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Original

Expression of *N*-acetylglucosaminyltransferase V in Intrahepatic Cholangiocarcinoma and Its Association with Clinicopathological Findings

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Purpose: *N*-acetylglucosaminyltransferase V (GnT-V), an enzyme that catalyzes the β1-6 branching of *N*-acetylglucosamine on asparagine-linked oligosaccharides of cellular proteins, enhances the malignant behaviors of carcinoma cells in experimental models. We previously reported that GnT-V expression in pathological tumor stage II gallbladder carcinoma (GBC) correlates with postsurgical survival and postsurgical recurrence of distant organ metastasis. This study aimed to examine GnT-V expression in intrahepatic cholangiocarcinoma (ICC) and determine its association with clinicopathological findings. **Method:** GnT-V expression was evaluated by immunohistochemistry in each curatively resected ICC specimen from 72 patients (72 cases). Thereafter, the association of GnT-V expression with clinicopathological findings was examined. **Results:** Of the 72 ICC cases, 42 showed positive staining for GnT-V and the remaining 30 demonstrated negative staining. Patients with ICCs having low GnT-V expression had shorter survival time than patients with ICCs having high GnT-V expression, although the difference was not statistically significant ($p = 0.31$). In all of the 72 cases, the frequency of postsurgical recurrence was not significantly different in terms of GnT-V expression. **Conclusion:** Although GnT-V was found to be expressed in more than half of the ICC cases in this study, it may not be a useful marker for scaling the aggressiveness of ICC because the mechanisms underlying ICC metastasis possibly involve different molecular pathways that are not affected by GnT-V expression.

Key Words: intrahepatic cholangiocarcinoma, *N*-acetylglucosaminyltransferase V, malignant behavior

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a fatal cancer, and the only curative treatment for patients with ICC is surgery[1]. However, the recurrence rate is high even after curative resection. According to the American Joint Committee on Cancer (AJCC) 7th Edition of TNM Staging, the 5-year survival rate of stage I to IV was 62%, 27%, 14%, and 0%, respectively[2]. Previous studies have shown that the most common site of recurrence is the liver[3)~5)]. Thus, if postoperative recurrence of ICC can be prevented, patient survival could be greatly improved.

Among several kinds of glycosyltransferases, *N*-acetylglucosaminyltransferase V (GnT-V) is one of the most important enzymes which are associated with carcinogenesis and tumor aggressiveness (i.e., invasion and metastasis)[6)~8)]. GnT-V is involved in the synthesis of β1-6 GlcNAc branching formation on *N*-glycans. GnT-V is also essential for tumor growth and metastasis, as previously shown in GnT-V-deficient mice[9]. The mechanisms underlying the modulation of tumor metastasis by GnT-V may involve the upregulation of signaling of many growth factor receptors on the cell surface by the suppression of receptor endocytosis[10], the enhancement of certain kinds of protease activity[11], and the

Table 1 Patient description and number of cases for each intrahepatic cholangiocarcinoma (ICC) stage (2000-2008)

Patient description n or mean ± SD	M/F	Age	Surgical procedures		
			Hep[a]	Hep with EBR[b]	Hep with PV, IVC[c]
Intrahepaticcholangiocarcinoma (n = 72)	52/20	64.8 ± 11.1	41	20	11
ICC stage*					
Stage I (n = 20)	13/7	64.7 ± 12	13	7	0
Stage II (n = 17)	11/6	65.7 ± 12.5	14	1	2
Stage III (n = 32)	26/6	64.8 ± 10.5	14	10	8
Stage IV (n = 3)	2/1	62 ± 4.3	0	2	1

*Based on the American Joint Committee on Cancer classification.

[a]: hepatectomy alone.

[b]: hepatectomy with extrahepatic bile duct resection.

[c]: hepatectomy with partial resection of the portal vein or inferior vena cava.

stimulation of angiogenesis as a cofactor[12].

Immunohistochemical studies of GnT-V have shown that GnT-V expression is positively correlated with the poor prognosis of certain kinds of cancer[13][14]. GnT-V is one of the Golgi enzymes that modulate branching of oligosaccharides in cells. In fact, an immunofluorescent study of GnT-V in B16 mouse melanoma cells showed its localization in Golgi apparatus[13]. Our study also showed Golgi localization of GnT-V in cancer tissues.

Furthermore, we previously reported the strong positive correlations of GnT-V expression with postsurgical survival and the recurrence of distant organ metastasis in 90 cases of pathological tumor stage II (pT2) gallbladder carcinoma (GBC)[15]. However, GnT-V expression has not yet been investigated in human cholangiocarcinoma.

In this retrospective analysis, we investigated the immunohistochemical expression of GnT-V in each ICC specimen resected from 72 patients (72 cases) and determined the association of GnT-V expression with clinicopathological findings.

This study aimed to evaluate whether GnT-V is an important prognostic factor and a useful marker for scaling the aggressiveness of ICC.

Materials and Methods

Patients

Patient description and number of cases for each ICC stage are shown in Table 1. ICC specimens from 72 patients (52 men and 20 women) were analyzed. The study was approved by the Research and Ethics Committee of Tokyo Women's Medical University. They were selected consecutively by reviewing the pathologic findings, and patients who had died from other diseases were excluded. The ICC specimens of all the patients were curatively resected with a free surgical margin. The mean age of the patients was 64.8 ± 11.1 years (range, 26-83 years). These patients underwent surgery for ICC between 2000 and 2008 at the Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University Hospital. ICC was definitively diagnosed on the basis of histological findings and classified according to the tumor-node-metastasis classification of the AJCC 6th Edition[16]. Of the 72 cases, 20 were in stage I, 17 stage II, 32 stage III, and 3 stage IV. The surgical procedures were as follows: hepatectomy alone in 41 patients, hepatectomy with extrahepatic bile duct resection in 20 patients, and hepatectomy with partial resection of the portal vein or inferior vena cava in 11 patients (Table 1). Fourteen patients had hepatitis C virus, 3 patients had hepatitis B virus, and 1 had both B and C virus. Eleven patients had liver cirrhosis, and 5 patients had chronic hepatitis. No patients had certain other diseases such as hepatolithiasis or primary sclerosing cholangitis. Before surgery, no patient had undergone chemotherapy or radiotherapy.

The follow-up periods until April 2008 ranged from 1 to 79 months (mean, 14 months). Of the 72 patients who had undergone curative resection with a free surgical margin, 42 were alive as of April 2008 and 30 died from intrahepatic metastasis,

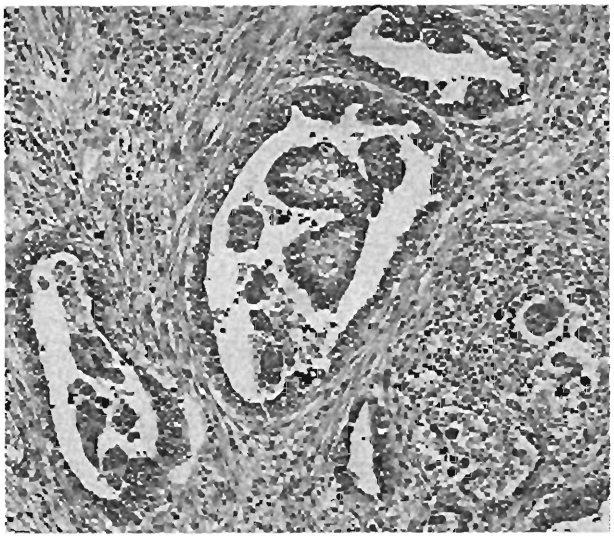

Fig. 1 Immunostaining of GnT-V
Typical positive case which shows Golgi localization of GnT-V in cancer tissues.

Table 3 Association between histopathological findings and immunohistochemical localization of GnT-V

GnT-V	Negative	Positive	p*
Number	30 (100%)	42 (100%)	
Histological grade			
G1	1 (3)	3 (7)	0.862
G2-4	29 (97)	39 (93)	
Intrahepatic metastasis			
Negative	25 (83)	32 (76)	0.462
Positive	5 (17)	10 (24)	
Vascular invasion			
Negative	10 (33)	13 (31)	0.831
Positive	20 (67)	29 (69)	
Lymph node metastasis			
Negative	19 (63)	25 (60)	0.744
Positive	11 (37)	17 (40)	

There were no significant differences in the parameters of pathological malignancies between the 2 staining groups.
*X^2 for independence test.

Table 2 GnT-V expression rates in the negative and positive staining cases according to tumor stage

	Negative	Positive	p*
ICC (n=72)	30	42	0.861
Stage I (n=20)	8	12	
Stage II (n=17)	6	11	
Stage III (n=32)	15	17	
Stage IV (n=3)	1	2	

The GnT-V expression rates between the negative and positive staining cases were not significantly different for all tumor stages.
*X^2 for independence test.

distant organ metastasis, lymph node metastasis, or peritoneal dissemination. No patient had died from other disease or had been lost to follow-up.

GnT-V immunostaining

ICC tissues that had been preserved in 10% formalin and then embedded in paraffin were serially sectioned at 2 μm thickness, mounted on silane-coated slides, and deparaffinized. The slides were immersed in 0.3% hydrogen peroxide in methanol for 20 min to deplete endogenous peroxidase. After washing with phosphate buffered saline (PBS), the slides were incubated with a protein blocking agent for 5 min at room temperature in a humidity chamber. The slides were then stained by the indirect immunoperoxidase method using an anti-GnT-V antibody, 22G12 (Fuji-revio, Tokyo, Japan) at a 1 : 3,000 dilution rate. A negative control was prepared using 2% bovine serum albumin (BSA) instead of the mAb. Details of the procedure were described previously[13].

Evaluation of the tissue sections was performed by a single pathologist who was blinded to the clinical characteristics and histopathological findings. Immunohistochemical analysis of the total number of cancerous epithelia in each section of surgical specimens was evaluated. The immunohistochemical expression of GnT-V was classified into positive or negative (Fig. 1).

Statistical analysis

Statistical evaluations of data were analyzed using the X^2 for independence test. Survival curves of the postsurgical outcome of the 72 patients who underwent curative resection of ICC were analyzed using the Kaplan-Meier method. Differences in the survival of the 72 patients were analyzed by the log-rank test. Several clinicopathological factors were subjected to multivariate regression analysis using the Cox proportional hazards regression model. A p value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Immunohistochemical staining and GnT-V expression in ICC

Of the 72 ICC cases, there were 42 cases (58%) in

Table 4 Postsurgical recurrence patterns of ICC

GnT-V	Negative	Positive	p*
Number	30 (100%)	42 (100%)	
Total number of recurrence	21 (70)	20 (48)	0.06
Liver metastasis	10 (33)	8 (19)	0.168
Distant organ metastasis	4 (13)	9 (21)	0.379
Lymph node metastasis	7 (23)	3 (7)	0.06
Peritoneal dissemination	3 (10)	1 (2)	0.164

There were no significant differences in the frequencies and patterns of recurrence between the 2 staining groups.
*X^2 for independence test.

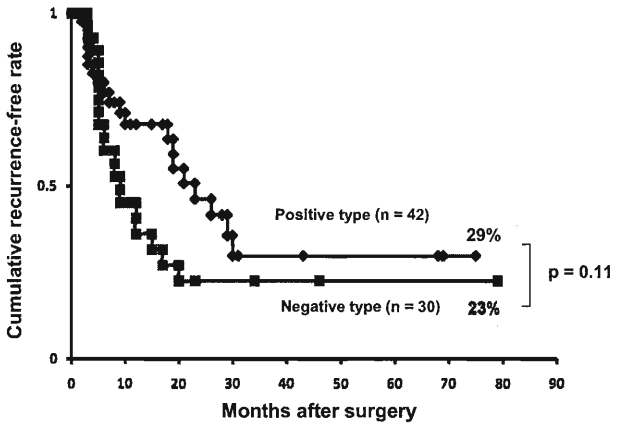

Fig. 2 Association between postsurgical recurrence-free rate and GnT-V expression
There was no significant difference in the cumulative recurrence-free rates between the positive type and the negative type.

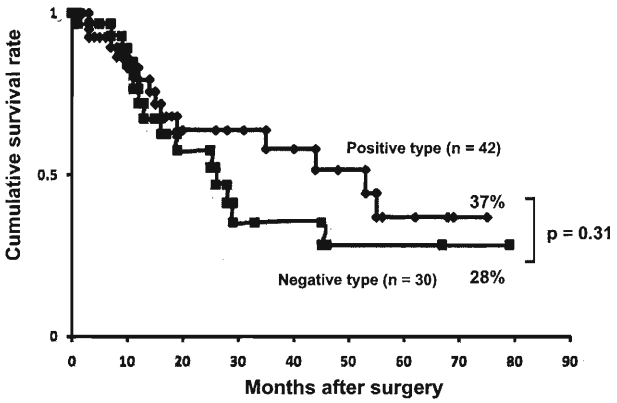

Fig. 3 Association between postsurgical survival rate and GnT-V expression
There was no significant difference in the cumulative survival rates between the positive type and the negative type.

which GnT-V was expressed in cancer tissues, and they were defined as positive. The remaining 30 cases (42%) that did not express GnT-V in cancer tissues were defined as negative.

The GnT-V expression rates between the negative and positive staining cases were not significantly different for all tumor stages (Table 2).

Association between parameters of pathological malignancies and GnT-V expression in patients with ICC

A comparison of the positive staining and negative staining of GnT-V was made with particular reference to the parameters of pathological malignancies, namely, histological grade, intrahepatic metastasis, vascular invasion, and lymph node metastasis (Table 3). There were no significant differences in the parameters of pathological malignancies between GnT-V expression types.

Association between pattern of recurrence in patients with ICC and GnT-V expression in the specimens

The postsurgical pattern of recurrence of the 72 ICC cases was compared in terms of GnT-V expression (Table 4). Of the 42 cases showing positive staining, 8 had liver metastasis, 9 had distant organ metastasis, 3 had lymph node metastasis, and 1 had peritoneal dissemination. Of the 30 cases showing negative staining, 10 had liver metastasis, 4 had distant organ metastasis, 7 had lymph node metastasis, and 3 had peritoneal dissemination. There were no significant differences in the frequencies and patterns of recurrence between the 2 staining groups.

Association between postsurgical recurrence-free rate of patients with ICC and GnT-V expression in the specimens

The overall postsurgical recurrence-free rate of

Table 5 Multivariate regression analysis of prognostic factors

Variable	Hazard ratio	C.L.	p
Histology*	-	-	0.983
Intrahepatic metastasis	3.670	1.644-8.195	0.002
Vascular invasion	2.471	0.691-8.834	0.164
Lymph node metastasis	2.851	1.237-6.573	0.014
GnT-V expression	0.458	0.206-1.017	0.055

*Histology: poorly differentiated adenocarcinoma or others.

Table 6 Stepwise multivariate regression analysis of prognostic factors

Variable	Hazard ratio	C.L.	p
Intrahepatic metastasis	4.932	1.241-31.975	0.026
Vascular invasion	3.355	0.898-23.613	0.077
Lymph node metastasis	11.241	2.532-34.578	0.001
GnT-V expression	4.165	0.061-0.945	0.041

Variable	Hazard ratio	C.L.	p
Intrahepatic metastasis	6.236	1.561-40.299	0.013
Lymph node metastasis	2.851	3.282-41.966	0.001
GnT-V expression	0.458	0.077-1.000	0.060

the 72 patients with ICC was compared in terms of GnT-V expression (Fig. 2). The cumulative recurrence-free rate of patients in the negative staining group tended to be lower than that of patients in the positive staining group. However, the difference was not statistically significant (23% vs 29%; p = 0.11).

Association between postsurgical survival rate of patients with ICC and GnT-V expression in the specimens

The overall postsurgical survival rate of the 72 patients with ICC was compared in terms of GnT-V expression (Fig. 3). The cumulative survival rate of patients in the negative staining group tended to be lower than that of patients in the positive staining group respectively. However, the difference was not statistically significant (28% vs 37%; p = 0.31).

A summary of the results of the multivariate regression analysis of prognostic factors for ICC is shown in Table 5. In the analysis, intrahepatic metastasis (p = 0.002) and lymph node metastasis (p = 0.014) were found to be statistically significant independent risk factors. GnT-V was not a statistically significant independent risk factor (Table 5). Furthermore, intrahepatic metastasis (p = 0.013) and lymph node metastasis (p = 0.001) were found to be important risk factors by stepwise multivariate regression analysis (Table 6).

Discussion

GnT-V expression is closely associated with the survival outcomes of patients with several kinds of cancers[13)14)]. We have recently reported that in pT_2 GBC, the survival rate of patients in the positive staining group was significantly lower than that of patients in the negative staining group[15)]. In this study, we investigated relations between clinicopathological features, surgical outcomes, and the expression of GnT-V in ICC. The results of the present study showed a tendency for GnT-V expression to inversely correlate with postsurgical recurrence and survival outcomes of patients with ICC (Tables 4, 5). In particular, the results of multivariate regression analysis showed a higher correlation of GnT-V expression with post surgical prognosis than with histology or vascular invasion (Table 5).

Malignant transformation of glandular epithelia is accompanied by alterations in the biochemical and biological characteristics of glycoproteins. Elevated levels of β1-6 branching of *N*-acetylglucosamine, transferred by GnT-V, are shown to be positively

correlated with metastatic potential and tumor invasiveness in several reports. Moreover, GnT-V functions as an angiogenesis inducer that has a completely different function from the original function of glycosyltransferase[12]. A secreted type of GnT-V protein has specifically been shown to promote angiogenesis *in vitro* and *in vivo*[17)18)]. In agreement with the above-mentioned biological roles of GnT-V, our recent *in vitro* and *in vivo* experiments using GBC cells have also shown that the cellular expression levels of GnT-V are positively correlated with malignant behaviors, such as rapid cell growth, potent angiogenic capability, and high metastatic potential (unpublished results).

The reasons why GnT-V expression showed a tendency to inversely correlate with ICC aggressiveness in this study remain unknown. Several reports showed that GnT-V expression was inversely correlated with poor prognosis of certain kinds of cancer[19)20)]. This discrepancy might be dependent on whether or not cancer cells have target proteins of GnT-V or a protease involved in GnT-V cleavage.

It was reported that the expression and immunohistochemical localization of a cancer-associated glycoprotein, mucin core polypeptide 1 (MUC1), correlated with the aggressiveness of ICC[21)] and with that of GBC[22)]. Carcinoma cells expressing MUC1 are less sensitive to cytolysis by human lymphokine-activated killer lymphocytes[23)~26)] and MUC1 overexpression inhibits integrin-mediated extracellular matrix interaction[27)]. Moreover, MUC1 on the cell membrane destabilizes cell-to-cell adhesion and allows carcinoma cells to migrate and metastasize[28)]. These reports may therefore be helpful to speculate that the mechanisms underlying ICC metastasis possibly involve molecular pathways that are not affected by GnT-V expression.

On the other hand, more advanced cases were included in this retrospective analysis than in other studies[13)15)] so it may be difficult to evaluate the biological role of GnT-V in ICC correctly.

In conclusion, GnT-V was found to be expressed in more than half of the ICC cases and GnT-V expression showed a tendency to inversely correlate with ICC aggressiveness, so it may be a useful marker for scaling the low malignant potential of ICC. However, because of the large number of advanced cases in this study, caution is needed to draw any conclusion regarding the correlation between GnT-V expression and ICC biological malignancy. Thus far, lymph node metastasis is considered to be the most important prognostic factor for ICC[29)~32)]. In this study, intrahepatic metastasis and lymph node metastasis were evaluated as important prognostic factors. However, as the accurate assessment of ICC intrahepatic metastasis and lymph node metastasis is very difficult in daily clinical practice, there is a crucial need to accumulate more cases to further investigate the biological markers that correlate with ICC lymph node or distant organ metastasis.

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The authors declare no conflicts of interest.

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肝内胆管癌における糖転移酵素 *N*-アセチルグルコサミン転移酵素Ⅴ（GnT-V）発現とその臨床病理学的意義

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〔目的〕癌細胞表面の糖鎖構造はその悪性挙動に深く関与する．糖転移酵素 GnT-V は，ノックアウトマウスの解析結果より，癌の増殖・転移に必須の分子であることが証明されており，様々な癌種において生物学的悪性度との関連性が報告されている．以前我々は，pT2 胆嚢癌（GBC）の GnT-V 陽性例において，術後遠隔臓器転移再発が多く，陰性例と比較し有意に予後不良であることを報告した．しかし，他の胆道癌に関しての GnT-V 発現と臨床病理学的意義に関する報告は過去にない．そこで，肝内胆管癌（ICC）における GnT-V 発現と予後および術後再発との関連性について検討を行った．〔方法〕ICC 治癒切除 72 例を対象とし，GnT-V 発現を免疫組織学的にて解析し，その結果を臨床病理学的因子および術後予後と比較検討した．〔結果〕GnT-V の免疫組織学的発現は陽性 42 例，陰性 30 例であった．GnT-V 発現の有無と病理組織学的因子との間に有意な相関関係は認められなかった．GnT-V 陽性例は陰性例と比較し術後 5 年生存率は高い傾向にあったが有意差を認めなかった．（$p=0.31$）また，GnT-V 発現の有無と術後再発率，再発様式との間に有意差は認めなかった．〔結語〕ICC においては，GnT-V と関連のない機序の癌増殖・転移経路の存在が示唆された．