ABSTRACT:
The effect of oxaliplatin against colorectal cancer is superior to that of cisplatin, but the molecular mechanism(s) involved is not clear. We found previously that oxaliplatin, but not cisplatin, was transported by human (h) and rat organic cation transporter 3 (OCT3/SLC22A3). In the present study, we examined whether hOCT3 was significantly involved in the oxaliplatin-induced cytotoxicity and accumulation of platinum in colorectal cancer. The level of hOCT3 mRNA in the colon was 9.7-fold higher in cancerous than in normal tissues in six Japanese patients (P = 0.0247). In human colorectal cancer-derived cell lines, the mRNA of hOCT3 was highly expressed compared with that of other organic cation transporters. The release of lactate dehydrogenase (LDH) and accumulation of platinum with oxaliplatin treatment were increased in SW480 cells transfected with hOCT3 cDNA compared with empty vector-transfected cells. T84 and SW837 cells, with high levels of hOCT3, released more LDH and accumulated more platinum after oxaliplatin treatment than low hOCT3-expressing cells such as SW480, HCT116, HT28, and Lovo. However, the amount of platinum accumulated after cisplatin treatment did not differ among these six cell lines. The levels of hOCT3 expression in colon and rectum were also higher in cancerous than in normal tissues in Caucasian patients as determined by dot blotting. In conclusion, the hOCT3-mediated uptake of oxaliplatin into the cancers was suggested to be important for its cytotoxicity, and hOCT3 expression may be a marker for cancer chemotherapy including oxaliplatin.

Platinum agents are widely used in the treatment of cancers. Cis-diamminedichloroplatinum II (cisplatin) was the first platinum agent to be synthesized and has played an essential role in cancer chemotherapy for 30 years. However, severe nephrotoxicity and an increase in resistance to cisplatin therapy limit continuous clinical use. Trans-L-1,2-diaminocyclohexaneoxalatoplatinum II (oxaliplatin) is a third-generation platinum agent, which is less nephrotoxic than cisplatin. Moreover, its spectrum of activity and mechanisms of action or resistance differ from those of cisplatin (Raymond et al., 2002; Fuertes et al., 2003; Wang and Lippard, 2005). Oxaliplatin is used against colorectal cancers as a key drug in FOLFOX regimens, and its objective response rate for colorectal cancer is superior to that of cisplatin (Loehrer et al., 1988; Grem et al., 1993; de Gramont et al., 2000; Andre et al., 2004). However, the molecular mechanism(s) underlying the clinical results and the reason that oxaliplatin has such a potent anticolorectal cancer effect compared with cisplatin are unclear.

The organic cation transporters (OCT/SLC22A) and multidrug and toxin extrusion (MATE/SLC47A) family transport cationic drugs, toxins, and endogenous metabolites (Inui et al., 2000; Terada and Inui, 2008). Previously, we determined that the severity of the nephrotoxicity of platinum agents depends on the amount of platinum accumulated in the kidney, and OCT and MATE could play predominant roles in the renal handling of these agents (Yonezawa et al., 2005, 2006; Yokoo et al., 2007). We also reported that oxaliplatin, but not cisplatin, was selectively transported by rat (r) or human (h) organic cation transporter 3 (OCT3/SLC22A3) (Yonezawa et al., 2006; Yokoo et al., 2007). OCT3 mRNA was found in placenta, intestine, heart, brain, and kidney, but the distribution in the membrane and physiological role of OCT3 are not yet clearly understood (Kekuda et al., 1998).

We hypothesized that the substrate specificity and expression level of OCT3 affect the difference in the anticancer effect of platinum agents against colorectal cancer. In the present study, we examined in SW480 cells transfected with hOCT3 cDNA compared with empty vector-transfected cells. T84 and SW837 cells, with high levels of hOCT3, released more LDH and accumulated more platinum after oxaliplatin treatment than low hOCT3-expressing cells such as SW480, HCT116, HT28, and Lovo. However, the amount of platinum accumulated after cisplatin treatment did not differ among these six cell lines. The levels of hOCT3 expression in colon and rectum were also higher in cancerous than in normal tissues in Caucasian patients as determined by dot blotting. In conclusion, the hOCT3-mediated uptake of oxaliplatin into the cancers was suggested to be important for its cytotoxicity, and hOCT3 expression may be a marker for cancer chemotherapy including oxaliplatin.

Expression for the Cytotoxic Effect of Oxaliplatin
in Colorectal Cancer

Sachiko Yokoo, Satohiro Masuda, Atsushi Yonezawa, Tomohiro Terada, Toshiya Katsura, and Ken-ichi Inui

Department of Pharmacy, Kyoto University Hospital, Faculty of Medicine, Sakyo-ku, Kyoto, Japan

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ABBREVIATIONS: cisplatin, cis-diamminedichloroplatinum II; oxaliplatin, trans-L-1,2-diaminocyclohexaneoxalatoplatinum II; FOLFOX, folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin; OCT, organic cation transporter; MATE, multidrug and toxin extrusion; r, rat; h, human; DMEM, Dulbecco’s modified Eagle’s medium; FBS, fetal bovine serum; MPP, 1-methyl-4-phenylpyridinium acetate; ICP-MS, inductively coupled plasma-mass spectrometry; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; HEK, human embryonic kidney.
and compared the levels of OCT3 mRNA in colorectal and normal colorectum and among colorectal cancer-derived cell lines. In addition, the cytotoxicity and platinum accumulation in cultured cells caused by the treatment with oxaliplatin or cisplatin were examined.

Materials and Methods

Cell Culture. Human colorectal cancer-derived cell lines, T84 (CCL-248; American Type Culture Collection, Manassas, VA), SW480 (CCL-228; American Type Culture Collection), HCT116 (91091005; European Collection of Cell Cultures, Wiltshire, UK), HT29 (HTB-38; American Type Culture Collection), SW837 (JCRB9115; Health Science Research Resources Bank, Osaka, Japan), and Lovo (JCRB9083; Health Science Research Resources Bank, Osaka, Japan) were used. Human embryonic kidney (HEK)293 cells (CRL-1573; American Type Culture Collection) were used as a host for gene transfection (Yonezawa et al., 2006). Cell lines were cultured in an atmosphere of 5% CO2-95% air at 37°C. Dulbecco’s modified Eagle’s medium (DMEM) (Sigma-Aldrich) was used for T84, HT29, HCT116, Lovo, and HEK293. DMEM containing 10% FBS and 1% nonessential amino acid (Invitrogen) was used for SW480, HT29, HCT116, and HEK293. DMEM containing 10% FBS and 1% nonessential amino acid (Invitrogen) was used for SW837, and a 1:1 mixture of DMEM and nutrient medium Ham’s F12 medium (Sigma-Aldrich) with 10% FBS was used for T84, HT29, and Lovo cells were seeded onto 24-well plates or 96-well plates at a density of 4.0 × 10^3 cells/ml. SW480 and HCT116 cells were seeded at 2.0 × 10^5 cells/ml, and SW837 cells were seeded at 5.0 × 10^5 cells/ml. Seventy-two hours after the seeding, the cells were used for the experiments.

Transfection. For a transient expression system, pCMV6-XL4 plasmid vector DNA (OriGene Technologies, Rockville, MD) containing hOCT3 cDNA was purified using an EndoFree Plasmid Mega Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer’s instructions (Yonezawa et al., 2006). The day before transfection, HEK293 or SW480 cells were seeded onto poly-d-lysine-coated and noncoated 24-well plates, respectively. The cells were transfected with 800 ng of plasmid DNA per well in a combination of empty vector and hOCT3 cDNA using 2 μl of Lipofectamine 2000 (Invitrogen) per well according to the manufacturer’s instructions. The amount of hOCT3 cDNA was 800 ng except in the experiment examining the transporter cDNA dependence. Forty-eight hours after the transfection, the cells were used for the experiments.

Cytotoxicity Assay. The cytotoxicity of oxaliplatin was measured with a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells were seeded on 24-well plates were incubated with DMEM containing 10% FBS and oxaliplatin (Wako Pure Chemical Industries, Osaka, Japan) or cisplatin (Sigma-Aldrich) for 2 min or 1 h. After this incubation, the cells were trypsinized, washed with PBS, and reseeded into 96-well plates. The medium was collected, and the LDH activity in it was measured using a LDH Cytotoxicity Detection Kit (Takara Bio Inc., Shiga, Japan), according to the manufacturer’s instructions. LDH release (percent) was calculated as described previously (Yonezawa et al., 2006). For the caspase assay, cells were incubated...
with medium containing oxaliplatin for 8 h. After the incubation, caspase 3/7 activity was determined by using a Caspase-Glo 3/7 Assay (Promega, Madison, WI), according to the manufacturer’s instructions. Caspase activity (fold increase) represents (caspase 3/7 activity in oxaliplatin-treated cells)/(caspase 3/7 activity in cells without oxaliplatin).

**Isolation of Total RNA and Real-Time PCR.** Total RNA was isolated from each cell line on 24-well plates using an RNeasy Mini Kit (QIAGEN) according to the manufacturer’s instructions, and the concentrations of total RNA were measured by spectrophotometry. Total RNA was reverse-transcribed with random hexamers using Superscript II reverse transcriptase (Invitrogen), followed by digestion with RNase H (Invitrogen). For the detection of the expression of hOCT3 mRNA in cancerous or normal colon and rectum, the same batch of cDNA samples as used by Terada et al. (2005) was subjected to real-time PCR. Detailed information about the patients was given in the report of Terada et al. (2005). The conditions and primer-probe sets for real-time PCR were described previously (Motohashi et al., 2002; Masuda et al., 2006). The glycerinaldehyde-3-phosphate dehydrogenase mRNA level was used as an internal control. This study was conducted in accordance with the Declaration of Helsinki and its amendments and was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee.

**Cancer Profiling Array.** The cDNA cancer profiling array, Cancer Profiling Array I (Clontech, Mountain View, CA) was used. It includes normalized cDNAs from cancer and corresponding normal tissues from individual patients, amplified using SMART technology. Preparation of the cDNA probe for hOCT3, hybridization to the array, and signal detection on X-ray film were performed using the DIG High Prime DNA Labeling and Detection Starter Kit II (Roche Ltd., Basel, Switzerland) according to the manufacturer’s instructions. The relative intensity of each dot was determined densitometrically using ImageJ 1.38x (National Institutes of Health, Bethesda, MD).

**Statistical Analysis.** Data are expressed as means ± S.E. Data were analyzed statistically using the paired Student’s t test. Probability values of less than 0.05 were considered statistically significant.

**Results**

**Expression of hOCT3 mRNA in Normal and Cancerous Colorectal Tissues.** The expression of hOCT3 mRNA in colon (n = 6) or rectal (n = 10) tissue derived from Japanese patients was measured by real-time PCR. Figure 1 shows the difference in the expression between normal and cancerous colorectum. In cancerous colon tissue, the level of hOCT3 mRNA was significantly higher than that in normal tissue, and the mean increase in individuals was 9.7-fold (Fig. 1A). The median values of hOCT3 in normal and cancerous colon tissue were 0.44 (range 0.24–1.59) and 5.59 (range 0.20–8.62) zmol/μg of total RNA, respectively (P = 0.0247, by the paired Student’s t test). hOCT3 mRNA expression in rectum tended to increase in cancerous tissue, but the difference was not significant (Fig. 1B). The median values of hOCT3 in normal and cancerous rectal tissue were 0.87 (range 0.39–5.17) and 1.26 (range 0.41–17.1) zmol/μg of total RNA, respectively (P = 0.363, by the paired Student’s t test).

**mRNA Expression of Organic Cation Transporters in Colorectal Cancer-Derived Cell Lines.** We examined the expression of hOCT1, hOCT2, hOCT3, hMATE1, and hMATE2-K mRNA in colorectal cancer-derived cell lines, T84, SW480, HCT116, HT29, SW837, and Lovo, by real-time PCR. The hOCT3 transcript was found in all of these cells except HCT116 and was strongly detected in T84 and SW837 (Fig. 2). hMATE1 mRNA was only expressed in SW480. However, the mRNA expression of hOCT1, hOCT2, hMATE1, and hMATE2-K in these cells was almost negligible.

**[3H]MPP Uptake by Colorectal Cancer-Derived Cell Lines.** To check the functional activity of hOCT3 in cultured cells, we measured the cellular uptake of its typical substrate, [3H]MPP. The accumulation of [3H]MPP was greater in T84 cells, SW480 cells expressing hOCT3, and HEK293 cells expressing hOCT3 than in SW480 cells, SW480 cells transfected with vector cDNA, and HEK293 cells transfected with vector cDNA (Fig. 3A). In addition, we examined [3H]MPP uptake in other colorectal cancer-derived cell lines, HCT116, HT29, SW837, and Lovo. SW837 showed the highest level of activity to transport [3H]MPP among these six cell lines (Fig. 3B). The transport activity of the cells was confirmed, and then these cells and expression systems were used in subsequent experiments on the cytotoxicity and the cellular transport of platinum agents.

**hOCT3 Expression and Oxaliplatin-Induced Cytotoxicity.** We examined the effect of hOCT3 expression in a colon cancer-derived cell line, SW480. When SW480 cells transfected with 800 ng of empty vector or hOCT3 were treated with 500 μM oxaliplatin for 6 h and subsequently cultured in normal medium for 24 h, the release of LDH into the culture medium was increased by the expression of hOCT3 (Fig. 4A). In addition, we measured the amount of LDH released by treatment with 500 μM oxaliplatin in other colorectal cancer-derived cell lines. The amount of LDH released was greatest in...
SW837 and was also large in T84 and Lovo cells (Fig. 4B). SW480, HCT116, and HT29 cells showed little release of LDH with oxaliplatin treatment.

In addition, caspase 3/7 activity induced by treatment with 50 μM oxaliplatin was examined in these cell lines. The most potent activation of caspase 3/7 was in SW837 but T84 and Lovo cells also showed strong caspase 3/7 activity (Fig. 4C). The results of caspase activity were consistent with those of LDH release.

Transport of Oxaliplatin. We examined the accumulation of oxaliplatin with the increase of hOCT3 cDNA on transfection of SW480 cells (Fig. 5A), because almost no hOCT3 mRNA was found in SW480 cells (Fig. 2). When SW480 cells transfected with 50 to 800 ng of hOCT3 cDNA per well were treated with 1000 μM oxaliplatin for 1 h, the level of platinum accumulated in the cells was increased, depending on the amount of hOCT3 cDNA transfected (Fig. 5A). Based on these results, we determined the platinum accumulation in T84 cells, SW480 cells, and SW480 cells transfected with 800 ng of hOCT3 cDNA. When treated with 100, 500, or 1000 μM oxaliplatin for 1 h, T84 cells and SW480 cells expressing hOCT3 transported oxaliplatin extensively in a concentration-dependent manner compared with SW480 cells or SW480 cells transfected with empty vector (Fig. 5B). Moreover, we examined the amount of platinum accumulated after the treatment with oxaliplatin in other colorectal cancer-derived cell lines, HCT116, HT29, SW837, and Lovo. Platinum was most abundant in SW837 cells at all three concentrations when the cells were incubated with the culture medium containing oxaliplatin for 2 min (Table 1). The same tendency was observed when they were treated for 1 h (Table 2). In HT29 and Lovo cells, the amount of platinum accumulated was approximately half of that in SW837 cells, and the levels in SW480 and HCT116 cells were low compared with those in other cultured cells.

Relation among hOCT3 mRNA Expression, LDH Release, and Platinum Accumulation. When cultured cells were treated with 500 μM oxaliplatin, the release of LDH was increased by the hOCT3 mRNA expression (Fig. 6A). The accumulation of platinum in the cells after the incubation with 500 μM oxaliplatin was also dependent on hOCT3 mRNA expression (Fig. 6B). By combining the data from Fig. 6, A and B, the release of LDH was also comparable with the accumulation of platinum (Fig. 6C). On the other hand, when cells were treated with 500 μM cisplatin, the accumulation of platinum was independent of hOCT3 mRNA expression (Fig. 6D).

Cancer Profiling Array. We examined the differences in hOCT3 expression between normal and cancerous tissues derived from Caucasians using dot blotting, and the density of each dot was quantified using ImageJ 1.38x (Fig. 7). In the colon, the level of hOCT3 was significantly higher in cancerous tissues (Fig. 7A). This result was consistent with that in Fig. 1A. A significant increase of hOCT3 expression was also observed in the rectum and stomach (Fig. 7, B and C). Inversely, a significant decrease of hOCT3 expression in cancerous tissue was detected in the uterus, breast, ovary, and lung (Fig. 7, D–G). In the kidney, there was no significant difference in hOCT3 mRNA expression between normal and cancerous tissue (Fig. 7H).
platinum induced by the treatment with oxaliplatin (Fig. 6, A and B). These results suggested that hOCT3 expression is a candidate marker for the efficacy of oxaliplatin treatment. Moreover, the release of LDH and accumulation of platinum caused by the incubation with cisplatin was independent of the hOCT3 mRNA level (Fig. 6D). This result was consistent with the report that cisplatin was not transported by hOCT3 (Yonezawa et al., 2006). Therefore, hOCT3 expression is suggested to be closely associated with the anticancer activity of oxaliplatin but not that of cisplatin.

Cisplatin plays an essential role in chemotherapy against solid tumors of the prostate, bladder, lung, testis, liver, and brain (Ho et al., 2003). However, the effect of cisplatin on colorectal cancer is weak. Loehr et al. (1988) and Grem et al. (1993) reported rates of response of colorectal cancer to cisplatin-based chemotherapy of 22 and 19%, respectively. On the other hand, for oxaliplatin-based chemotherapy, de Gramont et al. (2000) reported that the response rate was 50%. The differences in molecular mechanisms whereby cisplatin has a weak effect but oxaliplatin has a strong effect on colorectal cancer have been unclear. The anticancer activity and resistance to platinum agents have been considered to be related to the DNA repair pathway, nucleotide excision repair, base excision repair, mismatch repair, and double-strand break repair, or the substrate specificity of copper transporters, CTR1, ATP7A, and ATP7B (Kelland, 2007). However, recently, we and others reported the contribution of organic cation transporters in the cellular transport of platinum agents (Ciarimboli et al., 2005; Yonezawa et al., 2005, 2006; Zhang et al., 2006; Yokoo et al., 2007; Kitada et al., 2008). Zhang et al. (2006) reported that the effect of oxaliplatin against colon cancer was related to the expression of hOCT1 and hOCT2. Kitada et al. (2008) reported that the levels of ATP7A and hOCT1 mRNA affect the sensitivity to oxaliplatin. However, we reported that oxaliplatin was transported by both human and

## Discussion

Oxaliplatin has a much more potent anticolorectal cancer effect than cisplatin (Grem et al., 1993; de Gramont et al., 2000). However, the molecular mechanism(s) that cause the difference in the effect has not been made clear. We previously determined that oxaliplatin but not cisplatin was transported by OCT3 (Yonezawa et al., 2006; Yokoo et al., 2007). Therefore, we hypothesized that the level of hOCT3 in cancerous tissues contributed to the superior anticancer effect of oxaliplatin. In the present study, the level of hOCT3 mRNA was significantly higher in cancerous colon than in normal colon tissues derived from Japanese patients (Fig. 1A). In addition, this tendency was reproduced in Caucasians using a cancer profiling array (Fig. 7, A and B). These findings indicated that the level of hOCT3 mRNA was heightened by colorectal cancerous transformation independent of ethnicity.

In human colorectal cancer-derived cell lines, hOCT3 mRNA expression was correlated with the release of LDH and accumulation of

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<th>Cell Lines</th>
<th>Platinum Accumulation</th>
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<tbody>
<tr>
<td></td>
<td>100 μM</td>
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<tr>
<td>T84</td>
<td>0.82 ± 0.03</td>
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<tr>
<td>SW480</td>
<td>0.48 ± 0.01</td>
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<tr>
<td>HCT116</td>
<td>0.46 ± 0.03</td>
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<tr>
<td>HT29</td>
<td>0.64 ± 0.01</td>
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<tr>
<td>SW837</td>
<td>1.07 ± 0.02</td>
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<tr>
<td>Lovo</td>
<td>0.61 ± 0.01</td>
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### TABLE 2

Platinum accumulation in colorectal cancer-derived cell lines (1 h)

Colorectal cancer-derived cell lines were treated with medium containing 100, 500, or 1000 μM oxaliplatin for 1 h. After being washed, these cells were solubilized in 0.5 N NaOH, and the amount of platinum was determined by ICP-MS. Each value represents the mean ± S.E. for four wells.

<table>
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<tbody>
<tr>
<td></td>
<td>100 μM</td>
</tr>
<tr>
<td>T84</td>
<td>14.0 ± 0.3</td>
</tr>
<tr>
<td>SW480</td>
<td>4.9 ± 0.1</td>
</tr>
<tr>
<td>HCT116</td>
<td>6.0 ± 0.2</td>
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<tr>
<td>HT29</td>
<td>8.7 ± 0.1</td>
</tr>
<tr>
<td>SW837</td>
<td>16.7 ± 0.4</td>
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<tr>
<td>Lovo</td>
<td>9.6 ± 0.0</td>
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rat OCT2 and OCT3, but not by OCT1 (Yonezawa et al., 2006; Yokoo et al., 2007). In the present study, only hOCT3 mRNA was found in the six cell lines derived from colorectal cancers, and the cytotoxicity of oxaliplatin was associated with the expression level. Based on these findings and the present results, at least in colorectal cancer, OCT3 is thought to be important for sensitivity to oxaliplatin.

In the six colorectal cancer-derived cell lines, hOCT3 mRNA levels were markedly higher than hOCT1, hOCT2, hMATE1, or hMATE2-K mRNA levels (Fig. 2). Previously, we reported that oxaliplatin was also transported by hOCT2 (Yonezawa et al., 2006). However, in these cell lines, the expression of hOCT2 mRNA was little detected by real-time PCR (Fig. 2). Therefore, the contribution of hOCT2 to the anticancer effect of oxaliplatin was suggested to be small. The transport activity of hOCT3 in these cells was confirmed by using \( ^{3}H \)MPP, a typical substrate of OCT3 (Fig. 3). Okuda et al. (2000) reported that the cytotoxicity of cisplatin differed at low and high doses, that is, 30 and 1000 \( \mu \)M cisplatin induced apoptosis and necrosis, respectively. In the present study, we used two indexes of cytotoxicity, LDH release and caspase 3/7 activity, as indicators of necrosis and apoptosis, respectively. Both LDH release and caspase activity showed a similar tendency; that is, values were high in cell lines expressing high levels of hOCT3 mRNA (Figs. 2 and 4, B and C). From these results, the hOCT3-mediated cellular accumulation of oxaliplatin might be a trigger for the subsequent cytotoxic effects.

Although the cytotoxicity of oxaliplatin in T84 cells was lower than expected, given the expression level of hOCT3 (Fig. 6A), the LDH release in these cells correlated quite well with the platinum accumulation (Fig. 6C). These results suggest some mechanisms including an unknown oxaliplatin efflux transporter to reduce the intracellular platinum concentration in T84 cells compared with that in SW837 cells.

We had reported that the nephrotoxicity caused by treatment with platinum agents was closely associated with their renal accumulation, which is determined by the substrate specificity of the OCT and MATE families (Yonezawa et al., 2005, 2006; Yokoo et al., 2007). There had also been a report that the uptake of imatinib, a tyrosine kinase inhibitor effective in the treatment of chronic myeloid leukemia, was mediated by hOCT1 (Thomas et al., 2004). Recently, two groups showed that hOCT1 was a determinant of outcome in imatinib-treated chronic myeloid leukemia (White et al., 2007; Wang et al., 2008). Patients with a high level of hOCT1 had a greater probability of achieving a cytogenetic response and superior progression-free and overall survival (Wang et al., 2008). These reports showed the participation of hOCT1 in the clinical effects of imatinib. Therefore, the results of this study, that the cytotoxicity of oxaliplatin depended on hOCT3 expression, may be expanded to include effectiveness in clinical cases.

OCT3 is widely distributed in many tissues (Kekuda et al., 1998), but its function has been examined mainly in the brain (Wu et al., 2000).
FIG. 7. The differences in hOCT3 expression between normal and cancerous tissues. The differences in hOCT3 expression between normal and cancerous tissue were examined by dot blotting. The density of each dot was quantified using ImageJ 1.38x. Figures represent the colon (A, n = 39), rectum (B, n = 18), stomach (C, n = 23), uterus (D, n = 42), breast (E, n = 35), ovary (F, n = 14), lung (G, n = 20), and kidney (H, n = 11). The bars represent median values.
in cancers that express high levels of hOCT3 compared with normal tissue may lead to good clinical results. In conclusion, the uptake of oxaliplatin into the cancer cells via hOCT3 was suggested to be an important mechanism for its cytotoxicity, and the expression of hOCT3 in cancers may become a marker for including oxaliplatin in cancer chemotherapy.

References


References


References


References


Address correspondence to: Dr. Ken-Ichi Inui, Department of Pharmacy, Kyoto University Hospital, Sakyu-ku, Kyoto 606-8507, Japan. E-mail: inui@kuhp.kyoto-u.ac.jp