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• *BRIEF REPORTS* •

Syndecan-1 and E-cadherin expression in differentiated type of early gastric cancer

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Abstract

AIM: To elucidate the role and alterations of syndecan-1 and E-cadherin expression in different cellular phenotypes of differentiated-type gastric cancers (DGCs).

METHODS: A total of 120 DGCs at an early stage, and their adjacent mucosa, were studied both by immunohistochemistry. Syndecan-1 and E-cadherin were assessed by immunohistochemical staining with anti-syndecan-1 and anti-E-cadherin antibodies, respectively. Based on immunohistochemistry, DGCs and their surrounding mucosa were divided into four types: gastric type (G-type), ordinary type (O-type), complete-intestinal type (CI-type), and null type (N-type).

RESULTS: Syndecan-1 expression was significantly lower in G-type cancers (29.4%) than in O-type (79.6%) and CI-type cancers (90%) (P<0.05, respectively), but E-cadherin did not show this result. In addition, syndecan-1 expression was significantly reduced in DGCs comprised partly of poorly differentiated adenocarcinoma or signet-ring cell carcinoma, compared to DGCs demonstrating papillary and/or tubular adenocarcinoma (P<0.05). G-type intestinal metaplasia (IM) surrounding the tumors was observed in 23.8% of G-type, 4.9% of O-type, and 6.7% of CI-type cancers (P<0.05; G-type *vs* O-type). Reduction of syndecan-1 expression was significant in G-type IM (25%) compared to non-G-type IM (75%; P<0.05).

CONCLUSION: Loss of syndecan-1 plays a role in the growth of G-type cancers of DGCs at an early stage, and the reduction of syndecan-1 expression in IM surrounding the tumors may influence the growth of G-type cancer.

Key words: Gastric cancer; Cellular phenotype; Syndecan-1

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INTRODUCTION

Gastric cancer is one of the most common malignant tumors of the gastrointestinal tract worldwide. In the past decade, infection with *Helicobacter pylori* has received wide attention for its potential role in the induction and progression of gastric cancer. However, the molecular pathways involved in gastric carcinogenesis are still poorly understood. Basic research has produced remarkable advances in our understanding of cancer biology. Among the most important of these advances was the recognition that syndecan-1 plays a role as a cell adhesion molecule, similar to E-cadherin, and is associated with the maintenance of epithelial morphology. However, the expression of syndecan-1 was augmented during epithelial regeneration and rearrangement in the stomach and other tissues[1-3]. E-cadherin is a member of the transmembrane glycoprotein family and is responsible for the epithelial cell-cell adhesion molecule expressed by epithelial cells. Inactivation of the E-cadherin gene and abnormal expression of its protein are considered to be correlated with the dedifferentiation of gastric cancer cells with gastric phenotype[4-8], but not the intestinal phenotype.

Gastric cancers with gastric phenotype have a poor outcome[9] and higher malignant potential in the incipient phase of invasion and metastasis compared to those with other phenotypes. Differentiated-type gastric cancers (DGCs) with gastric phenotype are likely to change to undifferentiated-type adenocarcinomas in the invasive portion of the tumor. Phenotypic classification may be useful for predicting the biologic behavior and choosing the therapeutic strategy[10]. To our knowledge, however, there are no data that compare the expression of syndecan-1 and E-cadherin in human gastric cancer. The aim of this study was to clarify the role and alterations of syndecan-1 expression in comparison with those of E-cadherin in different cellular phenotypes of DGCs, by using immunohistochemical staining.

MATERIALS AND METHODS

Specimens

One hundred and sixty patients (86 men, 74 women, average

age 52 years, range 21-60 years) with early gastric cancer were included in this study. DGC specimens were randomly selected from the histopathology files of our hospital between 2000 and 2003. Written informed consent was obtained from the patients before the interview for this study. Pathologic findings such as tumor size, depth of invasion, lymphatic invasion, blood vessel invasion, and lymph node metastasis were found from surgical files.

Early gastric cancers were defined as cancers with invasion limited to the submucosal layer. These tumors had been treated by surgical operation, all of which included the adjacent normal mucosa. The specimens were fixed in 40 g/L formaldehyde and embedded in paraffin wax, and 4-μm consecutive sections were used for histologic examination by hematoxylin-eosin (H&E) staining and immunohistochemistry.

Histologic classification of the intramucosal lesions was carried out according to the general rules established by the Padova classification[11]. DGCs were divided into two types, as follows, according to Koseki's classification[12]: solely differentiated type, composed of DGCs demonstrating papillary and/or tubular adenocarcinoma; and complex type, comprised predominantly of DGCs and partly of poorly differentiated adenocarcinoma or signet-ring cell carcinoma.

Immunohistochemistry and classification of phenotypic expression

Fresh 4-μm-thick serial sections were cut from routinely fixed, paraffin-embedded blocks and placed on poly-L-lysine-coated slides (Sigma Chemical, Poole, UK). One slide of each specimen was stained with hematoxylin-eosin and used to confirm the recorded histological classification. Immunohistochemical staining of syndecan-1 and E-cadherin was performed in accordance with standard procedures on 4-μm-thick sections of formalin-fixed, paraffin-embedded sequential tissue sections[13]. Antigen retrieval was performed by boiling for 12 min in an aluminum pressure cooker (Prestige, UK) at 103 kPa in pre-heated 10 mol/L sodium citrate buffer (pH 6.0). After cooling in running tap water, the slides were rinsed in 0.1 mol/L phosphate-buffered saline (PBS; pH 7.4). Nonspecific staining was blocked by incubation of the sections in normal horse serum for 30 min, prior to application of the primary monoclonal antibody to syndecan-1 (Serotec, Kidlington, UK) at a concentration of 0.001 mg/mL. This is an IgG1 antibody which reacts specifically with syndecan-1, as revealed by molecular cloning. After incubation in a moist chamber overnight at room temperature, the slides were washed in PBS and incubated for 30 min with biotinylated horse antimouse IgG (Vectastain Elite ABC kit; Vector Laboratories, Burlingame, CA). Slides were washed and then incubated for 30 min with avidin-biotin complex (Vectastain Elite ABC kit), according to the manufacturer's recommendations. Staining was performed by incubation with 3-3 diaminobenzidine (DAB; Sigma) activated with hydrogen peroxide. Slides were counter-stained with Mayer's hematoxylin. Negative controls were obtained by replacing primary antibody with PBS.

The avidin-biotin peroxidase complex method was employed for the detection of human gastric mucin (HGM; Novocastra Laboratories, Newcastle, UK), MUC2 (Novocastra Laboratories), CD10 (Novocastra Laboratories). Paradoxical concanavalin A (Con A) staining, identifying class III mucins in mucous neck and pyloric gland cells, was employed, according to the method of Katsuyama and Spicer[14]. HGM staining the surface of normal gastric epithelium and Con A were defined as gastric phenotype markers. MUC2 is a glycoprotein expressed predominantly in goblet cells, and CD10 expression is seen at the brush border on the luminal surface of epithelial cells. MUC2 and CD10 were defined as intestinal phenotype markers.

Classification of tissues

DGCs and normal mucosa surrounding the tumors were classified into four types based on the mucin phenotype, according to a modification of the classification of Ohmura[15]: gastric type (G-type), ordinary type (O-type), complete-intestinal type (CI-type), and null type (N-type). The criteria for each phenotype are shown in Table 1.

These cellular phenotypes were evaluated both in tumor cells and in the background normal mucosa surrounding the tumors.

Table 1 Criteria for cellular phenotype

	HGM expression	Con A expression	MUC2 expression	CD10 expression
G-type	(+)	(+)	(-)	(-)
O-type	(+)	(+)	(+)	(+)
CI-type	(-)	(-)	(+)	(+)
N-type	(-)	(-)	(-)	(-)

G-type, gastric type; O-type, ordinary type; CI-type, complete-intestinal type; N-type, null type.

Grading of intestinal metaplasia (IM)

Intestinal metaplasia (IM) in the surrounding mucosa within 1 cm of the cancer was classified according to the classification of Egashira *et al*[16]: negative, slight (with scattered IM); moderate (with continuous IM but scattered nonmetaplastic glands in between); and severe (with continuous IM). In this study, IM was divided into two groups based on the classification of Egashira *et al*[16], for cellular phenotype: (1) that showing G-type expression (G-type IM); and (2) that not showing G-type mucin (non-G-type IM).

Evaluation of syndecan-1 and E-cadherin immunostaining

The results of immunohistochemical staining were evaluated independently by two observers. Immunohistochemical reaction intensities of syndecan-1 were classified into four grades. Briefly, -, no staining; ±, weak staining or strong staining in fewer than 25% of tumor cells; +, moderate staining or strong staining in only 25-75% of tumor cells; and ++, strong staining of more than 75% of tumor cells. The sections for syndecan-1 were judged positive when more than 25% of cancer cells (+ or ++) were stained; others were judged negative. Concerning E-cadherin staining, its expression was demonstrated not only in the plasma membranes but also in the cytoplasm of tumor cells. The latter staining pattern of E-cadherin was suggested to reflect dysfunction of the cadherin cell adhesion system[17]. Therefore, reduced expression and cytoplasmic localization

of E-cadherin in more than 20% of tumor cells was defined as abnormal expression[17]. Staining of syndecan-1 and E-cadherin in IM was compared with that in foveolar epithelium. Sections were regarded as negative when the staining intensities of IM showed weak expression compared to those of foveolar epithelium; sections were regarded as positive when the staining intensities of IM were similar to those of foveolar epithelium. Normal gastric foveolar epithelium was used as an internal positive control.

Statistics

Statistical analysis was performed by the Mann-Whitney *U*-test between two independent groups, and by the χ^2 test and Fisher's exact probability test between two proportions. Statistical significance was defined as $P<0.05$.

RESULTS

Mucin phenotype and pathological factors

The results are summarized in Table 2. There was no significant difference in the tumor size among the phenotypes. Forty-one surgically resected specimens had submucosal invasion. Of the 120 gastric cancers evaluated, 12 (10%) did not express any cellular phenotype (N-type). In the remaining 108 cases, G-type was observed in 34 cases (28.3%), O-type in 54 cases (45%), and CI-type in 20 cases (16.7%). The frequency of complex type was significantly higher in G-type (52.9%, 18 of 34) and N-type (75%, 9 of 12) compared with O-type (11.1%, 6 of 54) and CI-type cancers (10%, 2 of 20), as shown in Table 2. The G-type and N-type cancers were associated with a higher rate of lymphatic/venous invasion than O-type and CI-type cancers, although no significant differences were found in lymph node metastasis among the cellular phenotypes.

Syndecan-1 immunohistochemistry

Syndecan-1 protein was mainly stained at the basolateral surfaces of the foveolar epithelium, IM (Figure 1A), and tumor cells (Figure 1B). Stromal plasma cells were also stained for syndecan-1.

Table 2 Correlation of pathological factors and expression of syndecan-1 and E-cadherin in each mucin phenotype

	G-type (n = 34)	O-type (n = 54)	CI-type (n = 20)	N-type (n = 12)	P
Tumor size (cm, mean±SD)	3.5±0.9	2.9±0.7	3.1±0.6	2.7±0.4	NS
Histology					
Solely differentiated type	16	45	18	3	<0.05[a,c]
Complex type	18	9	2	9	<0.05[a,c]
Lymphatic and/or venous invasion[1]	17	14	5	5	<0.05[e,g]
Lymph node metastasis	7	8	1	4	NS
Syndecan-1 expression	10	43	18	8	<0.05[a,c]
E-cadherin expression	22	32	15	8	NS
IM	21	41	15	8	NS
IM with G-type[2]	5	2	1	0	<0.05[a]

[a]$P<0.05$ *vs* O-type; [c]$P<0.05$ *vs* CI-type; [e]$P<0.05$ *vs* O-type; [g]$P<0.05$ *vs* CI-type G-type, gastric type; O-type, ordinary type; CI-type, complete-intestinal type; N-type, null type; NS, not significant. [1]Evaluated in 41 surgically resected specimens with submucosal invasion. [2]Evaluated in 85 cases with positive for IM.

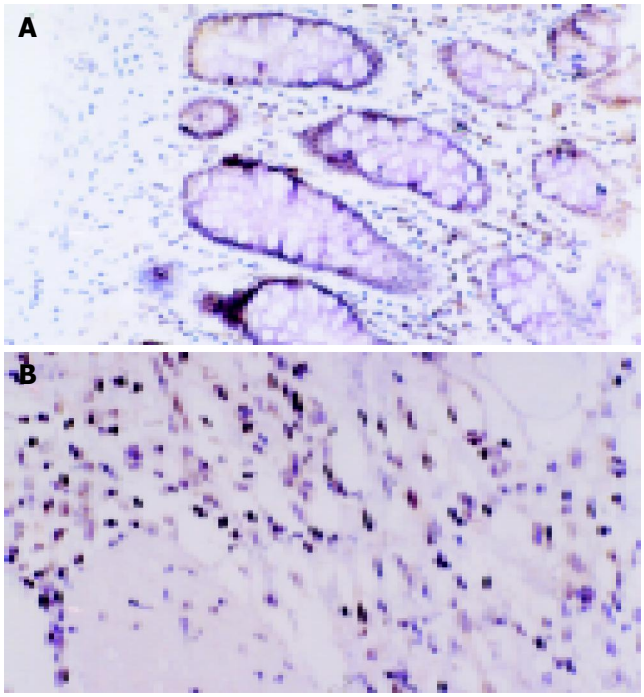

Figure 1 Expression of syndecan-1 in gastric mucosa on semi-serial sections. **A**: Positive staining with anti-syndecan-1 antibody is found at the basolateral surfaces of foveolar epithelial cells, IM and at the cell surfaces of stromal plasma cells. **B**: Positive staining is noted at the basolateral surfaces of cancer cells and at the cell surfaces of stromal plasma cells.

Correlation of syndecan-1 and E-cadherin expression with cellular phenotype and pathological factors

The expression of syndecan-1 protein was seen in 10 (29.4%) G-type, 43 (79.6%) O-type, 18 (90%) CI-type, and 8 (66%) N-type, and was significantly lower in G-type than in O-type and CI-type cancers ($P<0.05$, respectively). However, there was no significant correlation between the expression of E-cadherin and any cellular phenotype (Table 2). Complex-type cancer showed a significant reduction or loss of syndecan-1 expression compared with the solely differentiated-type cancer ($P<0.05$). Moreover, the expression of syndecan-1 was markedly decreased in poorly differentiated-type cancer cells, and was sparse in DGCs, whereas E-cadherin expression was not reduced in cancer cells. Lymphatic and/or venous invasion tended to be correlated with syndecan-1 expression ($P>0.05$), whereas, with regard to lymph node metastasis, a significant correlation was noticed for E-cadherin ($P<0.05$), but not for syndecan-1 (Tables 3 and 4).

Correlation of syndecan-1 and E-cadherin with cellular phenotype and intestinal metaplasia (IM)

IM in the surrounding mucosa was observed in 21 (61.8%) G-type cancers, in 41 (75.9%) O-type, in 15 (75%) CI-type, and in 8 (66.7%) N-type cancers, none of these differences being statistically significant (Table 2). IM with gastric phenotype was seen in only 9.4% of IM (8 of 85). The remaining 90.5% of IM (77 of 85) did not show G-type. Interestingly, G-type IM in the surrounding mucosa was observed in 5 cases (23.8%) of G-type cancers, but in 2 (4.9%) of O-type cancers, only 1 (6.7%) of CI-type, and

Table 3 Correlation of pathological factors and expression of syndecan-1

	Syndecan-1 expression		*P*
	Positive (*n* = 80)	Negative (*n* = 40)	
Histology			
Solely differentiated type	66	16	<0.05
Complex type	14	24	<0.05
Lymphatic and/or venous invasion[1]	28	13	NS
Lymph node metastasis	12	8	NS
IM with G-type[2]	2	6	<0.05

G-type, gastric type; NS, not significant. [1]Evaluated in 41 surgically resected specimens with submucosal invasion. [2]Evaluated in 85 cases with positive for IM.

Table 4 Correlation of pathological factors and E-cadherin

	E-cadherin expression		*P*
	Positive (*n* = 77)	Abnormal (*n* = 43)	
Histology			
Solely differentiated type	57	29	NS
Complex type	20	14	NS
Lymphatic and/or venous invasion[1]	23	18	NS
Lymph node metastasis	7	13	<0.05
IM with G-type[2]	4	4	NS

G-type, gastric type; NS, not significant. [1]Evaluated in 41 surgically resected specimens with submucosal invasion. [2]Evaluated in 85 cases with positive for IM.

none (0%) of N-type cancers (Table 4). Therefore, G-type IM was accompanied significantly more often by G-type cancers than by non-G-type, including O-type and CI-type cancers ($P<0.05$; Table 4). In addition, G-type IM was observed significantly more often in cancers with negative expression of syndecan-1 (75%) than in those with positive expression (25%; $P<0.05$), although there was no such relation for E-cadherin expression (Table 4). Reduction or loss of syndecan-1 expression and abnormal expression of E-cadherin were not seen in foveolar epithelium.

DISCUSSION

Syndecans are a family of cell-surface transmembrane heparan-sulfate proteoglycans. The sugar side chains of syndecan are structurally related to heparin and have functional cytoplasmic and extracellular domains that are thought to participate in both cell-cell and cell-extracellular matrix adhesion[18-21]. Syndecan-1 is expressed not only in epithelial tissue but also in fibroblasts and plasma cells[22-24]. Studies of the role of syndecan-1 in malignant transformation have revealed that syndecan-1 expression is associated with the maintenance of epithelial morphology and inhibition of invasion[25,26]. Reduced expression of syndecan-1 was associated with malignant transformation in hepatocellular carcinoma[27] and with poor prognosis in colorectal carcinoma[28]. Furthermore, the expression of syndecan-1 was augmented during epithelial regeneration and rearrangement in the stomach[29]. Syndecan-1 plays an important role in cell-cell adhesion, and many studies have examined the role of syndecan-1 in oncogenesis[22-28].

A number of authors have reported about an association between E-cadherin expression and gastric cancers[17,30]. However, there are few studies evaluating syndecan-1 in comparison with other adherent molecules, including E-cadherin, in other malignancies[31,32]. And there are no data that compare syndecan-1 and E-cadherin expression in each cellular phenotype in early gastric cancers. In the present study, we found that syndecan-1 expression was significantly reduced in G-type cancers and G-type IM compared with the other phenotypes of cancers and IM. Furthermore, G-type IM was accompanied significantly more often by G-type cancers than by O-type and CI-type cancers. These data suggest that the reduction of syndecan-1 may play a role in the growth of both G-type gastric cancer and G-type IM. G-type cancers are considered to have a more aggressive nature when compared with cancers of other cellular phenotypes[9,10]. Therefore, the altered expression of syndecan-1 in early-stage gastric cancers may alter the biological behavior of the transformed epithelial cells and affect the invasive characteristics. In addition, assessment of the expression level of syndecan-1 may serve as a novel biomarker for predicting the malignant potential of cancers.

Human gastric foveolar epithelium, IM, and most DGC cells expressed syndecan-1 protein and mRNA, as reported previously[29]. Syndecan-1 was mainly localized at the basolateral surfaces of the cells, implying that it participates in cell-cell and cell-extracellular matrix adhesion[17-21]. The expression of syndecan-1 was lost or reduced in G-type cancers, which were significantly associated with complex type cancers, comprised predominantly of DGCs and partly of poorly differentiated adenocarcinoma or signet-ring cell carcinoma. It is reported that DGCs with gastric phenotype tend to change to undifferentiated-type adenocarcinomas[33]. Therefore, the reduction of syndecan-1 might affect dedifferentiation, which appears as the loss of tumor glandular formation. Previous report indicates that the detachment of invading cancer cells from the nests was more frequently observed in syndecan-1-negative colorectal cancers[28]. As for E-cadherin, however, its expression did not relate to cellular phenotype or to histologically complex type cancer. A report by Koseki *et al*[12], showed that G-type cancer frequently demonstrated the abnormal expression of E-cadherin. Blok *et al*[34], speculated that a reduction or loss of E-cadherin expression, with the concomitant acquisition of a morphologically diffuse growth pattern, might be responsible for the development of poorly differentiated and/or dedifferentiated cells in intestinal-type gastric cancer (which corresponds to our complex type cancer). The reasons for the discrepancy in these results are considered to be the differences of patient numbers examined and of the incidence of complex type in G-type cancers. Another explanation might be a defect in the catenin part of E-cadherin/catenin complex[34]. Day *et al*[31], reported that a greater reduction of syndecan-1 expression than of E-cadherin expression was seen in the transition from moderate to severe dysplasia in colon tumors. This result suggests that the changes in the expression of syndecan-1 probably occur before those in E-cadherin, perhaps influencing the expression of the latter adhesion molecule[32]. Thus, our data are in agreement with their results. IM is generally known to be a precursor of DGC[35,36]. In this study, we

focused on IM with different cellular phenotypes in the development of DGCs. Similar to our current finding, Egashira *et al*[16], have described that the IM surrounding G-type cancers showed gastric phenotype at a significantly higher incidence than it showed intestinal phenotype. The reduction of syndecan-1 expression was seen in IM alone, but not in gastric foveolar epithelium. Syndecan-1 expressed in IM was observed in both complete-type and incomplete-type IM, implying that syndecan-1 expression is not associated with cell differentiation in IM. The mechanism by which the functional loss of syndecan-1 contributes to the phenotypic expression of G-type IM is unclear. However, tumor phenotype in the early stage is widely thought to resemble that of the tissue of origin. It is, therefore, probable that the histogenesis of G-type cancer occurs in the pathway through which IM exhibits gastric phenotype, with functional loss of syndecan-1.

The present study showed that the immunoreactivity of E-cadherin appeared to be a more useful predictor of lymph node metastasis than syndecan-1, although many investigations of the relationship between E-cadherin and lymph node and/or vascular invasion have had controversial findings[1,2,5,6,8,30,34]. We find here that the expression of syndecan-1 was not associated with lymph node metastasis, although lymphatic and/or venous invasion tended to be higher in cancers with a reduction or loss of syndecan-1 expression than in those with positive expression. Further studies are necessary to clarify the value of syndecan-1 compared with that of E-cadherin for predicting metastasis.

In conclusion, the present study shows that syndecan-1 may play a role in gastric cellular phenotyping and dedifferentiation in DGCs at an early stage, and it also shows that the reduction of syndecan-1 expression in the mucosa surrounding the tumors may influence the growth of gastric phenotype cancer. In the current study, the number of cancers analyzed may be small, particularly considering that four different categories of cellular phenotypes were compared. Thus, further investigations will be required with a larger sample size in order to confirm more clearly the expression of syndecan-1 and E-cadherin in various cellular phenotypes of gastric cancers and the background mucosa.

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