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ARTICLE

Expression of Orotate Phosphoribosyltransferase (OPRT) in Hepatobiliary and Pancreatic Carcinoma

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The purpose of this study was to clarify the role of orotate phosphoribosyltransferase (OPRT) in the progression of hepatobiliary and pancreatic carcinomas. Representative sections from 8 surgically resected pancreatic carcinomas, 5 gallbladder carcinomas and 19 hepatocellular carcinomas (HCCs) were examined microscopically. Sites of pancreatic intraepithelial neoplasia (PanIN) were counted, and histologic subtypes of invasive ductal carcinoma of the pancreas (IDC) were determined. Gallbladder carcinomas and HCCs were examined histologically, and the subtypes and spread patterns were assessed. Expression of OPRT was examined immunohistochemically. A total of 75 PanINs were identified. Expression of OPRT increased as lesions progressed from early to high-grade PanINs (PanIN-1A and -1B versus PanIN-2 and -3, p=0.0004). Three (37.5%) of the 8 pancreatic IDCs were positive for OPRT. In the remaining 5 cases, OPRT was expressed only in the neoplastic ducts adjacent to PanIN-3s. In gallbladder carcinomas, mucosal neoplastic epithelium showed dense cytoplasmic expression in 4 of the 5 cases, but expression was absent in the deeply invasive lesions. Among HCCs, 15 of the 19 cases were negative for OPRT in the central area of the tumor, but 8 of the 19 cases expressed OPRT in vascularly invasive lesions. Our data suggest that OPRT is involved in early events of pancreatic and gallbladder carcinogenesis and invasion of HCC. (Pathology Oncology Research Vol 13, No 2, 105–113)

Key words: OPRT, pancreatic carcinoma, gallbladder carcinoma, hepatocellular carcinoma, pancreatic intraepithelial neoplasia (PanIN)

Introduction

Orotate phosphoribosyl transferase (OPRT) is a nucleotide metabolic enzyme that is essential for cell proliferation and is a key enzyme for conversion of 5-fluorouracil (5-FU) to its active form in tumor tissues.[1] Recently, several studies revealed that the expression of OPRT is increased in several types of carcinoma, including gastric, lung, and metastatic colorectal carcinoma.[1-5] Moreover, on the basis of the specific function of this molecule, expression analyses of OPRT have been reported to be useful for predicting the clinical response to 5-FU-based chemotherapy.[6,7] Nakano et al.[6] reported that OPRT status is a significant prognostic factor for the survival of resected non-small-cell lung carcinoma patients treated postoperatively with UFT. However, assessments of the pattern of expression with more detailed morphologic descriptions are necessary to clarify the function of OPRT in tumors. To our knowledge, there have been no reports describing the association of expression of OPRT protein with carcinogenesis of hepatobiliary-pancreatic carcinoma.

Pancreatic intraepithelial neoplasia (PanIN) is a putative precursor lesion of pancreatic carcinoma.[8] On the basis of molecular data including expression profiles of mucins and oncogenes, it has been suggested that normal epithelium develops sequentially from PanIN to invasive ductal carcinoma (IDC).[9-11] Recently, we reported that the gastric epithelial transcription factor SOX2 is involved in the later events of pancreatic carcinogenesis.[12] To clarify the steps involved in the progression of carcinoma, analyses of the expression of many molecules, including transcription factors and metabolic enzymes, are needed. In the present study, we used immunohistochemistry (IHC) to analyze expression of OPRT in surgically resected specimens of

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PanIN, pancreatic IDC, gallbladder carcinoma and hepatocellular carcinoma (HCC) to better understand the development and progression of hepatobiliary and pancreatic carcinomas.

Materials and methods

Cases

A total of 8 pancreatic carcinomas, 5 gallbladder carcinomas and 19 HCCs were selected. These specimens were retrieved from the Department of Surgical Oncology at the Research Institution for Radiation Biology and Medicine of Hiroshima University, Hiroshima, Japan and the Department of Surgery at Saisekai-Kure Hospital in Kure, Japan between 1995 and 2004. All were diagnosed clinically and pathologically as advanced carcinoma. None of the patients had undergone preoperative chemotherapy or radiotherapy. Representative paraffin-embedded tissue blocks from each case were obtained. Hematoxylin and eosin-stained sections from each case were screened by microscopy.

Table 1. **Histopathologic classification of pancreatic IDC cases**

Case	*Age*	*Sex*	*Site*	*S*	*Type*	*Ly or V*	*Ne*	*Size*	*T*	*N*	*Stage*
1	60	M	H	+	Well	+	+	6.0	3	0	III
2	67	M	H	–	Well	+	+	4.5	3	1	III
3	68	M	H	–	Well	–	–	6.0	2	0	II
4	59	F	H	+	Mod	+	–	5.5	3	0	III
5	59	M	T	+	Poor	+	+	2.5	3	1	III
6	79	M	B	+	Poor	+	+	4.8	3	2	IVa
7	73	M	H	–	Poor	+	+	4.0	3	0	III
8	77	M	H	+	Poor	+	+	6.0	2	1	III

M: male; F: female; S: serosal invasion; Site: location of the main tumor; H: head of the pancreas; B: body of the pancreas; T: tail of the pancreas; Well: well-differentiated adenocarcinoma; Mod: moderately differentiated adenocarcinoma; Poor: poorly differentiated adenocarcinoma; Ly or V: lymphatic or vascular invasion; Ne: intrapancreatic neural invasion; Size: cm, in diameter; T and N grade, and Stage are on the basis of The Japanese Pancreas Society's classification.

Histologic classification of tumors

Pancreatic carcinomas. Histopathologic characterization of the 8 pancreatic carcinomas included assessment of the size and histologic type of the main tumor. In addition, the presence of serosal infiltration, vascular, lymphatic and perineural invasion, cancerization of the main pancreatic duct, and lymph node metastasis were assessed. Staging was based on the criteria given in the General Rules for the Study of Pancreatic Cancer, 4th edition, by the Japanese Pancreas Society.

Ducts adjacent to the main tumor were assessed. Epithelium lining the ducts was classified histologically as PanIN-1A, -1B, -2, or -3. PanIN lesions were graded according to the criteria established at the National Cancer Institute-sponsored Pancreas Cancer Conference in September 1999 (Park City, UT, USA). In brief, PanIN-1As were defined as lesions comprising tall columnar cells with basally located nuclei. PanIN-1Bs were defined as lesions forming micropapillary growths or showing pseudostratified architecture. PanIN-2s were defined as lesions with cells showing loss of polarity and nuclear enlargement. PanIN-3s were defined as lesions containing cells with remarkable nuclear abnormalities and luminal necrosis. Two to 13 PanIN lesions were found in each representative section.

Gallbladder carcinomas. The histopathologic examination of 5 gallbladder carcinomas included assessment of depth of invasion, presence of vascular invasion, and histologic subtype. In addition, extension of carcinoma cells into the Rokitansky-Aschoff sinuses (RAS) was detected in all 5 cases. Invasion to the RAS was defined histologically according to the following criteria:[11] 1) neoplastic ducts connecting to the surface epithelium, 2) neoplastic ducts containing non-neoplastic biliary cells, and 3) tumorous lesions appearing as long, branching, duct-like structures reaching the subserosal connective tissues.

Hepatocellular carcinomas. Histopathologic examination of HCCs included assessment of the presence of vascular or bile duct invasion, invasion to the capsule, differentiation, histologic subtype, and background diseases in the nontumorous liver parenchyma. Histopathologic subtypes were assessed as follows.[14] Moderately differentiated adenocarcinoma was classified to one of two subtypes: thick trabecular pattern or pseudoglandular pattern. Poorly differentiated carcinoma was defined as tumor showing medullary growth pattern and having scant cytoplasm or short spindle morphology.

Immunohistochemistry (IHC)

Immunohistochemical staining for OPRT was carried out with a polyclonal anti-OPRT antibody (1:1000, Taiho, Tokyo, Japan) as the primary antibody. The LSAB Kit (Dako, Carpinteria, CA, USA) was used for immunohistochemical analyses. Paraffin-embedded sections were deparaffinized in xylene and rehydrated through a graded series of ethanol. After blocking endogenous peroxidase activity with 3% H_2O_2 in methanol for 10 min, sections were incubated with the primary antibody for 8 h at 4ºC, followed by sequential 10-min incubations with biotinylated anti-rabbit IgG and peroxidase-labeled streptavidin. Staining was completed after 10-min incubation with the substrate-chromogen solution, then sections were counterstained with 0.1% hematoxylin. Results of

the antibody staining were graded according to the percentage of stained target cells. Staining was considered positive if at least 25% of the cells were stained. In addition, in each sample, we assessed and compared the expression patterns and localization between epithelial or pre-cancerous components and invasive components.

Statistical analysis

OPRT staining was characterized and compared statistically between cases. Analysis was performed with SPSS software (Version 10.5, SPSS, Inc., Chicago, IL, USA). A p value of less than 0.05 was regarded as statistically significant.

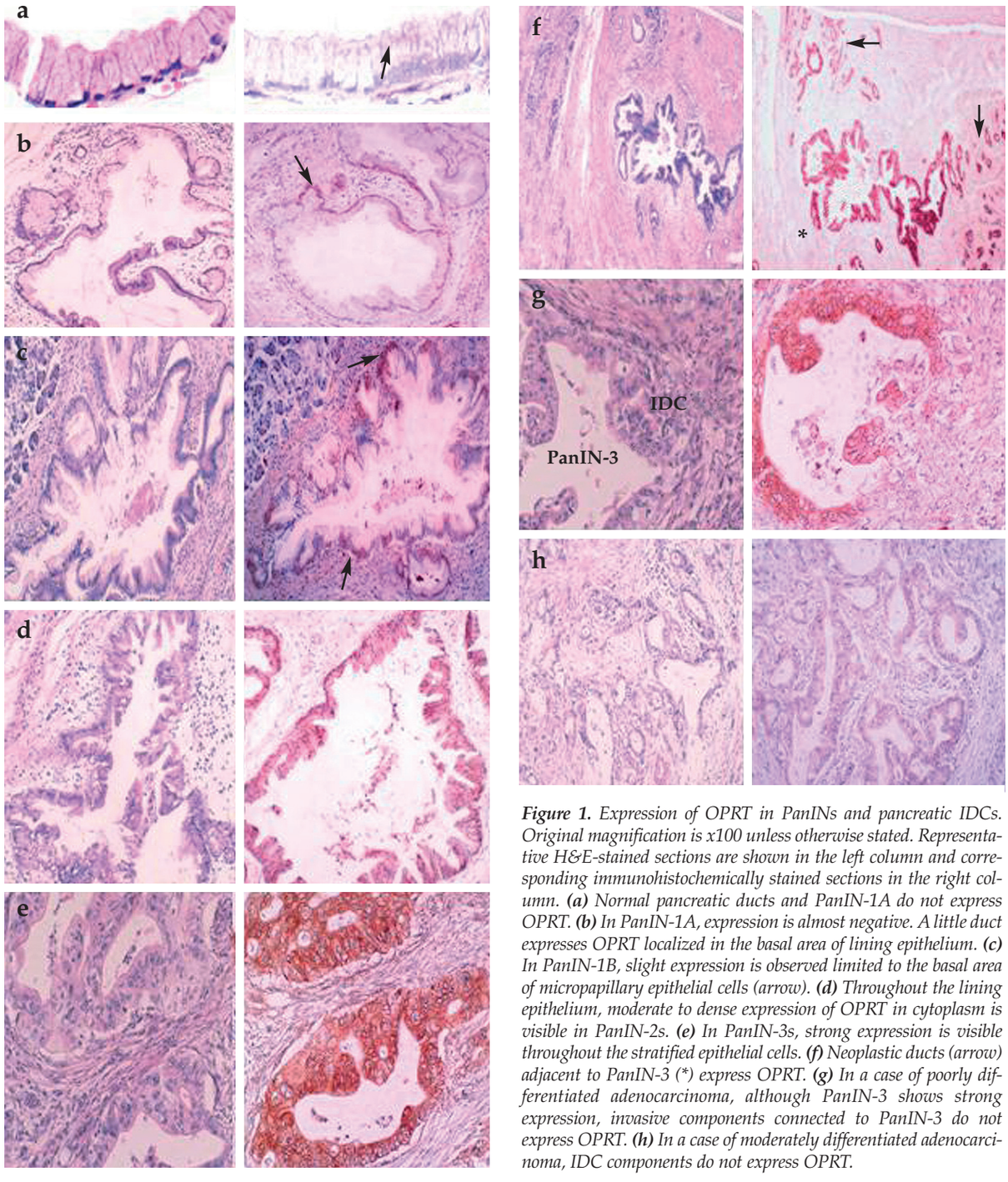

Figure 1. *Expression of OPRT in PanINs and pancreatic IDCs. Original magnification is x100 unless otherwise stated. Representative H&E-stained sections are shown in the left column and corresponding immunohistochemically stained sections in the right column.* ***(a)*** *Normal pancreatic ducts and PanIN-1A do not express OPRT.* ***(b)*** *In PanIN-1A, expression is almost negative. A little duct expresses OPRT localized in the basal area of lining epithelium.* ***(c)*** *In PanIN-1B, slight expression is observed limited to the basal area of micropapillary epithelial cells (arrow).* ***(d)*** *Throughout the lining epithelium, moderate to dense expression of OPRT in cytoplasm is visible in PanIN-2s.* ***(e)*** *In PanIN-3s, strong expression is visible throughout the stratified epithelial cells.* ***(f)*** *Neoplastic ducts (arrow) adjacent to PanIN-3 (*) express OPRT.* ***(g)*** *In a case of poorly differentiated adenocarcinoma, although PanIN-3 shows strong expression, invasive components connected to PanIN-3 do not express OPRT.* ***(h)*** *In a case of moderately differentiated adenocarcinoma, IDC components do not express OPRT.*

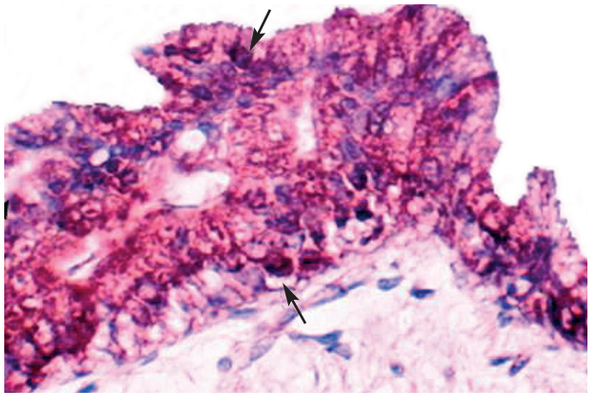

Figure 2. *Nuclear localization (arrow) of OPRT in PanIN-3 (x400)*

Results

Histopathologic characteristics and classification of pancreatic IDCs

Sixteen sections from 8 surgically resected cases of IDC were examined. Histopathologic features are presented in *Table 1*. Serosal invasion was present in 5 (62.5%) of the 8 cases. Vascular invasion and intrapancreatic perineural invasion were present in 7 (87.5%) and 6 (75.0%) of the 8 cases, respectively. Three cases were well-differentiated adenocarcinomas, while the remaining 4 cases were poorly differentiated adenocarcinomas showing vascular and perineural invasion. In addition, a total of 75 PanINs, including 18 PanIN-1As, 17 PanIN-1Bs, 24 PanIN-2s and 16 PanIN-3s were identified by histopathologic assessment of the 16 representative sections.

Immunoreactivity and localization of OPRT in PanINs and pancreatic IDCs

IHC revealed that OPRT was not expressed in normal pancreatic ducts (*Fig. 1a*). In PanIN-1As and PanIN-1Bs, slight expression of OPRT was observed and was limited to the basal area of the papillary epithelium (*Fig. 1b,c*). However, with progression of the PanIN grade, the frequency and strength of OPRT expression significantly increased (*Table 2*). Expression of OPRT was observed in 87.5% of PanIN-2s and 81.3% of PanIN-3s (PanIN-1A + -1B versus PanIN-2 + -3: p=0.0004). High-grade PanINs expressed OPRT throughout the cytoplasm of cells comprising the lining epithelium (*Fig. 1d,e*). Around luminal necrotic lesions in PanIN-3, strong nuclear distribution was observed (*Fig. 2*).

Of the 8 cases with IDC, 3 showed staining of OPRT (*Table 2*). The 3 OPRT-positive cases included a well-differentiated, a moderately differentiated and a poorly differentiated adenocarcinoma. Staining was mainly limited to neoplastic ducts around PanIN-3s (*Fig. 1f*). In the 5 OPRT-negative cases (*Fig. 1h*), corresponding high-grade PanINs expressed OPRT (*Fig. 1g*).

Histopathologic evaluation of gallbladder carcinomas

The 5 resected gallbladder carcinomas included 4 papillary adenocarcinomas and 1 poorly differentiated adenocarcinoma (*Table 3*). All 5 cases had invaded to the subserosa. One papillary adenocarcinoma showed invasion to the liver parenchyma. In all 5 cases, extension to the RAS was observed.

Expression of OPRT in gallbladder carcinoma

In all 4 papillary adenocarcinomas, mucosal carcinoma lesions were positive for OPRT (*Table 4, Fig. 3a*). Expression was observed mainly in cytoplasm, and some cells showed strong granular expression (*Fig. 4*). Interestingly, in the subserosally invasive components expression was not maintained (*Fig. 3d*). However, tumor cells connected to the surface epithelial neoplastic lesions and dilated neoplastic ducts in the muscular propria showed strong cytoplasmic expression of OPRT (*Fig. 3b,c*). We considered these OPRT-positive components as RAS-extensive lesions.

Table 2. **Expression of OPRT in normal pancreatic ducts, PanINs, and IDCs**

Case	*Normal*	*PanIN-1A*	*–1B*	*–2*	*–3*	*IDC*
1	–	0/1	1/5	2/2	1/1	–
2	–	0/4	0/1	5/5	2/2	–
3	–	0/0	0/2	3/5	1/2	+
4	–	0/5	1/3	2/2	2/2	+
5	–	0/0	0/0	1/1	1/1	–
6	–	0/3	2/2	3/3	1/3	+
7	–	0/2	0/0	2/2	3/3	–
8	–	0/3	0/4	3/4	2/2	–
Total	0/8	0/18	4/17	21/24	13/16	3/8

Table 3. **Histopathologic evaluation of gall bladder carcinoma cases**

Case	*Subtype*	*Depth*	*Ly or V*	*N*
1	Pap	SS	+	+
2	Pap	SI	+	+
3	Pap	SS	+	–
4	Pap	SS	–	+
5	Poor	SS	+	–

Pap: papillary adenocarcinoma; Poor: poorly differentiated adenocarcinoma; Depth: depth of invasion; SS: invasion to the subserosal propria; SI: invasion to the liver parenchyma; N: presence of lymph node metastasis

Table 4. **Expression of OPRT in gallbladder carcinoma**

Case	*Sup*	*RAS*	*Inv*	*Ly or V*
1	+	+	–	–
2	+	+	–	+
3	+	+	–	–
4	+	+	–	n. e.
5	–	–	–	–

Positivity of expression of OPRT in various components; Sup: carcinoma cells in the mucosal epithelium; RAS: carcinoma cells extending into RAS; Inv: deeply invasive area; Ly or V: vascularly or lymphatic invasive area, n. e. = not evaluable

Histopathologic evaluation of HCCs

The 19 resected cases of HCC included 14 moderately and 3 poorly differentiated adenocarcinomas, 1 well-differentiated carcinoma and 1 scirrhous type carcinoma (*Table 5*). Capsule formation was observed in 14 cases, and 9 of the 14 cases showed infiltration of the capsule. Vascular or bile duct invasion was observed in 9 of the 19 cases. Nontumorous liver parenchyma showed cirrhosis in 13 cases, and the remaining 6 cases showed chronic hepatitis.

Expression of OPRT in HCC

Neither the case of well-differentiated HCC nor 13 cases of moderately differentiated HCC with thicker trabecular pattern expressed OPRT in the central area of the tumor (*Table 6, Fig. 5a,b*). Only 3 of the 19 cases were positive for OPRT in the central area of the tumor, one case of poorly differentiated adenocarcinoma (*Fig. 5c*), 1 case of pseudoglandular type carcinoma (*Fig. 5d*) and 1 case of scirrhous-type carcinoma (*Fig. 5e*). In the poorly differentiated adenocarcinoma, expression was localized partially to nuclei. In addition, vascularly invasive HCC lesions (*Fig. 5f-h*) and HCC lesions infiltrating the capsule (*Fig. 5i*) showed strong nuclear expression (*Fig. 6*) in 7 cases, including 5 cases that were negative for OPRT in the central area of the tumor.

Discussion

A number of enzymes have been shown to be involved in the process of activation and/or degradation of 5-FU and are potential candidates for predicting chemosensitivity to 5-FU. Among these, OPRT is a key enzyme related to the first step in activation of 5-FU and has been shown to be an important enzyme that helps to predict sensitivity to 5-FU and its related derivatives. Recently, results of basic and clinical studies have suggested that OPRT levels are associated with sensitivity to 5-FU. Ochiai et al.[7] reported

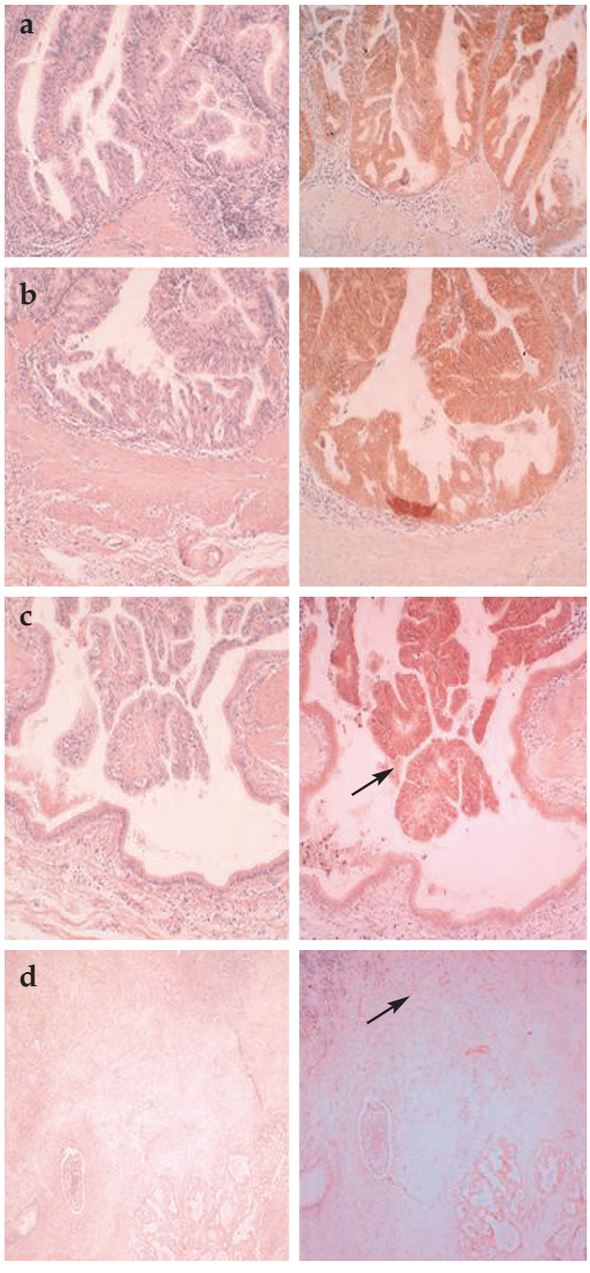

Figure 3. *Expression of OPRT in gallbladder carcinomas. Original magnification is x100 unless otherwise stated. Representative H&E-stained sections are shown in the left column, and corresponding immunohistochemically stained sections in the right column.* ***(a)*** *Strong cytoplasmic expression is observed in the mucosal area of all 4 papillary adenocarcinomas.* ***(b,c)*** *Expression was maintained in the RAS lesions connecting to the mucosal carcinomatous cells.* ***(d)*** *Expression is weakened or absent in the deeply invasive lesions (arrow)*

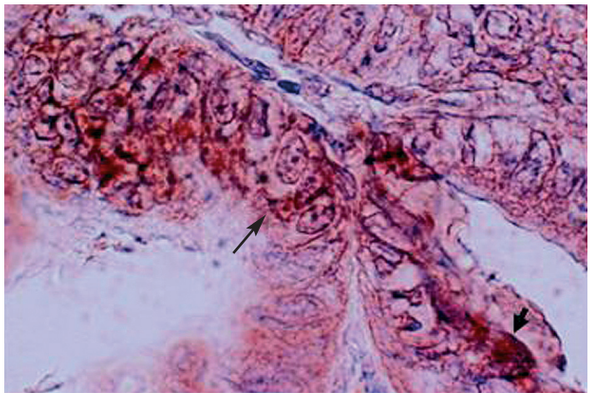

Figure. 4. *Granular cytoplasmic expression (arrow) of OPRT in neoplastic duct of gallbladder carcinoma (X 400).*

that the 5-year survival rate of patients with high OPRT activity, who underwent 5-FU-based adjuvant chemotherapy for colorectal carcinoma, was significantly better than that of the low OPRT activity group. Nakano et al.[6] reported that patients with OPRT-positive non-small-cell lung carcinoma had significantly higher survival than did those with OPRT-negative tumors. Similar results have been reported for gastric and bladder carcinomas.[15] It has been reported that tumor OPRT activity is associated significantly with tumor stage, nodal status or invasion. In previous studies, OPRT staining was observed in the cytoplasm, but it was visible only in neoplastic ducts.[4,6] To evaluate OPRT expression pattern in tumor tissues, several components of tumors, including vascular invasive lesions, carcinoma in situ and stromal invasive lesions, must be studied. Because of the small number of cases in the present study, we could not detect any possible correlation between OPRT expression and the clinical behavior of tumors, including prognostic significance or responsiveness to 5-FU-based chemotherapy. In addition, little is known about OPRT expression status in hepatobiliary and pancreatic tumors. Therefore, the present study was designed to evaluate OPRT expression patterns in pancreatic and gallbladder carcinomas and HCCs and in tumor components including intraductal or mucosal neoplastic lesions and invasive lesions. In cases of pancreatic carcinoma, we found that OPRT was expressed more frequently and at higher levels in high-grade PanINs (PanIN-2 and -3) than in normal pancreatic ducts or early PanINs (PanIN-1A and -1B). In 5 of the 8 resected IDCs, IDC components were negative for OPRT, whereas adjacent high-grade PanINs were frequently positive.

In high-grade PanINs, OPRT was distributed throughout the lining epithelium. Previous studies have focused primarily on the stepwise progression of pancreatic carcinoma related to mutation of several oncogenes or overexpression of mucins.[9-11] Recently, we reported that the gas-

Table 5. **Histopathologic evaluation of HCC cases**

Case	*Subtype*	*Fc / inf*	*V*	*Non-tumor*
1	Pseudo	+/+	+	LC
2	Thicker	+/−	−	LC
3	Thicker	+/−	−	CH
4	Thicker	+/+	+	LC
5	Thicker	−	+	CH
6	Thicker	−	−	LC
7	Thicker	+/+	+	LC
8	Thicker	+/−	+	LC
9	Poor	+/+	+	CH
10	Thicker	+/−	−	LC
11	Thicker	+/−	−	LC
12	Well	−	−	LC
13	Sci	−	−	LC
14	Thicker	−	+	CH
15	Thicker	+/+	−	LC
16	Poor	+/+	+	LC
17	Thicker	+/+	−	LC
18	Thicker	+/+	−	CH
19	Poor	+/+	+	CH

Pseudo: pseudoglandular type of moderately differentiated adenocarcinoma; Thicker: thicker trabecular type of moderately differentiated adenocarcinoma; Poor: poorly differentiated adenocarcinoma; Sci: scirrhous type carcinoma; Fc: capsule formation; inf: infiltration to the capsule; V: portal or bile duct invasion; Non-tumor: histologic background of non-tumorous liver tissues; LC: liver cirrhosis; CH: chronic hepatitis

Table 6. **Expression of OPRT in HCC**

Case	*Center*	*Per*	*V*
1	+	+	+
2	−	−	n. e.
3	−	−	n. e.
4	−	−	−
5	−	−	−
6	−	−	n. e.
7	−	+	+
8	−	+	+
9	−	+	+
10	−	−	n. e.
11	−	+	n. e.
12	−	−	n. e.
13	+	+	n. e.
14	−	−	+
15	−	−	n. e.
16	−	+	+
17	−	−	n. e.
18	−	−	n. e.
19	+	+	+

Positivity of expression of OPRT in various components; Center: central area of the tumor; Per: peripheral area of the tumor including infiltrative area in the capsule; V: vascularly or bile duct invasive components, n. e. = not evaluable

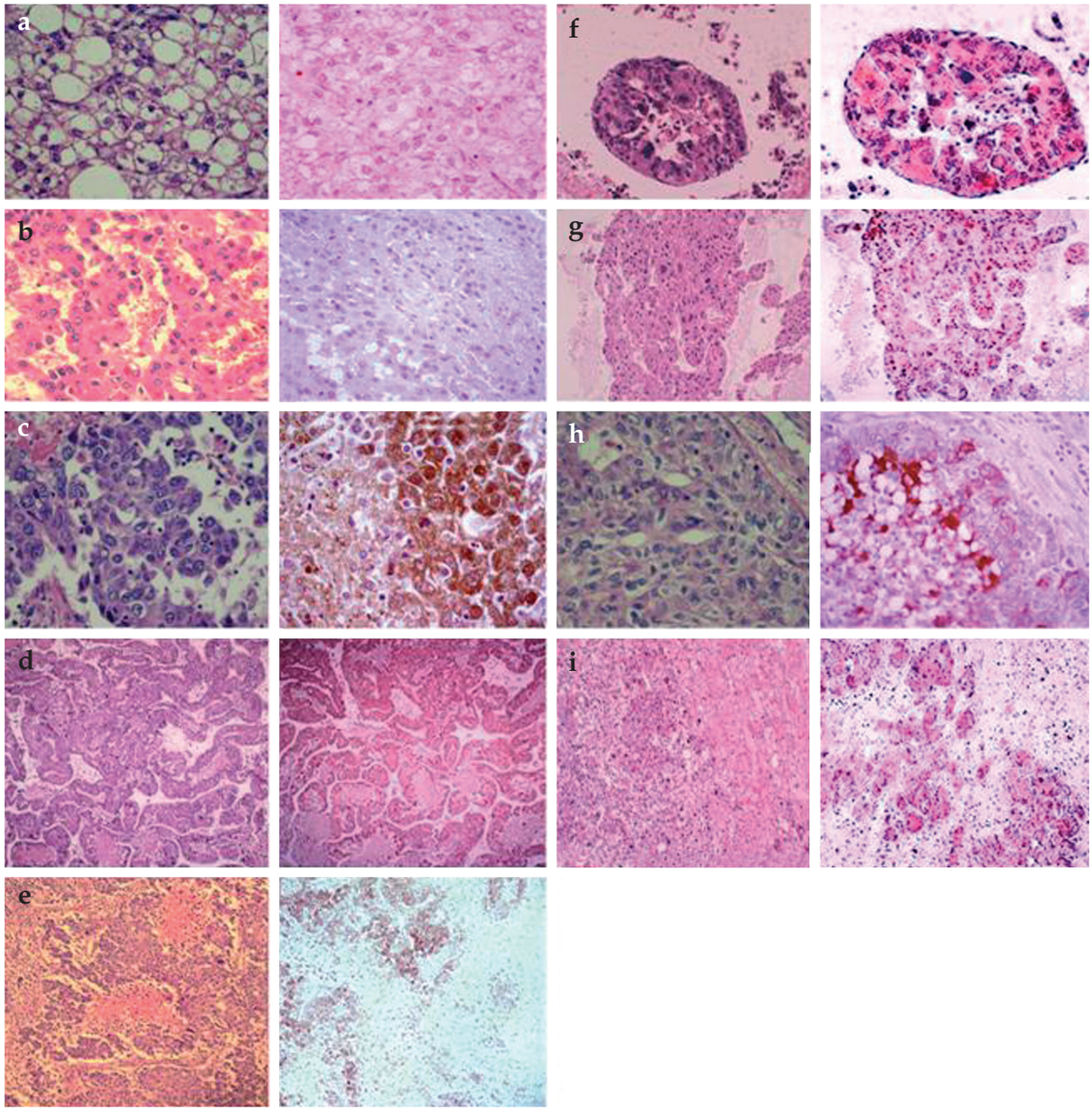

Figure. 5. *Expression of OPRT in HCCs. Original magnification is x100 unless otherwise stated. Representative H&E-stained sections are shown in the left column, and corresponding immunohistochemically stained sections in the right column.* ***(a)*** *OPRT is not expressed in well-differentiated carcinoma with marked fatty changes.* ***(b)*** *In a case of moderately differentiated HCC with thick trabecular pattern, OPRT is not expressed.* ***(c)*** *Poorly differentiated HCC diffusely expresses OPRT localized mainly in the cytoplasm and partially in the nuclei.* ***(d)*** *Cytoplasmic expression is observed in pseudoglandular-type HCC.* ***(e)*** *In a case of scirrhous-type HCC, cytoplasmic expression is observed throughout the tumor.* ***(f-h)*** *Nuclear expression is observed in vascularly invasive lesions of poorly differentiated HCC.* ***(i)*** *OPRT is expressed in a lesion invading the capsule.*

tric epithelial transcription factor SOX2 is involved in later events of pancreatic carcinogenesis (from PanIN-3 to IDCs).[12] The results of our studies suggest that molecules other than oncogenes or mucins are involved in stepwise progression of pancreatic carcinoma.

Four of the 5 gallbladder carcinomas showed moderate to dense cytoplasmic expression of OPRT in the mucosal neoplastic epithelium. All 4 cases maintained expression of OPRT in the lesions extending into the RAS, but expression was negative in the lesions invading the serosa or

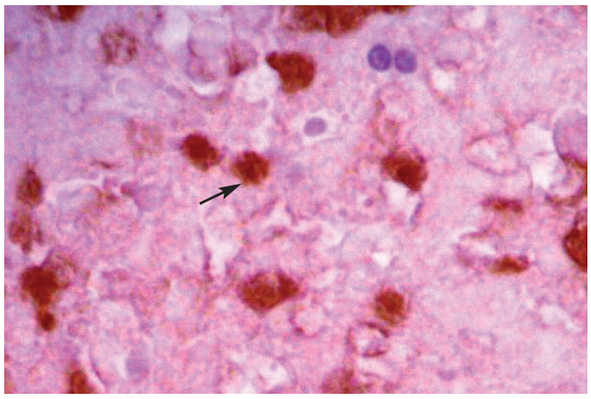

Figure. 6. *A higher magnification image of nuclear expression of OPRT in poorly differentiated HCC (x1000)*

lesions invading the liver parenchyma. Invasive carcinoma in the RAS is considered an early event in carcinogenesis because the RAS are connected with the surface epithelium.[13] Therefore, we believe that expression of OPRT is involved in an early event in the development of gallbladder carcinoma. However, immunohistochemical analyses of OPRT expression in 19 cases of HCC yielded conflicting results. Among HCCs, 16 of 19 cases lacked expression of OPRT in the central area of the tumor, but expression was increased in the infiltrative area of the capsule and in the vascularly invasive lesions. These results suggest that expression of OPRT is involved in invasion and infiltration of HCC.

Our IHC of OPRT in 3 different tumors revealed that OPRT staining in tumor tissues was higher than that in surrounding normal tissues. This suggests that 5-FU is converted more effectively to the active nucleotide form in tumor tissue. However, the reason for the discrepancy in OPRT expression patterns between pancreatic and gallbladder carcinomas and HCCs is not clear. In the 5 pancreatic carcinomas negative for OPRT in IDCs, corresponding high-grade PanINs expressed high levels of OPRT. In general, once a protein is expressed by a PanIN, this expression is maintained through the different stages of progression. This discrepancy observed in pancreatic carcinomas is similar to the observation of negative immunoreaction for serosally invasive lesions in gallbladder carcinomas. In contrast, in HCC vascularly invasive lesions and poorly differentiated HCC components expressed high levels of OPRT. In patients with advanced pancreatic or gallbladder carcinoma, the rate of response to 5-FU-based chemotherapy is reported to be 10-20%.[16, 17] In patients with advanced HCC, the rate of response to 5-FU-based chemotherapy or intraarterial therapy is approximately 50%.[18] Our observation suggests that the status of immunoreactivity for OPRT is associated with 5-FU sensitivity. However, because OPRT is related to the first step of 5-FU phosphorylation,[19] it is unlikely that 5-FU metabolism varies between tumor types. Upstream molecules that regulate OPRT expression must be identified.

In the present study, some tumor cells showed nuclear localization of OPRT. This localization pattern was present in the luminal necrotic lesions of PanIN-3s and cancer cells in vascularly invasive lesions of HCC. Because OPRT is a metabolic enzyme, expression is expected to be limited to the cytoplasm, and the reason for the altered localization is not clear. We believe that in tumor components showing nuclear localization for OPRT, its expression is regulated by upstream molecules. For example, it has been reported that claudin-1, a member of tight junction proteins, shows nuclear localization in liver metastatic lesions from colorectal carcinoma, whereas it is localized in cell membranes of normal epithelial cells and mucosal epithelial components of colorectal carcinomas.[20] Dhawan et al. reported that beta-catenin/Tcf activation activates expression of the claudin-1 gene. In several carcinomas, dissociation of the beta-catenin and APC/axin/GSK3beta complex leads to accumulation of free beta-catenin, which translocates to the nucleus, resulting in activation of downstream target genes involved in carcinogenesis.[21]

Nuclear translocation of several molecules has been explained by regulation of this beta-catenin/Tcf pathway. In addition, an experimental study has suggested that the downregulation of OPRT expression in human cancers is due to the loss of chromosome 3q13.[22] Interestingly, gsk3beta, a molecule that degrades free beta-catenin, is located on 3q13. The beta-catenin/Tcf pathway may be related to regulation of OPRT. Further functional analyses are needed to clarify the significance of the change in localization and loss of OPRT expression in carcinoma.

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