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RESEARCH PAPER

Organic Anion Transporting Polypeptides Expressed in Pancreatic Cancer May Serve As Potential Diagnostic Markers and Therapeutic Targets for Early Stage Adenocarcinomas

Amanda Hays • Udayan Apte • Bruno Hagenbuch

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ABSTRACT

Purpose Organic Anion Transporting Polypeptides (OATPs) are expressed in various epithelial tissues in the body. Because they can be expressed in cancers and because they can transport anticancer drugs, OATPs could be potential targets for cancer therapy. Therefore we examined their expression in human pancreatic ductal adenocarcinomas.

Methods Expression of all 11 human OATPs was measured at the mRNA level and OATPs with highest expression were characterized at the protein level.

Results Transcripts of *SLCO1B3*, *SLCO2A1*, *SLCO3A1* and *SLCO4A1* were detected in all the tested pancreatic tissues. OATP1B3, OATP2A1, OATP3A1 and OATP4A1 protein expression was confirmed in these tissues and expression of all four transporters increased in pancreatic adenocarcinoma compared to normal pancreas. OATP1B3 expression was highest in pancreatic hyperplasia and stage one adenocarcinomas compared to stage two and three adenocarcinomas.

Conclusion OATP1B3, OATP2A1, OATP3A1 and OATP4A1 are up-regulated in pancreatic adenocarcinoma and could potentially be used to target anticancer drugs to pancreatic cancer. Additionally, because expression of OATP1B3 is highest in pancreatitis and stage one adenocarcinoma, which leads to pancreatic cancer, OATP1B3 is a potential marker to diagnose patients with early stage pancreatic adenocarcinomas.

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A. Hays • U. Apte • B. Hagenbuch (✉)
Department of Pharmacology, Toxicology and Therapeutics
The University of Kansas Medical Center, 3901 Rainbow Blvd.
Kansas City, Kansas 66160, USA
e-mail: bhagenbuch@kumc.edu

B. Hagenbuch
The University of Kansas Cancer Center, Kansas City, Kansas, USA

KEY WORDS cancer biomarker · OATP · pancreatic ductal adenocarcinoma · SLCO · uptake transporters

ABBREVIATIONS

ABC	ATP-binding cassette
ADM	acinar to ductal metaplasia
CAII	carbonic anhydrase II
MDR	multidrug resistance
OATP	organic anion transporting polypeptide
SLCO	solute carrier family of the OATPs

INTRODUCTION

Pancreatic cancer remains one of the most difficult cancers to treat clinically. Commonly, patients remain asymptomatic until diagnosed with a late stage of pancreatic adenocarcinoma and often do not respond to surgery or conventional chemotherapy. For this reason, there is an urgent need for more effective diagnostics and therapeutics for this disease (1–3).

Relapse and incomplete recovery from this disease can be a result of multidrug resistance (MDR) (4). A very well characterized mechanism of multidrug resistance in cancer is the over-expression of efflux transporters, members of the ATP-binding cassette (ABC) transporter superfamily. Fueled by ATP, these efflux transporters pump anticancer drugs out of cancer cells leading to drug ineffectiveness and ultimately resistance (5). One way to overcome MDR would be to target these efflux transporters by developing selective inhibitors, also called reversal agents (6–9). Unfortunately these attempts have so far not been successful and recent attention has shifted to a different class of potential therapeutic targets, namely uptake transporters. Several uptake transporters that belong to the solute carrier family (SLC) can transport anticancer drugs and their expression has

been implicated in chemosensitivity of cancer cells (10). Consequently, downregulation of these uptake transporters could also contribute to chemoresistance of cancer cells. As an example, expression of the nucleoside transporter ENT1 can cause chemosensitivity in tumors for numerous nucleoside analogs including gemcitabine and capecitabine because these drugs are transported into the cancer cells more efficiently when ENT1 is expressed. In contrast, downregulation of ENT1 expression can result in chemoresistance for nucleoside analogs (11). Similarly, the expression of the copper transporter CPT1 which can transport cisplatin into cells was downregulated by cisplatin in cultured ovarian cancer cells resulting in cisplatin resistance in these cells (12).

Organic Anion Transporting Polypeptides (OATPs) are a class of uptake transporters belonging to the solute carrier family of the OATPs (*SLCO*) gene superfamily (13,14). OATPs mediate the Na^+-independent uptake of a wide range of structurally diverse endogenous and exogenous compounds including bile acids, hormone conjugates, peptides, toxins, as well as a multitude of therapeutic drugs (15). OATPs are expressed in the epithelia of many different tissues in the body and have altered expression profiles in various cancers. For example, the liver-specific OATP1B3, under normal conditions, is exclusively expressed at the basolateral membrane of human hepatocytes (16,17). However, several studies showed OATP1B3 expression in cancers of the colon (17–19), prostate (20), breast (21), ovary (22), lung (23) and bone (24).

The expression of OATPs in many different cancers combined with their ability to transport cancer drugs, suggests that OATPs could potentially serve as therapeutic targets for cancer drug delivery into cancer cells (25). Recently, Kounnis and colleagues studied the expression of three OATPs in pancreatic cancer (26). We wanted to extend this study and evaluated the expression of all 11 human OATPs in pancreatic cancer and expanded on the understanding of OATP1B3 expression at different stages of pancreatic adenocarcinomas.

MATERIALS AND METHODS

Materials

The fresh frozen human tissues used in this study were provided by the Biospecimen Shared Resource of the University of Kansas Cancer Center (Kansas City, KS). Quantigene Plex 2.0 System Reagents were purchased from Panomics Inc. (Fremont, CA). Fetal bovine serum was obtained from Hyclone (Logan, UT). Anti-OATP1B3 (sc-47273), OATP2A1 (sc-103085), OATP3A1 (sc-66566) and OATP4A1 (sc-51169) goat polyclonal antibodies used in the immunofluorescence analyses were purchased from Santa Cruz Biotechnology Inc. (Santa Cruz, CA) and do not cross-react with other OATP family members. Because OATP1B3 and OATP1B1 share 80% amino acid identity the specificity of the OATP1B3 antibody was validated using a stable cell line over-expressing OATP1B1 or OATP1B3 (Supplementary Material Figure S1). The anti-OATP1B3 antibody used for immunohistochemical staining analyses on the tissue microarray was raised against the C-terminal 14 amino acids which are specific for OATP1B3 and was obtained from Sigma (St. Louis, MO). The pancreas tissue microarrays were purchased from US Biomax (Rockville, MD) and Cybrdi (Rockville, MD).

Messenger RNA Quantification

Frozen pancreas tissue samples were homogenized with a glass-teflon tissue homogenizer in a hypotonic buffer (1 mM NaCl, 5 mM Tris–HCl pH 7.5) containing protease inhibitors (Complete Protease Inhibitor Cocktail, Roche, Indianapolis, IN) and mRNA expression of OATPs was determined using the QuantiGene Plex 2.0 Reagent System (Panomics Inc., Fremont, CA). Bead-based oligonucleotide probe sets specific for all 11 human OATP genes were developed by Panomics Inc. Samples were analyzed using a Bio-Plex System Array reader with Luminex 100xMAP technology, and data were acquired using Bio-Plex Data Manager software version 5.0 (Bio-Rad Laboratories, Hercules, CA). Assays were performed according to the manufacturer's protocol (Panomics Inc). All data were standardized to the internal control ribosomal protein L13A.

Immunofluorescence Staining on Fresh Frozen Tissues

Frozen pancreas tissue samples were cut into 6 μm sections with a cryostat onto positively charged slides. The slides were then fixed and permeabilized using a 2% paraformaldehyde and 1% Triton X-100 solution for 10 min, and blocked with 5% donkey serum for 1 h. Sections were incubated overnight at 4°C with polyclonal antibodies for OATPs diluted 1:100 in 1% donkey serum in PBS. After washing in PBS, slides were incubated with an anti-goat AlexaFluor 594 antibody (Invitrogen, Carlsbad, CA) diluted 1:1000 in 0.1% PBS-Tween for 1 h and after a final wash, sections were mounted in Prolong Gold containing DAPI (Invitrogen, Carlsbad, CA). For negative controls, the sections were incubated with secondary antibody only.

Immunohistochemistry Staining on Paraffin-Embedded Tissue Microarray

Tissue array slides containing 197 pancreas specimens (120 cases of ductal adenocarcinomas, 4 adenosquamous

carcinomas, 13 islet cell carcinomas, 6 metastatic carcinomas, 2 hyperplasias, 11 inflammations, 20 normal tissues adjacent to cancer and 21 normal tissues) from autopsies were used for these studies. Following deparrafinization and rehydration, sections were quenched with 3% hydrogen peroxide solution for 10 min. Antigen retrieval was conducted by boiling the slides in citrate buffer (pH=7.4) for 20 min, followed by washing with PBS two times and blocked with 5% normal donkey serum (Sigma) for 1 h. Sections were incubated overnight at 4°C with affinity purified polyclonal anti-OATP1B3 antibody at a 1:30 concentration. After washing, slides were incubated with biotin-conjugated secondary antibody (Jackson Immuno Research Labs, West Grove, PA) for 30 min at room temperature, and the signal was detected using an ABC Elite kit (Vector Laboratories, Burlingame, CA) following the manufacturer's protocol. The tissues were stained with DAB chromagen, counterstained with hematoxylin, dehydrated, coverslipped and mounted with cytoseal (Richard-Allen scientific, Kalamazoo, MI). For negative controls, the sections were incubated with secondary antibody only.

Pathological Evaluation

OATP1B3 expression was evaluated in all sections of the pancreatic cancer tissue microarray and scored in three independent evaluations within 14 days of staining. OATP1B3 expression was assessed according to the staining intensity for each specimen and graded as negative or positive staining. The percentage of staining intensity was calculated by comparing the stained specimens to total number of specimens for each category.

Calculation and Statistics

All calculations were performed using Prism 5 (GraphPad Software Inc., San Diego, CA). To determine statistical significance between groups, student's *t*-test was performed and $P<0.05$ was considered significant.

RESULTS

Transcripts of OATP1B3, OATP2A1, OATP3A1 and OATP4A1 are Expressed in Normal Human Pancreas and in Pancreatic Adenocarcinoma Tissue

To determine which OATPs are expressed in normal and cancerous human pancreatic tissue, we examined the expression of all eleven human OATPs at the messenger RNA level in seven normal pancreas tissues and four ductal adenocarcinomas or metastasis (Table I) using the Quantigene Plex 2.0 reagent system. Among the eleven OATPs, we identified the expression of only four OATPs in the tested samples: OATP1B3, OATP2A1, OATP3A1 and OATP4A1. The expression of the remaining OATPs OATP1A2, OATP1B1, OATP1C1, OATP2B1, OATP4C1, OATP5A1 and OATP6A1 were below the detection limit for all the tested tissue samples (data not shown). Transcripts of OATP4A1 were highest in all the pancreas samples followed by OATP2A1, OATP3A1 and OATP1B3 (Fig. 1). Transcript levels of OATP2A1 decreased in pancreatic adenocarcinomas compared to normal pancreatic tissues, however the difference was not statistically significant ($p<0.05$). Similarly, the transcript levels of OATP1B3, OATP3A1 and OATP4A1 were not statistically significant between normal pancreas and pancreatic adenocarcinoma tissues. These results suggest that OATP1B3, OATP2A1, OATP3A1 and OATP4A1 are the main OATPs expressed in human pancreas.

OATPs Expression is Higher in Pancreatic Adenocarcinomas than in Normal Pancreas at the Protein Level

To determine changes in OATP protein expression in pancreatic adenocarcinoma and normal tissues we used immunofluorescence staining. Our data show expression of OATP2A1, OATP3A1 and OATP4A1 in normal pancreas and adenocarcinoma tissues (Fig. 2). In contrast to the transcript data, OATP2A1, OATP3A1 and OATP4A1 expression was higher in pancreatic adenocarcinoma than in normal pancreas tissue as evidenced by more intense staining observed throughout the adenocarcinoma tumors. Thus OATP2A1, OATP3A1 and OATP4A1 expression is upregulated in pancreatic adenocarcinomas.

Furthermore, we investigated the expression of OATP1B3 in normal pancreas and pancreatic adenocarcinoma. Immunoflourescence staining revealed low or absent OATP1B3 expression in normal pancreas, which was increased in pancreatic adenocarcinoma tumor specimens (Fig. 3). OATP1B3 was expressed in the entire tumor specimen in two out of three cases and selectively in the epithelial cells that line the pancreatic ducts in one out of three cases. Ductal expression of OATP1B3 is especially visible in the pancreatic tumor sample 1952. We used normal human liver tissue as a positive control for these studies which has constitutive expression of OATP1B3. To determine the location of OATP1B3 expression in pancreatic tumors, we used co-IF with OATP1B3 and carbonic anhydrase II (CAII), a marker of ductal epithelium. Our results indicate that OATP1B3 was localized, but not restricted, to the ductal epithelium of pancreatic adenocarcinoma (Fig. 4). Overall, protein expression of OATP1B3, OATP2A1, OATP3A1 and OATP4A1 was low in normal human pancreas but increased in pancreatic adenocarcinoma tissue.

Table I Characteristics of Pancreatic Tissue Samples

Sample number	Tissue description	Histological grade	Pathological staging	Final diagnosis
1360	normal	N/A	N/A	
1613	normal	N/A	N/A	
1671	normal	N/A	N/A	
1675	normal	N/A	N/A	
1878	normal	N/A	N/A	
1369	normal	N/A	N/A	
1934	normal	N/A	N/A	
1369	tumor	G_2	$pT_2\ N_0\ M_X$	invasive moderately differentiated adenocarcinoma
1934	tumor	G_2	$pT_3\ N_0M_1$	moderately differentiated ductal adenocarcinoma
1952	tumor	G_2	$pT_3\ N_{1b}M_X$	invasive moderately differentiated ductal adenocarcinoma
1597	Metastasis to the Omentum	N/A	N/A	metastatic adenocarcinoma to the omentum

Pathological staging is in accordance with the Tumor, Node, Metastasis (TNM) classification system from the American Joint Committee on Cancer (AJCC). T: size and/or extent of the tumor, N: extent of spread to lymph nodes, M: presence of metastasis

OATP1B3 is Expressed in Chronic Pancreatitis and Earlier Stages of Adenocarcinoma

We further assessed the frequency and extent of OATP1B3 expression at different stages and types of pancreatic cancer. A description of the analyzed samples is given in Table II. The rationale to further evaluate the expression of OATP1B3 was that unlike other OATPs, under normal physiological conditions, OATP1B3 is selectively expressed in human hepatocytes. However, recent studies revealed OATP1B3 expression in a wide range of different cancers. Thus, given the limited OATP1B3 expression in normal pancreatic tissue, OATP1B3 could be a good marker for diagnostic purposes and a practical target for anticancer drug delivery into tumor cells. Therefore, we examined OATP1B3 expression on two pancreas cancer tissue microarrays using immunohistochemical staining. The results confirmed previous observations, indicating low expression of OATP1B3 in normal pancreas (10% of cases; n=21) and cancer adjacent normal pancreas tissue (20% of cases; n=20). Interestingly, OATP1B3 expression was high in hyperplasia, pancreatic inflammation and chronic pancreatitis

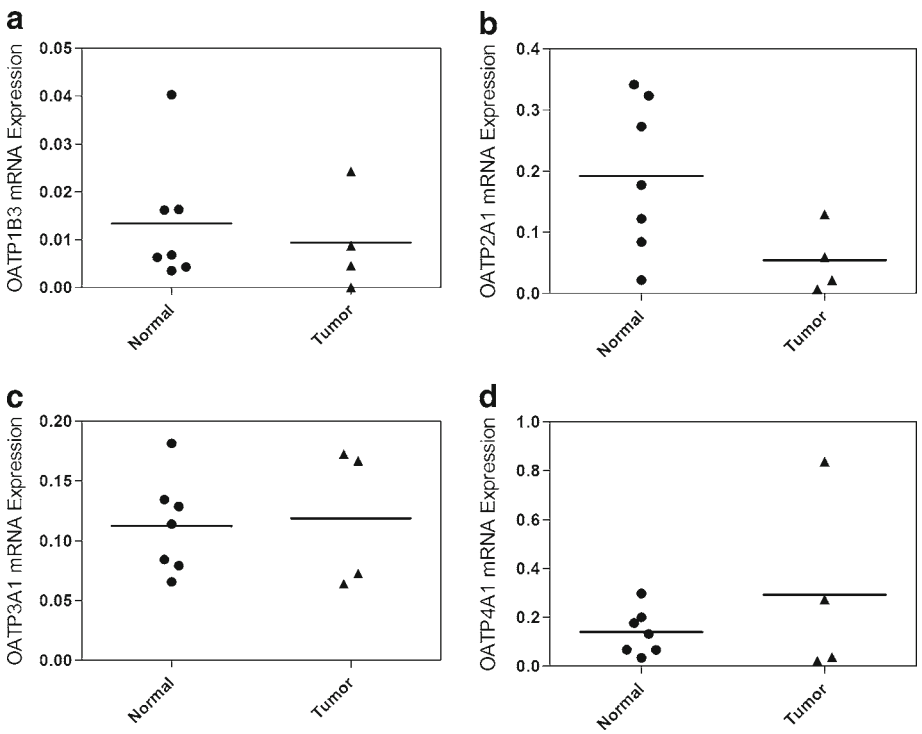

Fig. 1 Messenger RNA expression of OATPs in normal pancreas and pancreatic tumor samples. Messenger RNA expression of (**a**) OATP1B3, (**b**) OATP2A1, (**c**) OATP3A1 and (**d**) OATP4A1 in normal pancreas and pancreas cancer tissue samples was measured by Quantigene Plex 2.0 Reagent System. Data were normalized to the housekeeping gene ribosomal protein L13A. $P<0.05$ by unpaired t-test.

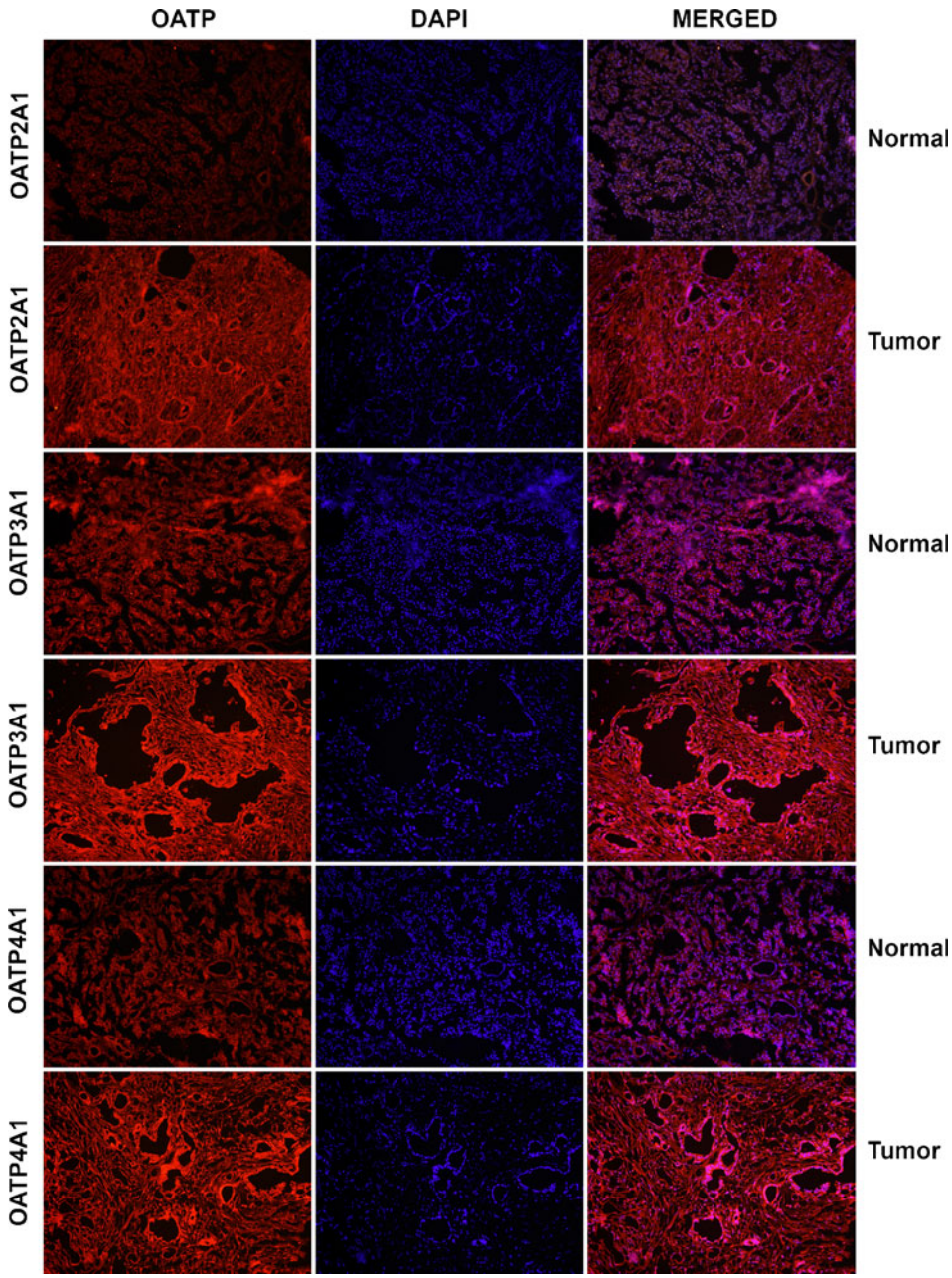

Fig. 2 Immunofluorescence staining of human pancreas tissue samples with anti-OATP antibodies. Immunofluorescence staining was conducted on frozen sections of normal and cancerous pancreatic tissues. The positive signal is visualized with red color for OATP2A1, OATP3A1, and OATP4A1. Nuclei are visualized in blue color with DAPI. All images are at 200× magnification.

specimens (38% of cases; n=13) (Fig. 5a). Similarly OATP1B3 was expressed in 30% of stage one pancreatic adenocarcinoma cases (n=26) (Fig. 5b), decreased in stage two (18% of cases; n=39) and stage three adenocarcinoma (13% of cases; n=15) (Fig. 5c) and was completely absent in metastatic tissues from primary pancreatic adenocarcinoma (n=6). Aside from pancreatic adenocarcinoma, we also evaluated OATP1B3 expression in two other types of pancreatic cancer, islet cell tumors and pancreatic adenosquamous carcinomas. OATP1B3 expression was absent in islet cell tumors (n=13), and, it was expressed in 50% of the adenosquamous carcinomas (n=4). These results revealed that OATP1B3 is highly expressed in pancreatic hyperplasia and early stage adenocarcinomas with decreasing expression in higher stage adenocarcinomas.

DISCUSSION

Pancreatic cancer remains a difficult cancer to treat clinically with multidrug resistance as one of the leading causes of relapse in these patients (1). The present study addressed the question of which major OATPs are expressed in pancreatic adenocarcinoma and to what extent OATP1B3

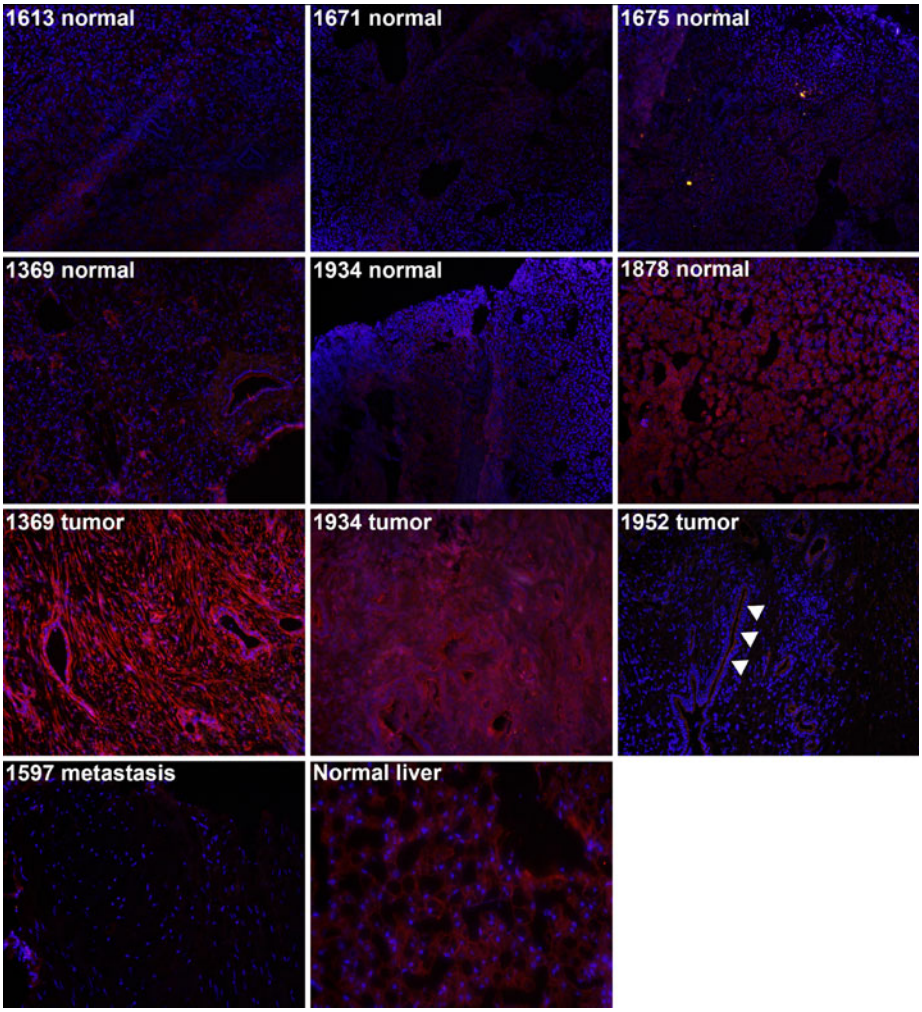

Fig. 3 Immunofluorescence staining of human pancreas tissue samples against OATP1B3. Immunofluorescence staining was conducted on frozen sections of normal and cancerous pancreatic tissues. The positive signal for OATP1B3 is visualized with red color. Nuclei are visualized in blue color with DAPI. Normal human liver was used as a positive control to confirm the specificity of the OATP1B3 polyclonal antibody and shows membranous staining in the hepatocytes. Expression of OATP1B3 in the tumor sample 1952 is restricted to the epithelial cells lining the acini (*white arrowheads*). All images are at 200× magnification except for the normal liver image which is a 400× magnification.

would be expressed in the different types and stages of pancreatic cancer. The results suggest that certain OATPs can potentially be used as a target to treat early stage pancreatic adenocarcinomas with cytotoxic chemotherapeutic drugs

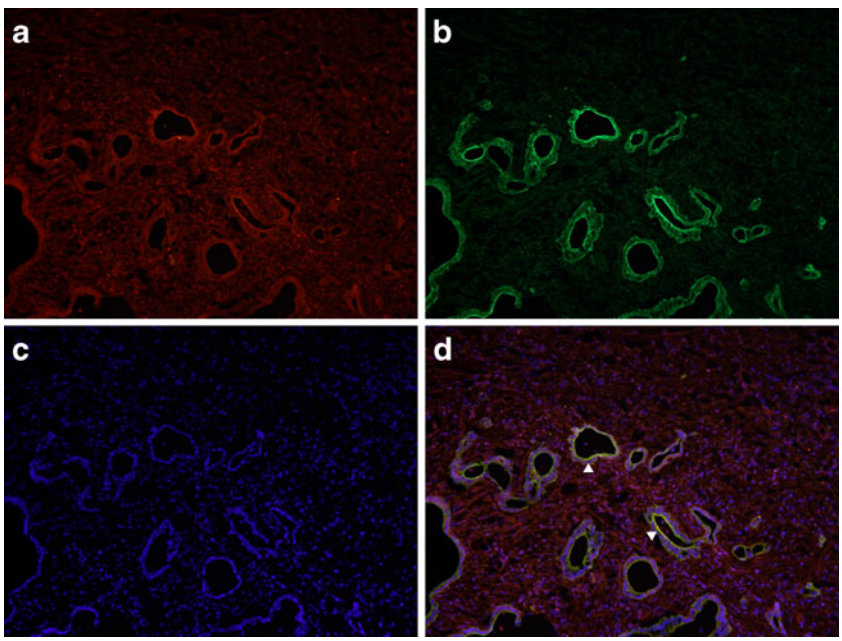

Fig. 4 Co-localization of OATP1B3 and Carbonic Anhydrase II in human pancreatic tumor tissue. Immunofluorescence staining was conducted on frozen sections of pancreatic cancer tissue. (**a**) Positive signal for OATP1B3 is visualized with *red color*; (**b**) the ductal marker, carbonic anhydrase II (CAII), is visualized in *green color*; (**c**) nuclei are visualized in *blue color* with DAPI; (**d**) the merged image shows an overlay of the nuclei, OATP1B3 and CAII for localization. *White arrowheads* point to the strongest co-localization of OATP1B3 and CAII. Images are at 200× magnification.

Table II Characteristics of Samples from Pancreas Tissue Microarrays

Tissue type	# of samples analyzed
Normal pancreas	21
cancer adjacent normal pancreas	20
Hyperplasia/Inflammation	13
Ductal adenocarcinoma Stage I	26
Ductal adenocarcinoma Stage II	39
Ductal adenocarcinoma Stage II	15
Ductal adenocarcinoma unstaged	40
Metastasis	6
Islet cell tumors	13
Adenosquamous carcinoma	4

that are substrates of these OATPs. In addition, the results indicate that OATP1B3 may serve as a potential biomarker for the development of early stage pancreatic adenocarcinoma.

Our first set of results demonstrates that the four major OATPs expressed in pancreatic adenocarcinoma include OATP1B3, OATP2A1, OATP3A1 and OATP4A1. Although expression of the four OATPs at the messenger RNA level was not statistically significant between normal pancreas and pancreatic adenocarcinoma, we found that OATP1B3, OATP2A1, OATP3A1 and OATP4A1 expression at the protein level was increased in adenocarcinoma compared to normal tissue as evident by immunofluorescence staining. These discrepancies between mRNA and protein expression levels could be due to different post-translational regulation of these OATPs in tumor tissues. Strong up-regulation of the proteins might be beneficial for the tumors because OATPs have been shown to be able to transport hormones (20,27) and might also transport some so far unidentified chemicals that are beneficial to tumor growth. Although mRNA expression levels can be useful for preliminary assessment of OATP expression in tissues, it remains important to assess the expression of OATPs at their functional protein level.

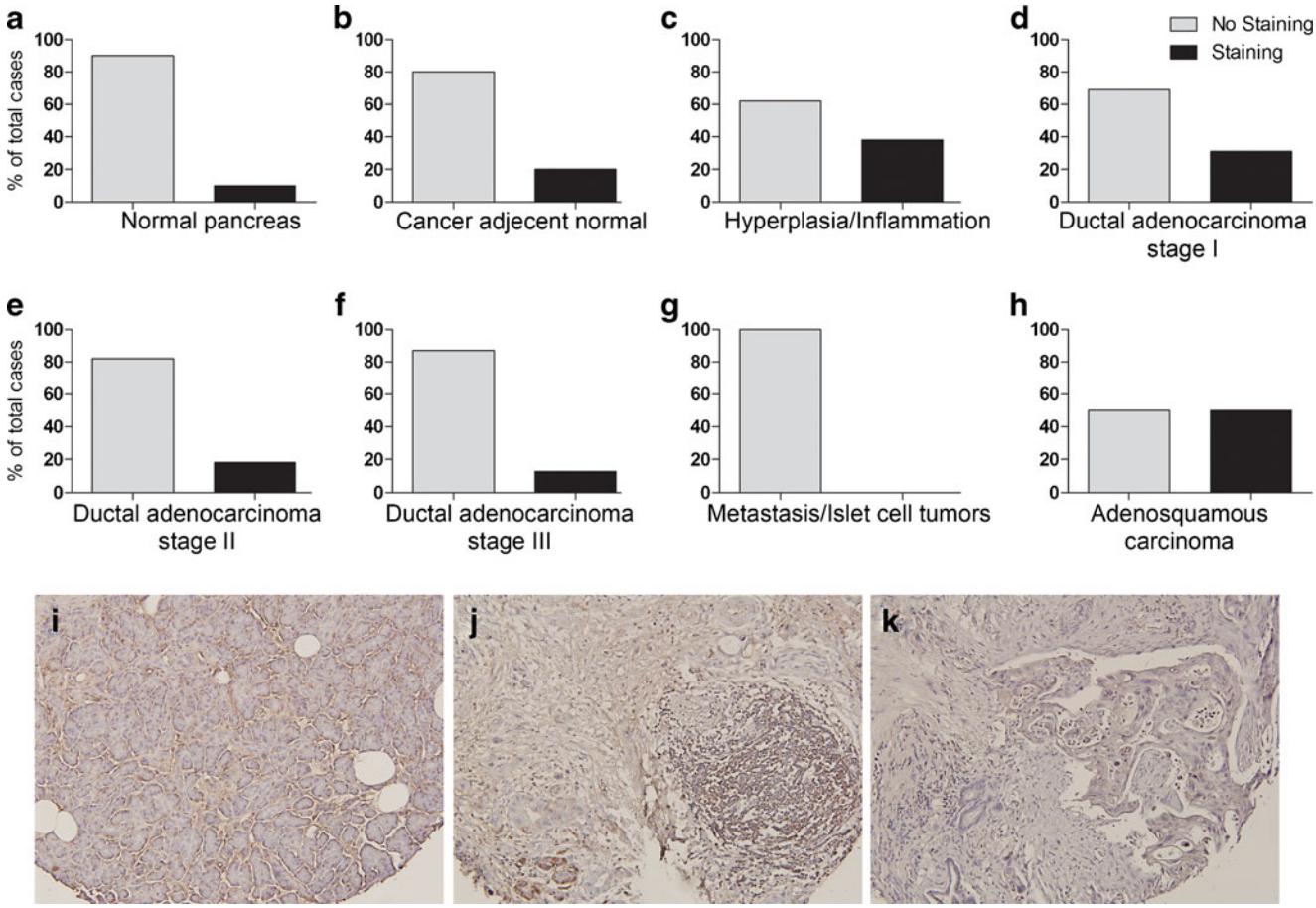

Fig. 5 Immunohistochemical staining of OATP1B3 on a pancreas tissue microarray. Tissue arrays containing paraffin-embedded sections were stained for OATP1B3 using immunohistochemistry. Staining intensity from the tissue microarray was scored as negative or positive staining. Percentage was calculated by the number of stained specimens compared to total number of specimens in (**a**) normal pancreatic tissue, (**b**) normal pancreas adjacent to cancer tissue, (**c**) hyperplasia and/or inflammation, (**d**) ductal adenocarcinoma stage one, (**e**) ductal adenocarcinoma stage two, (**f**) ductal adenocarcinoma stage three, (**g**) metastatic tumor from pancreas and/or islet cell tumors, and (**h**) pancreatic adenosquamous carcinoma. Representative photomicrographs of (**i**) chronic pancreatitis, (**j**) ductal adenocarcinoma stage one, and (**k**) ductal adenocarcinoma stage three.

OATP2A1 mainly functions in the transport of prostaglandins and is expressed ubiquitously throughout the body. Initial studies demonstrated that at the mRNA level OATP2A1 is expressed in many organs including normal pancreas (28). Follow-up studies showed OATP2A1 to be up-regulated in numerous different cancers as well as in malignant breast cancer tissue compared with its adjacent nonmalignant breast tissue (29). Both OATP3A1 and OATP4A1 are also ubiquitously expressed in a variety of different tissues in the body. Several reports indicate that both OATPs also share similar expression patterns in cancer and are expressed in the breast cancer cell lines MCF-7 and T-47D (27,30), in malignant breast tumor tissue (31), in malignant osteosarcoma cell lines (24) and in a variety of gastrointestinal cancer cell lines as well as in the pancreatic cancer cell line GI-103 (32). Due to the ability of many OATPs to transport hormones and their conjugates, it has been hypothesized that the expression of OATPs in cancer tissue could potentially contribute to the proliferation of hormone-dependent cancers (20,27). Thus, one potential therapeutic approach would be to develop OATP inhibitors to improve overall survival for patients with OATP-expressing cancers (25,33). Another potential approach for OATP-mediated cancer therapy would be the targeting of OATP-expressing cancers with cytotoxic cancer drugs that are substrates of these OATPs (25). However, so far there are no reports available yet that demonstrate transport of cancer drugs by OATP2A1, OATP3A1 or OATP4A1.

OATP1B3 did get increased attention recently, owing to its expression in a wide variety of cancers while its expression under normal physiological conditions is exclusive to the liver. Combined with this expression pattern, its ability to transport several cancer drugs, namely methotrexate (17,34), paclitaxel, docetaxel (35,36) and imatinib (37) makes OATP1B3 a more appropriate target for the delivery of anticancer drugs that mainly affect rapidly dividing cells. In 2001, Abe *et al.* were the first to demonstrate OATP1B3 expression in several pancreatic cancer cell lines by northern blot analysis. They also confirmed OATP1B3 protein expression in a single case of pancreatic cancer using immunohistochemical staining (17). Recently Kounnis *et al.* evaluated the expression of the three well characterized OATP1A2, OATP1B1 and OATP1B3 in two pancreatic cancer cell lines and in several biopsies of pancreatic cancer tissue (26). They concluded that all three OATPs are expressed in pancreatic cancer, but some discrepancies remain due to the use of antibodies with overlapping specificities or antibodies that have not been validated. In the present study, we confirmed their finding that OATP1B3 is expressed in pancreatic cancer tissue using a different OATP1B3 specific antibody. Furthermore, we were among the first to show that expression of OATP1B3 differs in different tumor types and stages of pancreatic cancer. Interestingly, our results showed the highest OATP1B3 expression in tissues that have pathological risk factors for the development of pancreatic cancer including tissues with mild and chronic hyperplasia and inflammation. In addition, OATP1B3 was expressed at highest levels in stage one followed by stage two pancreatic adenocarcinoma with little to no staining in stage three pancreatic adenocarcinoma or metastatic tissue. These results are in accordance with findings reported for the expression of OATP1B3 in colorectal cancer stages where OATP1B3 expression was highest in lower stage colorectal tumors (38). Another study demonstrated an increased trend of OATP1B3 expression in precancerous colon polyps (39). In another study, OATP1B3 expression was highest in stage one and two breast carcinoma compared to stage three breast carcinoma (21). Collectively, these data suggest that OATP1B3 could be used as a potential diagnostic marker in early stage cancer detection. This possibility should be further explored to investigate whether a non-invasive imaging procedure would be sensitive enough to detect OATP1B3-expressing cancers. It has recently been demonstrated in healthy volunteers that [^{11}C]telmisartan, a predominant substrate of OATP1B3 (40), is a safe substrate that can be used for PET imaging. Most of the injected [^{11}C]telmisartan accumulated in the liver and was also clearly detectable at later time points in the gallbladder and the small intestine (41). Thus, this or similar OATP1B3-selective PET imaging substrates could potentially be used to develop a non-invasive screening procedure to detect OATP1B3-expressing cancers. Such OATP1B3-expressing cancers could then potentially be targeted with anticancer drugs.

In future studies it would be interesting to investigate the regulation of OATP1B3 expression during the development of pancreatic ductal adenocarcinoma. Such studies should examine which signaling pathways regulate OATP1B3 expression during acinar to ductal metaplasia (ADM), the initial process of pancreatic adenocarcinoma development, where pancreatic acinar cells with chronic inflammation undergo morphogenesis into abnormal cells with ductal phenotypes (42) and might identify additional therapeutic targets.

In conclusion, OATPs may serve as potential diagnostic markers and therapeutic targets to improve pancreatic cancer therapy. In particular targeting OATP1B3 which has been shown to transport several anticancer drugs could be as useful as targeting efflux transporters in cancer therapy. Furthermore, our findings are the basis for further investigation of OATP1B3 regulation in pancreatic cancer and for further evaluation of OATP1B3 as a diagnostic marker for early cancer detection.

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