Rosuvastatin		
	Talinolol		

Anticancer drugs are highlighted in red.

Abbreviations: BSP, bromosulfophthalein; DHEA-S, dehydroepiandrosterone sulfate; DPDPE, [D-penicillamine^{2,5}]enkephalin.

OATP1B3 are thought to be important for uptake of a wide variety of xenobiotics into hepatocytes and can transport many of the aforementioned substrates, including estrone-3-sulfate and, in the case of OATP1B3, also testosterone (60). OATP1B1 has been implicated in the transport of the camptothecin analogs gimatecan and BNP1350 (74), the irinotecan metabolite 7-ethyl-10-hydroxycamptothecin (SN-38) (75), the cyclin-dependent kinase inhibitor flavopiridol (76), the Her2 tyrosine kinase inhibitor CP-724,714 (77), methotrexate (17, 78), and the bile-acid cisplatin derivative *cis*-diammine-chloro-cholylglysinate-platinum II (79). OATP1B3 transports methotrexate (17); the taxanes paclitaxel (80, 81) and docetaxel (80); and, to a lesser extent, imatinib (72). Yamaguchi and colleagues (82) have shown that OATP1B3 transports the irinotecan metabolite SN-38 but does not transport either paclitaxel or docetaxel. In addition, transport of the immunosuppressant rapamycin (sirolimus) has been demonstrated for both OATP1B1 and OATP1B3 (83). These findings show that several OATPs transport anticancer drugs as well as hormones and hormone precursors, all of which could affect the growth and survival of cancer cells. Thus, OATPs could play a role in cancer progression or response to treatment.

SNP: single-nucleotide polymorphism

OATP POLYMORPHISMS AND ANTICANCER DRUG DISPOSITION

Several studies have documented single-nucleotide polymorphisms (SNPs) of OATPs that are associated with reduced or absent protein function. Several of these SNPs have been linked to altered disposition of chemotherapeutic drugs and consequently increased adverse effects, confirming the importance of OATPs in the disposition of drugs. For example, methotrexate, a substrate of OATP1A2, has been implicated in serious adverse effects seen in patients. To identify potential contributors to varying methotrexate pharmacokinetics, common OATP1A2 polymorphisms were investigated (73). Among the 12 OATP1A2 polymorphisms studied, four showed altered transport of methotrexate in vitro. The common I13T OATP1A2 SNP showed enhanced methotrexate uptake, whereas R168C, E172D, and N278DEL variants showed significantly decreased methotrexate uptake (73). In addition, common polymorphisms of OATP1B1 may alter disposition of the irinotecan metabolite SN-38 and potentially contribute to the variable adverse gastrointestinal effects seen with this drug (75). Uptake of SN-38 was determined in cell lines expressing three common genetic polymorphisms of OATP1B1. Compared with the wild-type OATP1B1*1a, OATP1B1*15, which has an allelic frequency of 10.3% to 15.0%, had significantly reduced SN-38 uptake, suggesting that patients with this polymorphism may have altered SN-38 pharmacokinetics (75). This prediction was confirmed in vivo: Patients with the *SLCO1B1*15* polymorphism showed higher systemic exposure and lower clearance of SN-38 (84, 85). A similar study looked at the effect of three nonsynonymous SNPs of OATP1B3 on the pharmacokinetics of paclitaxel (86). However, none of the three genetic variations resulted in significantly different paclitaxel clearance or altered pharmacokinetic parameters.

Recently, van de Steeg et al. (87) generated the knockout mouse model *Slco1a/1b*$^{-/-}$, which lacks all OATP1A and OATP1B family members, to study the role of OATPs in the disposition of drugs such as paclitaxel and methotrexate. The *Slco1a/1b*$^{-/-}$ mice had higher plasma concentrations of both drugs, suggesting that proteins in the OATP1A or OATP1B family are involved in their distribution. Introducing polymorphic human OATPs into these null mice could provide a powerful tool to study their effect on drug disposition (87).

REGULATION OF OATPs IN CANCER

A recent review provides a detailed summary of the current knowledge about OATP regulation (88). However, there have not been extensive studies on how OATP expression is regulated within

cancer cells. OATP1A2 expression has been associated with expression of the nuclear receptor PXR (pregnane X receptor) in breast carcinoma tissue and its cell lines (44). In addition, a PXR response element was identified in the OATP1A2 promoter (45), suggesting that PXR could play a role in the upregulation of OATP1A2 seen in breast cancers. In 2004, it was suggested that OATP1B3 expression in HCC was downregulated via transcriptional repression by hepatocyte nuclear factor 3β (HNF3β) (53). A more recent study showed that DNA methylation-dependent gene silencing is involved in the regulation of OATP1B3 expression in several cancer cell lines (89). Posttranslational regulation also could be altered in cancer cells. Although OATPs are normally expressed on cell membranes, strong cytoplasmic staining is seen for both OATP1A2 in breast cancer and OATP1B3 in colon cancer. This could result from aberrant posttranslational regulation such as altered phosphorylation, which regulates cell surface expression of human OATP2B1 (90), rat Oatp1a1, and rat Oatp1a4 (91, 92). Owing to the limited knowledge in this area, further research is required to better understand the mechanism of OATP up- or downregulation in cancer and to determine what role, if any, it may play in cancer progression or treatment.

PXR: pregnane X receptor

THE ROLE OF OATPs IN CANCER DEVELOPMENT

As briefly discussed above, hormones and their conjugates are substrates of many OATPs, and therefore expression of OATPs in cancer might contribute to the proliferation of androgen- and estrogen-dependent tumors. Several studies have investigated whether OATP expression could affect the growth of hormone-dependent cancers such as breast and prostate cancers.

In 2004, Nozawa et al. showed that uptake of estrone-3-sulfate into T47-D breast cancer cells led to increased cell proliferation and was mediated by a Na^+-independent transport system (65). The authors detected OATP3A1 and OATP4A1 in these cells and suggested that these OATPs might be involved in estrone-3-sulfate uptake into these cells. In a follow-up study, estrone-3-sulfate uptake was measured into the breast cancer cell line MCF-7, and inhibition studies suggested that an OATP could be involved (66). On the basis of these findings, inhibition of the estrone-3-sulfate uptake system was proposed as a potential treatment for estrogen-responsive breast cancers (66). Meyer zu Schwabedissen et al. (45) showed that expression of OATP1A2 in T47-D cells was regulated via the nuclear receptor PXR, and treatment of these cells with the PXR activator rifampicin resulted in both increased expression of OATP1A2 and increased proliferation of the cells. Furthermore, when these estrogen-dependent cells were treated with the potent PXR antagonist A-792611, both decreased OATP1A2 expression and decreased proliferation were observed. This led the authors to propose targeting the regulation of OATP1A2 as a potential treatment for breast cancer (45).

OATP1B3 protein expression in various breast carcinomas has been correlated with various pathological parameters including tumor size, recurrence, and prognosis (61). OATP1B3 expression was shown in 50% of the breast cancer specimens analyzed. Surprisingly, expression of OATP1B3 was inversely correlated with tumor size and significantly associated with decreased recurrence and good prognoses. However, this correlation was seen only in postmenopausal women. OATP1B3 has thus been hypothesized to be implicated in a hormone-dependent growth mechanism in breast cancer (61).

Prostate cancer recurrence and progression have also been correlated with the expression of OATPs. An OATP1B3-related survival advantage for certain patients was seen in androgen-dependent prostate cancer (60). Although testosterone is a substrate of wild-type OATP1B3, a variant containing two SNPs, 334G and 699A, does not transport testosterone. Patients with the 334GG/699AA haplotype had an improved overall survival over 10 years (60). A separate study demonstrated that patients with the 334T allele of OATP1B3, which does transport testosterone,

had an increased prostate cancer mortality rate (59). This study also showed that patients with the rs12422149 polymorphism in the *SLCO2B1* gene, which had previously been shown to affect OATP2B1-mediated substrate uptake, had an increased risk of prostate-cancer-specific mortality (59).

OATP1B3 may also be involved in the response to anticancer chemotherapy. Overexpression of wild-type OATP1B3 in colon cancer cell lines treated with camptothecin and oxaliplatin conferred an antiapoptotic effect and reduced the transcriptional activity of p53, whereas a nonfunctional OATP1B3 did not have these effects (57).

Taken together, these studies demonstrate that OATP expression in cancer can be associated with a survival advantage or disadvantage for the tumor. However, additional research is required to elucidate the underlying molecular mechanisms and to identify the potentially involved transported substrates before such findings will lead to improved tumor diagnostics and treatment.

CONCLUSIONS

OATPs are expressed throughout the body and are generally responsible for the Na^+-independent uptake of a wide range of amphipathic compounds. Expression levels of OATPs are altered in many different types of cancers, and in several cancers these altered expression levels have been correlated with cancer stage. OATPs are capable of transporting multiple compounds that affect cancer cell growth and survival, including hormones, hormone precursors, and anticancer drugs.

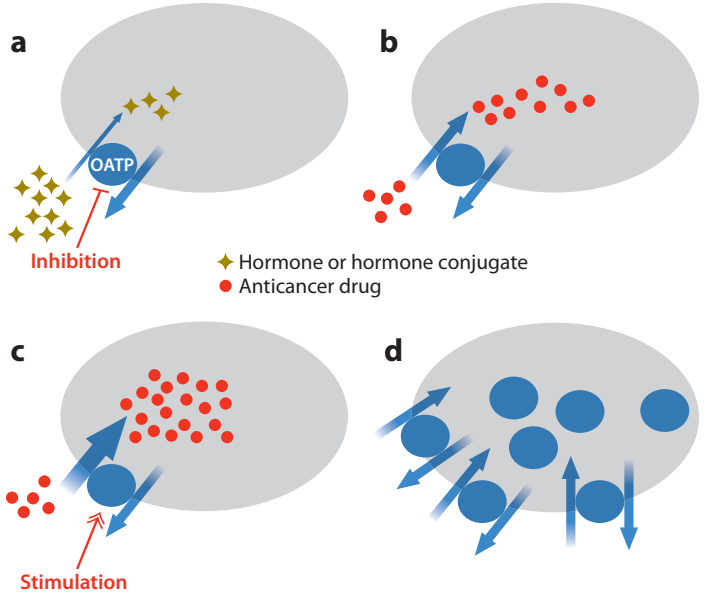

Figure 2

Potential mechanisms of organic anion transporting polypeptide (OATP)-mediated anticancer therapy. (*a*) Because OATPs can transport hormones, hormone conjugates, and additional chemicals (*yellow-brown diamonds*) that are beneficial for cancer growth, inhibition of the uptake of these "procancer" compounds into cancer cells could have antiproliferative effects. (*b*) OATPs can transport known anticancer drugs (*red circles*). Therefore, investigators could attempt anticancer therapy by designing novel chemotherapeutics that are OATP substrates. (*c*) Because some OATPs can be allosterically stimulated with small molecules, uptake of anticancer drugs (*red circles*) could be enhanced in the presence of such stimulators. (*d*) The membrane expression of OATPs in cancer cells could be regulated to increase or decrease transport into these cells.

Furthermore, uptake mediated by OATPs can be either inhibited or allosterically stimulated by small molecules. In addition, OATP polymorphisms have been associated with altered pharmacokinetics of anticancer drugs, altered transport of hormones, and cancer outcomes. These findings suggest that OATPs could be valuable targets for anticancer therapy in four ways: (*a*) OATP-mediated uptake of hormones, hormone conjugate, or unidentified growth promoting chemicals could be prevented with OATP-selective inhibitors (**Figure 2*a***); (*b*) novel anticancer drugs could be developed as OATP substrates to increase their uptake into OATP-expressing cancer cells (**Figure 2*b***); (*c*) uptake of anticancer drugs could be enhanced by allosteric stimulators (**Figure 2*c***); and (*d*) expression of OATPs in the plasma membrane could be modulated to increase or decrease uptake of various substrates into cancer cells (**Figure 2*d***). Further research is required to elucidate the role OATPs play in cancer development and anticancer drug transport and to determine how these uptake transporters can be rationally targeted in cancer treatment.

SUMMARY POINTS

1. Organic anion transporting polypeptides (OATPs) form a superfamily of transport proteins that transport large amphipathic organic anions into cells. Under normal physiological conditions, OATPs are expressed in various, mainly epithelial, tissues in the body. Recently, several OATPs have been shown to have altered expression in cancer tissue.
2. OATPs mediate the Na^+-independent uptake of a wide variety of endogenous and exogenous compounds, including bile acids, hormones and their conjugates, peptides, toxins, and numerous drugs such as anticancer drugs.
3. OATPs play an important role in the absorption, distribution, and excretion of drugs. Patients with OATP polymorphisms have been found to have altered pharmacokinetics for administered chemotherapeutic drugs.
4. OATPs have been suggested to play a role in cancer development and may serve as a potential therapeutic target for cancer treatment.

FUTURE ISSUES

1. We should pursue a detailed profile of OATP protein expression in normal and cancer tissue.
2. We need a better understanding of the mechanisms that lead to altered expression of OATPs in cancer.
3. We must elucidate the functional role OATPs play in cancer development or survival.
4. We need to determine the mechanism of the allosteric modulation of OATP-mediated transport.
5. We need to determine to what extent OATP expression or function can help in cancer diagnosis and therapy.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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LITERATURE CITED

1. Hagenbuch B, Meier PJ. 2003. The superfamily of organic anion transporting polypeptides. *Biochim. Biophys. Acta* 1609:1–18
2. Hagenbuch B, Meier PJ. 2004. Organic anion transporting polypeptides of the OATP/*SLC21* family: phylogenetic classification as OATP/*SLCO* superfamily, new nomenclature and molecular/functional properties. *Pflügers Arch.* 447:653–65
3. Wang P, Wang JJ, Xiao Y, Murray JW, Novikoff PM, et al. 2005. Interaction with PDZK1 is required for expression of organic anion transporting protein 1A1 on the hepatocyte surface. *J. Biol. Chem.* 280:30143–49
4. Hänggi E, Grundschober AF, Leuthold S, Meier PJ, St-Pierre MV. 2006. Functional analysis of the extracellular cysteine residues in the human organic anion transporting polypeptide, OATP2B1. *Mol. Pharmacol.* 70:806–17
5. Gui C, Hagenbuch B. 2008. Amino acid residues in transmembrane domain 10 of organic anion transporting polypeptide 1B3 are critical for cholecystokinin octapeptide transport. *Biochemistry* 47:9090–97
6. Gui C, Hagenbuch B. 2009. Role of transmembrane domain 10 for the function of organic anion transporting polypeptide 1B1. *Protein Sci.* 18:2298–306
7. Miyagawa M, Maeda K, Aoyama A, Sugiyama Y. 2009. The eighth and ninth transmembrane domains in organic anion transporting polypeptide 1B1 affect the transport kinetics of estrone-3-sulfate and estradiol-17β-D-glucuronide. *J. Pharmacol. Exp. Ther.* 329:551–57
8. Kullak-Ublick GA, Hagenbuch B, Stieger B, Schteingart CD, Hofmann AF, et al. 1995. Molecular and functional characterization of an organic anion transporting polypeptide cloned from human liver. *Gastroenterology* 109:1274–82
9. Steckelbroeck S, Nassen A, Ugele B, Ludwig M, Watzka M, et al. 2004. Steroid sulfatase (STS) expression in the human temporal lobe: enzyme activity, mRNA expression and immunohistochemistry study. *J. Neurochem.* 89:403–17
10. Gao B, Hagenbuch B, Kullak-Ublick GA, Benke D, Aguzzi A, Meier PJ. 2000. Organic anion-transporting polypeptides mediate transport of opioid peptides across blood-brain barrier. *J. Pharmacol. Exp. Ther.* 294:73–79
11. Lee W, Glaeser H, Smith LH, Roberts RL, Moeckel GW, et al. 2005. Polymorphisms in human organic anion-transporting polypeptide 1A2 (OATP1A2): implications for altered drug disposition and central nervous system drug entry. *J. Biol. Chem.* 280:9610–17
12. Glaeser H, Bailey DG, Dresser GK, Gregor JC, Schwarz UI, et al. 2007. Intestinal drug transporter expression and the impact of grapefruit juice in humans. *Clin. Pharmacol. Ther.* 81:362–70
13. Abe T, Kakyo M, Tokui T, Nakagomi R, Nishio T, et al. 1999. Identification of a novel gene family encoding human liver-specific organic anion transporter LST-1. *J. Biol. Chem.* 274:17159–63
14. König J, Cui Y, Nies AT, Keppler D. 2000. A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane. *Am. J. Physiol. Gastrointest. Liver Physiol.* 278:156–64
15. König J, Cui Y, Nies AT, Keppler D. 2000. Localization and genomic organization of a new hepatocellular organic anion transporting polypeptide. *J. Biol. Chem.* 275:23161–68
16. Hsiang B, Zhu Y, Wang Z, Wu Y, Sasseville V, et al. 1999. A novel human hepatic organic anion transporting polypeptide (OATP2): identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters. *J. Biol. Chem.* 274:37161–68
17. Abe T, Unno M, Onogawa T, Tokui T, Kondo TN, et al. 2001. LST-2, a human liver-specific organic anion transporter, determines methotrexate sensitivity in gastrointestinal cancers. *Gastroenterology* 120:1689–99
18. Okabe M, Szakács G, Reimers MA, Suzuki T, Hall MD, et al. 2008. Profiling SLCO and SLC22 genes in the NCI-60 cancer cell lines to identify drug uptake transporters. *Mol. Cancer Ther.* 7:3081–91

19. Pizzagalli F, Hagenbuch B, Stieger B, Klenk U, Folkers G, Meier PJ. 2002. Identification of a novel human organic anion transporting polypeptide as a high affinity thyroxine transporter. *Mol. Endocrinol.* 16:2283–96
20. Hagenbuch B. 2007. Cellular entry of thyroid hormones by organic anion transporting polypeptides. *Best Pract. Res. Clin. Endocrinol. Metab.* 21:209–21
21. Heuer H, Visser TJ. 2009. Pathophysiological importance of thyroid hormone transporters. *Endocrinology* 150:1078–83
22. Roberts LM, Woodford K, Zhou M, Black DS, Haggerty JE, et al. 2008. Expression of the thyroid hormone transporters monocarboxylate transporter-8 (*SLC16A2*) and organic ion transporter-14 (*SLCO1C1*) at the blood-brain barrier. *Endocrinology* 149:6251–61
23. Gao B, Huber RD, Wenzel A, Vavricka SR, Ismair MG, et al. 2005. Localization of organic anion transporting polypeptides in the rat and human ciliary body epithelium. *Exp. Eye Res.* 80:61–72
24. Schuster VL. 2002. Prostaglandin transport. *Prostaglandins Other Lipid Mediat.* 68–69:633–47
25. Choi K, Zhuang H, Crain B, Doré S. 2008. Expression and localization of prostaglandin transporter in Alzheimer disease brains and age-matched controls. *J. Neuroimmunol.* 195:81–87
26. Mandery K, Bujok K, Schmidt I, Wex T, Treiber G, et al. 2010. Influence of cyclooxygenase inhibitors on the function of the prostaglandin transporter organic anion-transporting polypeptide 2A1 expressed in human gastroduodenal mucosa. *J. Pharmacol. Exp. Ther.* 332:345–51
27. Kang J, Chapdelaine P, Parent J, Madore E, Laberge PY, Fortier MA. 2005. Expression of human prostaglandin transporter in the human endometrium across the menstrual cycle. *J. Clin. Endocrinol. Metab.* 90:2308–13
28. Tamai I, Nezu J, Uchino H, Sai Y, Oku A, et al. 2000. Molecular identification and characterization of novel members of the human organic anion transporter (OATP) family. *Biochem. Biophys. Res. Commun.* 273:251–60
29. Kullak-Ublick GA, Ismair MG, Stieger B, Landmann L, Huber R, et al. 2001. Organic anion-transporting polypeptide B (OATP-B) and its functional comparison with three other OATPs of human liver. *Gastroenterology* 120:525–33
30. Kobayashi D, Nozawa T, Imai K, Nezu J, Tsuji A, Tamai I. 2003. Involvement of human organic anion transporting polypeptide OATP-B (SLC21A9) in pH-dependent transport across intestinal apical membrane. *J. Pharmacol. Exp. Ther.* 306:703–8
31. Bronger H, König J, Kopplow K, Steiner HH, Ahmadi R, et al. 2005. ABCC drug efflux pumps and organic anion uptake transporters in human gliomas and the blood-tumor barrier. *Cancer Res.* 65:11419–28
32. Grube M, Köck K, Oswald S, Draber K, Meissner K, et al. 2006. Organic anion transporting polypeptide 2B1 is a high-affinity transporter for atorvastatin and is expressed in the human heart. *Clin. Pharmacol. Ther.* 80:607–20
33. Pizzagalli F, Varga Z, Huber RD, Folkers G, Meier PJ, St-Pierre MV. 2003. Identification of steroid sulfate transport processes in the human mammary gland. *J. Clin. Endocrinol. Metab.* 88:3902–12
34. St-Pierre MV, Hagenbuch B, Ugele B, Meier PJ, Stallmach T. 2002. Characterization of an organic anion-transporting polypeptide (OATP-B) in human placenta. *J. Clin. Endocrinol. Metab.* 87:1856–63
35. Huber RD, Gao B, Sidler Pfändler MA, Zhang-Fu W, Leuthold S, et al. 2007. Characterization of two splice variants of human organic anion transporting polypeptide 3A1 isolated from human brain. *Am. J. Physiol. Cell Physiol.* 292:795–806
36. Adachi H, Suzuki T, Abe M, Asano N, Mizutamari H, et al. 2003. Molecular characterization of human and rat organic anion transporter OATP-D. *Am. J. Physiol. Ren. Physiol.* 285:1188–97
37. Kindla J, Rau TT, Jung R, Fasching PA, Strick R, et al. 2011. Expression and localization of the uptake transporters OATP2B1, OATP3A1 and OATP5A1 in non-malignant and malignant breast tissue. *Cancer Biol. Ther.* 11(6):584–91
38. Fujiwara K, Adachi H, Nishio T, Unno M, Tokui T, et al. 2001. Identification of thyroid hormone transporters in humans: different molecules are involved in a tissue-specific manner. *Endocrinology* 142:2005–12
39. Sato K, Sugawara J, Sato T, Mizutamari H, Suzuki T, et al. 2003. Expression of organic anion transporting polypeptide E (OATP-E) in human placenta. *Placenta* 24:144–48

40. Mikkaichi T, Suzuki T, Onogawa T, Tanemoto M, Mizutamari H, et al. 2004. Isolation and characterization of a digoxin transporter and its rat homologue expressed in the kidney. *Proc. Natl. Acad. Sci. USA* 101:3569–74
41. Lee SY, Williamson B, Caballero OL, Chen YT, Scanlan MJ, et al. 2004. Identification of the gonad-specific anion transporter SLCO6A1 as a cancer/testis (CT) antigen expressed in human lung cancer. *Cancer Immun.* 4:13
42. Suzuki T, Onogawa T, Asano N, Mizutamari H, Mikkaichi T, et al. 2003. Identification and characterization of novel rat and human gonad-specific organic anion transporters. *Mol. Endocrinol.* 17:1203–15
43. Ballestero MR, Monte MJ, Briz O, Jimenez F, Gonzalez-San Martin F, Marin JJG. 2006. Expression of transporters potentially involved in the targeting of cytostatic bile acid derivatives to colon cancer and polyps. *Biochem. Pharmacol.* 72:729–38
44. Miki Y, Suzuki T, Kitada K, Yabuki N, Shibuya R, et al. 2006. Expression of the steroid and xenobiotic receptor and its possible target gene, organic anion transporting polypeptide-A, in human breast carcinoma. *Cancer Res.* 66:535–42
45. Meyer zu Schwabedissen HE, Tirona RG, Yip CS, Ho RH, Kim RB. 2008. 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.* 68:9338–47
46. Wlcek K, Svoboda M, Thalhammer T, Sellner F, Krupitza G, Jaeger W. 2008. Altered expression of organic anion transporter polypeptide (OATP) genes in human breast carcinoma. *Cancer Biol. Ther.* 7:1450–55
47. Hayeshi R, Hilgendorf C, Artursson P, Augustijns P, Brodin B, et al. 2008. Comparison of drug transporter gene expression and functionality in Caco-2 cells from 10 different laboratories. *Eur. J. Pharm. Sci.* 35:383–96
48. Liedauer R, Svoboda M, Wlcek K, Arrich F, Jä W, et al. 2009. Different expression patterns of organic anion transporting polypeptides in osteosarcomas, bone metastases and aneurysmal bone cysts. *Oncol. Rep.* 22:1485–92
49. Monks NR, Liu S, Xu Y, Yu H, Bendelow AS, Moscow JA. 2007. Potent cytotoxicity of the phosphatase inhibitor microcystin LR and microcystin analogues in OATP1B1- and OATP1B3-expressing HeLa cells. *Mol. Cancer Ther.* 6:587–98
50. Libra A, Fernetti C, Lorusso V, Visigalli M, Anelli PL, et al. 2006. 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.* 319:809–17
51. Cui Y, König J, Nies AT, Pfannschmidt M, Hergt M, et al. 2003. Detection of the human organic anion transporters SLC21A6 (OATP2) and SLC21A8 (OATP8) in liver and hepatocellular carcinoma. *Lab. Investig.* 83:527–38
52. Zollner G, Wagner M, Fickert P, Silbert D, Fuchsbichler A, et al. 2005. Hepatobiliary transporter expression in human hepatocellular carcinoma. *Liver Int.* 25:367–79
53. Vavricka SR, Jung D, Fried M, Grutzner U, Meier PJ, Kullak-Ublick GA. 2004. The human organic anion transporting polypeptide 8 (*SLCO1B3*) gene is transcriptionally repressed by hepatocyte nuclear factor 3β in hepatocellular carcinoma. *J. Hepatol.* 40:212–18
54. Vander Borght S, Libbrecht L, Blokzijl H, Faber KN, Moshage H, et al. 2005. Diagnostic and pathogenetic implications of the expression of hepatic transporters in focal lesions occurring in normal liver. *J. Pathol.* 207:471–82
55. Tsuboyama T, Onishi H, Kim T, Akita H, Hori M, et al. 2010. Hepatocellular carcinoma: hepatocyte-selective enhancement at gadoxetic acid–enhanced MR imaging—correlation with expression of sinusoidal and canalicular transporters and bile accumulation. *Radiology* 255:824–33
56. Jigorel E, Le Vee M, Boursier-Neyret C, Bertrand M, Fardel O. 2005. Functional expression of sinusoidal drug transporters in primary human and rat hepatocytes. *Drug. Metab. Dispos.* 33:1418–22
57. Lee W, Belkhiri A, Lockhart AC, Merchant N, Glaeser H, et al. 2008. Overexpression of OATP1B3 confers apoptotic resistance in colon cancer. *Cancer Res.* 68:10315–23
58. Lockhart AC, Harris E, LaFleur BJ, Merchant NB, Washington MK, et al. 2008. Organic anion transporting polypeptide 1B3 (OATP1B3) is overexpressed in colorectal tumors and is a predictor of clinical outcome. *Clin. Exp. Gastroenterol.* 1:1–7

59. Wright JL, Kwon EM, Ostrander EA, Montgomery B, Line DW, et al. 2011. Expression of *SLCO* transport genes in castration-resistant prostate cancer and impact of genetic variation in *SCLO1B3* and *SLCO2B1* on prostate cancer outcomes. *Cancer Epidemiol. Biomark. Prev.* 4:619–27
60. Hamada A, Sissung T, Price DK, Danesi R, Chau CH, et al. 2008. Effect of *SLCO1B3* haplotype on testosterone transport and clinical outcome in Caucasian patients with androgen-independent prostatic cancer. *Clin. Cancer Res.* 14:3312–18
61. Muto M, Onogawa T, Suzuki T, Ishida T, Rikiyama T, et al. 2007. Human liver-specific organic anion transporter-2 is a potent prognostic factor for human breast carcinoma. *Cancer Sci.* 98:1570–76
62. Holla VR, Backlund MG, Yang P, Newman RA, DuBois RN. 2008. Regulation of prostaglandin transporters in colorectal neoplasia. *Cancer Prev. Res.* 1:93–99
63. Wlcek K, Svoboda M, Riha J, Zakaria S, Olszewski U, et al. 2011. The analysis of organic anion transporting polypeptide (OATP) mRNA and protein patterns in primary and metastatic liver cancer. *Cancer Biol. Ther.* 11(9):801–11
64. Al Sarakbi W, Mokbel R, Salhab M, Jiang WG, Reed MJ, Mokbel K. 2006. The role of STS and OATP-B mRNA expression in predicting the clinical outcome in human breast cancer. *Anticancer Res.* 26:4985–90
65. Nozawa T, Suzuki M, Takahashi K, Yabuuchi H, Maeda T, et al. 2004. Involvement of estrone-3-sulfate transporters in proliferation of hormone-dependent breast cancer cells. *J. Pharmacol. Exp. Ther.* 311:1032–37
66. Nozawa T, Suzuki M, Yabuuchi H, Irokawa M, Tsuji A, Tamai I. 2005. Suppression of cell proliferation by inhibition of estrone-3-sulfate transporter in estrogen-dependent breast cancer cells. *Pharm. Res.* 22:1634–41
67. Hagenbuch B, Gui C. 2008. Xenobiotic transporters of the human organic anion transporting polypeptides (OATP) family. *Xenobiotica* 38:778–801
68. König J. 2011. Uptake transporters of the human OATP family: molecular characteristics, substrates, their role in drug-drug interactions, and functional consequences of polymorphisms. *Handb. Exp. Pharmacol.* 201:1–28
69. van Montfoort JE, Hagenbuch B, Groothius GMM, Koepsell H, Meier PJ, Meijer DK. 2003. Drug uptake systems in liver and kidney. *Curr. Drug Metab.* 4:185–211
70. Gui C, Miao Y, Thompson L, Wahlgren B, Mock M, et al. 2008. Effect of pregnane X receptor ligands on transport mediated by human OATP1B1 and OATP1B3. *Eur. J. Pharmacol.* 584:57–65
71. Roth M, Timmermann BN, Hagenbuch B. 2011. Interactions of green tea catechins with organic anion-transporting polypeptides. *Drug Metab. Dispos.* 39:920–26
72. Hu S, Franke RM, Filipski KK, Hu C, Orwick SJ, et al. 2008. Interaction of imatinib with human organic ion carriers. *Clin. Cancer Res.* 14:3141–48
73. Badagnani I, Castro RA, Taylor TR, Brett CM, Huang CC, et al. 2006. Interaction of methotrexate with organic-anion transporting polypeptide 1A2 and its genetic variants. *J. Pharmacol. Exp. Ther.* 318:521–29
74. Oostendorp RL, van de Steeg E, van der Kruijssen CM, Beijnen JH, Kenworthy KE, et al. 2009. Organic anion-transporting polypeptide 1B1 mediates transport of gimatecan and BNP1350 and can be inhibited by several classic ATP-binding cassette (ABC) B1 and/or ABCG2 inhibitors. *Drug. Metab. Dispos.* 37:917–23
75. Nozawa T, Minami H, Sugiura S, Tsuji A, Tamai I. 2005. 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.* 33:434–39
76. Ni W, Ji J, Dai Z, Papp A, Johnson AJ, et al. 2010. Flavopiridol pharmacogenetics: clinical and functional evidence for the role of SLCO1B1/OATP1B1 in flavopiridol disposition. *PLoS ONE* 5:e13792
77. Feng B, Xu JJ, Bi YA, Mireles R, Davidson R, et al. 2009. Role of hepatic transporters in the disposition and hepatotoxicity of a HER2 tyrosine kinase inhibitor CP-724,714. *Toxicol. Sci.* 108:492–500
78. Sasaki M, Suzuki H, Aoki J, Ito K, Meier PJ, Sugiyama Y. 2004. Prediction of in vivo biliary clearance from the in vitro transcellular transport of organic anions across a double-transfected Madin-Darby canine kidney II monolayer expressing both rat organic anion transporting polypeptide 4 and multidrug resistance associated protein 2. *Mol. Pharmacol.* 66:450–59

79. Briz O, Serrano MA, Rebollo N, Hagenbuch B, Meier PJ, et al. 2002. 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.* 61:853–60
80. Smith NF, Acharya MR, Desai N, Figg WD, Sparreboom A. 2005. Identification of OATP1B3 as a high-affinity hepatocellular transporter of paclitaxel. *Cancer Biol. Ther.* 4:815–18
81. Letschert K, Faulstich H, Keller D, Keppler D. 2006. Molecular characterization and inhibition of amanitin uptake into human hepatocytes. *Toxicol. Sci.* 91:140–49
82. Yamaguchi H, Kobayashi M, Okada M, Takeuchi T, Unno M, et al. 2008. Rapid screening of antineoplastic candidates for the human organic anion transporter OATP1B3 substrates using fluorescent probes. *Cancer Lett.* 260:163–69
83. Oswald S, Nassif A, Modess C, Keiser M, Hanke U, et al. 2010. Pharmacokinetic and pharmacodynamic interactions between the immunosuppressant sirolimus and the lipid-lowering drug ezetimibe in healthy volunteers. *Clin. Pharmacol. Ther.* 87:663–67
84. Takane H, Kawamoto K, Sasaki T, Moriki K, Kitano H, et al. 2009. Life-threatening toxicities in a patient with *UGT1A1*6/*28* and *SLCO1B1*15/*15* genotypes after irinotecan-based chemotherapy. *Cancer Chemother. Pharmacol.* 63:1165–69
85. Xiang X, Jada SR, Li HH, Fan L, Tham LS, et al. 2006. Pharmacogenetics of *SLCO1B1* gene and the impact of **1b* and **15* haplotypes on irinotecan disposition in Asian cancer patients. *Pharmacogenet. Genomics* 16:683–91
86. Smith NF, Marsh S, Scott-Horton TJ, Hamada A, Mielke S, et al. 2007. Variants in the *SLCO1B3* gene: interethnic distribution and association with paclitaxel pharmacokinetics. *Clin. Pharmacol. Ther.* 81:76–82
87. van de Steeg E, van Esch A, Wagenaar E, van der Kruijssen CMM, van Tellingen O, et al. 2011. High impact of Oatp1a/1b transporters on in vivo disposition of the hydrophobic anticancer drug paclitaxel. *Clin. Cancer Res.* 17:294–301
88. Svoboda M, Riha J, Wlcek K, Jaeger W, Thalhammer T. 2011. Organic anion transporting polypeptides (OATPs): regulation of expression and function. *Curr. Drug Metab.* 12(2):139–53
89. Ichihara S, Kikuchi R, Kusuhara H, Imai S, Maeda K, Sugiyama Y. 2010. DNA methylation profiles of organic anion transporting polypeptide 1B3 in cancer cell lines. *Pharm. Res.* 27:510–16
90. Köck K, Koenen A, Giese B, Fraunholz M, May K, et al. 2010. Rapid modulation of the organic anion transporting polypeptide 2B1 (OATP2B1, SLCO2B1) function by protein kinase C-mediated internalization. *J. Biol. Chem.* 285:11336–47
91. Choi JH, Murray JW, Wolkoff AW. 2011. PDZK1 binding and serine phosphorylation regulate subcellular trafficking of organic anion transport protein 1a1. *Am. J. Physiol. Gastrointest. Liver Physiol.* 300:384–93
92. Guo GL, Klaassen CD. 2001. Protein kinase C suppresses rat organic anion transporting polypeptide 1- and 2-mediated uptake. *J. Pharmacol. Exp. Ther.* 299:551–57

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Errata

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