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ORIGINAL ARTICLE

Association of low Syndecan-1 expression with adverse histopathological parameters in gastric carcinomas

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Summary

Purpose: *Since syndecan-1 is an adhesion molecule involved in tumor invasion and metastasis, we evaluated the relationship between syndecan-1 expression and histopathological features of gastric carcinomas.*

Methods: *Syndecan-1 expression was evaluated in 104 gastric carcinomas using immunohistochemistry.*

Results: *High, moderate and low syndecan-1 expression in carcinoma cells was observed in 17/104, 25/104 and 62/104 cases, respectively. High, moderate and low syndecan-1 expression in stromal cells was observed in 5/104, 22/104 and 77/104 cases, respectively. Low epithelial syndecan-1 expression was significantly associated with increased depth of invasion (p=0.034) and lymph vessel invasion (p=0.035). Low stromal syndecan-1 expression was significantly associated with histologic type (intestinal vs diffuse/mixed; p=0.04), increased histologic grade (p=0.04) and large tumor size (p=0.026).*

Conclusion: *Low levels of tumor and stromal syndecan- 1 expression were associated with adverse histopathological parameters in gastric carcinoma. This suggests that syndecan-1 expression may be helpful for assessing the aggressiveness of gastric carcinomas.*

Key words: *gastric carcinomas, immunohistochemistry, syndecan-1*

Introduction

Gastric carcinoma is one of the most common malignant tumors of the digestive system and its high incidence of mortality is mainly attributed to invasion and metastasis [1]. A decisive parameter in the development and metastasis of malignancies is the disruption of cell-cell and cell-matrix adhesion [1,2]. Syndecan-1 is a cell surface heparan sulfate proteoglycan that functions as an extracellular matrix receptor participating in cell-cell and cell-matrix adhesion [2-5]. Syndecan-1 is involved in tumor biology by altering adhesion, migration and cellular response to mitogenic factors [2-5].

The immunohistochemical expression of syndecan-1 was analyzed in many malignancies [1,6-22]. Interestingly, low syndecan-1 expression in tumor cells was associated with reduced survival in gastric, uterine cervix and head and neck carcinoma [7-19], and with a high metastatic potential in hepatocellular and colorectal carcinomas [20-22]. In contrast, increased syndecan-1 expression was

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associated with increased tumor aggressiveness and poor prognosis in pancreatic and breast carcinomas [23-26]. This difference may reflect tissue and/or tumor stage-specific function, and/or may reflect the multiple functions of syndecan-1.

Only a few studies analyzed the stromal expression of syndecan-1 in carcinomas. Stromal expression of syndecan-1 was reported in 9% of gastric carcinomas and stromal expression of syndecan-1 was correlated with a more aggressive clinical course in gastric, ovarian and breast carcinomas [27-30].

Interestingly, altered expression of syndecan-1 was associated with tumor growth and early dedifferentiation of differentiated-type gastric carcinomas (DGC) [31,32]. Although low syndecan-1 expression in both the neoplastic epithelium and stromal cells of gastric carcinomas was associated with poor prognosis [27,28], the evaluation of stromal immunostaining of syndecan-1 in these studies was presented only as positive or negative. Prompted by these findings we assessed the immunohistochemical expression of syndecan-1 in carcinoma and stromal cells using a more precise scoring system and examined the relation of syndecan-1 expression with various histopathological parameters.

Methods

Patients

One hundred and four patients (55 men and 49 women, age range 20-88 years) with gastric adenocarcinoma were included in this study. Carcinomas were classified according to the Lauren classification into intestinal, diffuse or mixed type. Fifty cases were classified as intestinal, 42 as diffuse and 12 as mixed type adenocarcinomas. Four cases were G1 (well differentiated), 24 G2 (moderately differentiated), and 76 G3 (poorly differentiated). The clinical and translational protocol was

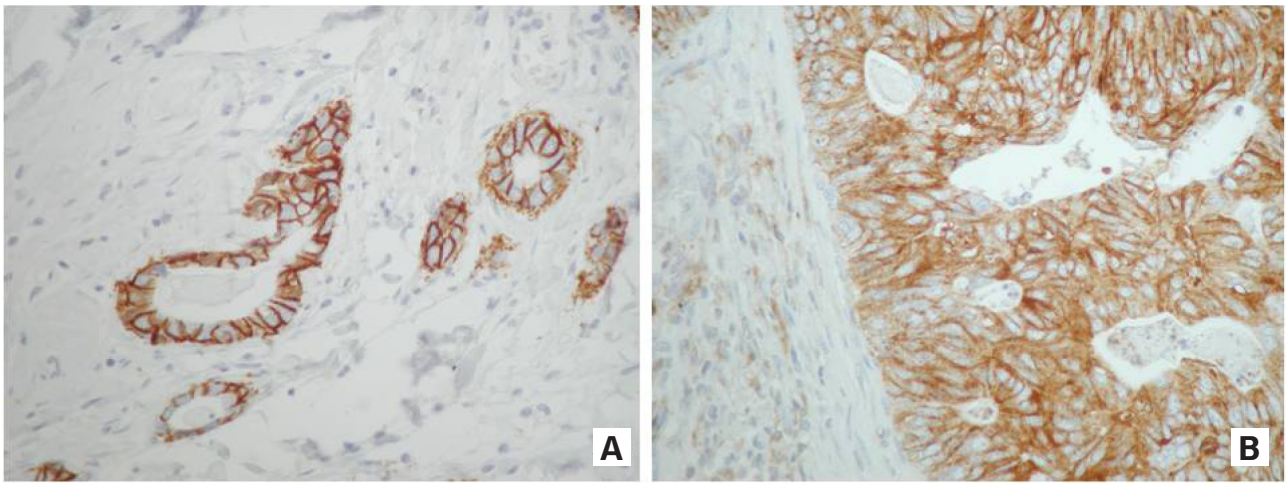

Figure 1. A: Strong syndecan-1 reactivity characterized by prominent membrane accentuation in carcinoma cells. Stromal cells are non-reactive (x100). **B:** Positive cytoplasmic staining of syndecan-1 (diffuse or granular pattern) (x200).

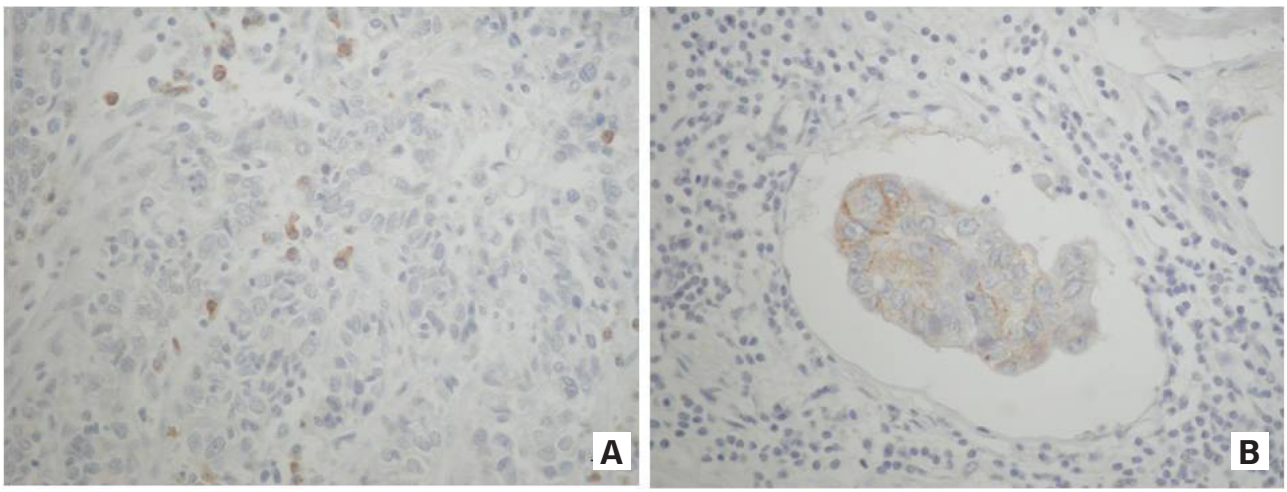

Figure 2. A: Low syndecan-1 expression in carcinoma cells (plasma cells served as positive internal control) (x100) and **B:** in lymphatic vessel invasion (x200).

Table 1. Distribution of epithelial and stromal expression of syndecan-1 in patients with gastric carcinoma

Expression level	*Epithelial*		*Stromal*	
(%)	*n*	*%*	*n*	*%*
<10	62	59.6	77	74
10-50	25	24.0	22	21.2
>50	17	16.3	5	4.8
Total	104	100	104	100

Table 2. Relations between epithelial expression of syndecan-1 and clinicopathological parameters in gastric carcinoma

Clinicopathological parameters	*Epithelial syndecan-1 (%)*			*p value*
	0<10	10-50	>50	
Gender				NS
Female	28	10	6	
Male	29	15	11	
Age, years				NS
<63	25	14	9	
>63	27	10	8	
Lauren classification				NS
Intestinal type	26	10	8	
Diffuse/mixed type	26	15	7	
Grade of differentiation				NS
G1	3	0	1	
G2/G3	50	23	15	
Lymph node metastases				NS
Yes	41	21	11	
No	14	3	5	
Lymph vessels invasion				**0.035**
Yes	35	19	9	
No	5	0	4	
Blood vessels invasion				NS
Yes	23	8	6	
No	16	7	6	
Nerves invasion				NS
Yes	30	13	9	
No	10	2	3	
Tumor size, cm				NS
<5	21	10	7	
>5	32	13	7	
Depth				**0.034**
Group A	1	1	3	
Group B	55	23	14	

Group A: mucosa/submucosa, Group B: muscularis propria /perigastric fat/serosa. Bold numbers denote statistical significance. NS: not significant

approved by the Hellenic Cooperative Oncology Group Protocol Review Committee and by the Bioethics Committee of the Aristotle University of Thessaloniki School of Medicine.

Immunohistochemistry

Immunohistochemical staining for syndecan-1 was performed on formalin-fixed, paraffin-embedded tissue sections with the standard avidin-biotin-immunoperoxidase method (ABC) (Elite ABC Kit, Vectastain; Vector, Burlingame, CA) according to the instructions of the manufacturer as described previously [33]. The mouse monoclonal antibody against human syndecan-1 (B-B4; Serotex, Oxford, UK) was used. Negative controls (omission of primary antibody) were used in all experiments. The level of immunoreactivity in epithelial and stromal cells was expressed by scoring the percentage of syndecan-1-positive cells into three groups: high >50% of cells positive; moderate 10-50% of cells positive; and low <10% of cells positive.

Statistics

SPSS 11.5 software package was used and statistical analysis was performed using the Chi-Square and the Mann-Whitney U tests. The results were considered as statistically significant when $p<0.05$.

Results

Epithelial expression of syndecan-1

The immunohistochemical localization of syndecan-1 was membranous and/or cytoplasmic (diffuse or granular) (Figure 1). High, moderate and low syndecan-1 staining of tumor cells was observed in 17/104 (16.3%), 25/104 (24%) and 62/104 (59.6%) cases, respectively (Table 1). Low syndecan-1 expression (Figure 2) showed significant positive correlation with histopathological features of tumor aggressiveness, such as increased depth of invasion and lymphatic vessels invasion. Indeed, syndecan-1 expression was lower in tumors penetrating the muscularis propria, perigastric fat or serosa compared to those penetrating mucosa or submucosa ($p=0.034$) (Table 2). Moreover, syndecan-1 expression was lower in tumors showing invasion of the lymphatic vessels ($p=0.035$) (Table 2). Syndecan-1 epithelial expression levels were not associated with gender, age, histological type of tumor (Lauren classification), grade of differentiation, tumor size, lymph node metastases, and invasion of blood vessels or nerves.

Stromal expression of syndecan-1

The immunohistochemical localization of syndecan-1 was membranous and/or cytoplasmic (diffuse or granular). High, moderate and low stromal staining was found in 5/104 (4.8%), 22/104 (22%)

and 77/104 (74%) cases, respectively (Table 1). Low levels of stromal syndecan-1 expression were associated with the histological type (intestinal vs diffuse/mixed, p=0.04), increased histologic grade (G1 vs G2/G3, p=0.04) and large tumor size (p=0.026) (Table 3). Syndecan-1 stromal non-neoplastic was not associated with gender, age, lymph node metastases, and invasion of blood vessels or nerves.

Expression of syndecan-1 in non-neoplastic gastric mucosa

Syndecan-1 expression was found mainly on basolateral surfaces of foveolar epithelial cells. Stromal cells, including plasma cells, were positive for syndecan-1 and, in some cases, endothelial cells were also positive.

Table 3. Relations between stromal expression of syndecan-1 and clinicopathological parameters in gastric carcinoma

Clinicopathological parameters	*Epithelial syndecan-1 (%)*			*p value*
	0<10	10-50	>50	
Gender				NS
Female	34	8	2	
Male	39	13	3	
Age, years				NS
<63	36	10	2	
>63	33	9	3	
Lauren classification				**0.04**
Intestinal type	34	6	4	
Diffuse/mixed type	35	13	0	
Grade of differentiation				**0.04**
G1	2	1	1	
G2/G3	67	19	2	
Lymph node metastases				NS
Yes	54	15	4	
No	15	6	1	
Lymph vessels invasion				NS
Yes	46	13	4	
No	7	1	1	
Vessels invasion				NS
Yes	30	6	1	
No	17	8	4	
Nerves invasion				NS
Yes	37	12	3	
No	10	4	1	
Tumor size, cm				**0.026**
<5	26	7	5	
>5	40	12	0	

Bold numbers denote statistical significance. NS: not significant

Discussion

We showed that low levels of syndecan-1 expression in tumor (epithelial) and stromal cells are associated with histopathological features indicating aggressiveness in gastric carcinomas. Indeed, low syndecan-1 expression in tumor cells was significantly correlated with increased depth of tumor penetration and invasion of the lymphatic vessels. Moreover, low syndecan-1 expression in stromal cells was significantly correlated with increased tumor histological grade and large tumor size. In keeping with our findings, low syndecan-1 expression was reported in various malignancies [7-22]. Moreover, low syndecan-1 expression was associated with a poorer prognosis in various malignancies including gastric carcinoma [7-19,27-32].

Syndecan-1 is involved in tumor biology by altering adhesion, migration, invasion, metastasis and cellular response to mitogenic factors [2-4]. Notably, recent reviews document that syndecans have a basic regulatory role in tumor progression [34-36].

The reduced syndecan-1 expression may be an early pathogenetic event contributing to tumor progression [20,21]. Increased invasion and metastasis are characteristic of highly malignant tumors, such as gastric carcinomas and reduced syndecan-1 may enhance the metastatic potential of these tumors. Interestingly, increased syndecan 1 expression may indicate an early clinical stage and a favorable prognosis in gastric cardiac adenocarcinoma [37]. Thus, changes in syndecan-1 expression in cancer, may reflect a regulatory role of syndecan-1 in the adhesion between cell-cell and cell-matrix and the motility of malignant cells.

The depth of tumor penetration and the lymph node status were reported as the most significant variables for survival in gastric carcinomas [28]. In this respect, we found that low epithelial syndecan-1 expression was significantly correlated to increased tumor penetration and invasion of lymphatic vessels. This suggests that low expression of syndecan-1 in carcinoma cells is associated with more invasive tumors. In other studies, the expression of syndecan-1 in tumor cells was not associated with lymph node metastasis in early gastric carcinoma, although lymphatic invasion tended to be higher in cancers with reduction of syndecan-1 expression [31,32]. We found no significant correlation between epithelial syndecan-1 expression and some histopathological parameters such as histologic type, grade and tumor size. In contrast, carcinomas of the uterine cervix have shown a significant association between low epithelial syndecan-1 expression and lymph node metastasis [11].

Although immunoreactivity in the tumor stroma was previously reported in only 9% of the gastric carcinomas [27,28], we observed extensive stromal syndecan-1 expression, similar to that found in pancreatic and colorectal carcinomas [38,39].

According to recent comprehensive reviews, stromal expression of syndecan-1 may have a negative prognostic value, in various malignant tumors [40,41]. In keeping with these findings, we demonstrated a significant correlation between low stromal expression of syndecan-1 and adverse histopathological parameters, such as increased tumor grade and large tumor size.

Interestingly, stromal cells were essential for the progression of ovarian carcinomas, where an altered phenotype of the tumor stroma cooperates with neoplastic epithelial cells to promote tumor progression [42].

Low syndecan-1 expression in gastric carcinoma cells was associated with intestinal type morphology and with large sized tumors (>5 cm) [27,28]. In contrast, we found that histologic type and tumor size were associated with low syndecan-1 expression in stromal cells but not in carcinoma cells. This difference could be attributed to the evaluation of the stromal expression of syndecan-1, which in the previous studies was reported only as negative or positive [27,28].

Stromal expression of syndecan-1 was demonstrated in infiltrating breast carcinomas [26]. The authors hypothesized that since syndecan-1 interacts with heparin-binding growth factors such as Fibroblast Growth Factor-2 (FGF-2), accumulation of syndecan-1 within the tumor stroma might contribute to the extensive angiogenesis and stromal proliferation characteristic of infiltrating breast carcinoma [26]. Stromal expression of syndecan-1 might be implicated in decreased cell adhesion and degradation of basement membranes. Thus, stromal expression of syndecan-1 could indicate aggressive behavior of carcinoma cells [1-4,42].

Heparan sulfates bind to various bioactive molecules (e.g., growth factors, chemokines) that regulate cell behavior in normal and pathological processes [2-4]. In the latter context, syndecan-1 may cooperate with various molecules to drive growth factor signaling, thus enhancing tumor growth and dissemination [43-45].

It has been suggested that syndecan-1 expression in stromal fibroblasts may create a favorable microenvironment for accelerated tumor growth by storing and presenting growth factors to the carcinoma cells, since syndecan-1 interacts through its extracellular heparan sulfate glycosaminoglycan chains with many epithelial mitogens, including FGF, HGF and EGF [2-4]. Moreover, it has been reported that, the notable alterations in both epithelial (tumor) and stromal expression of syndecan-1 in gastric carcinomas may be related to the modulatory role of syndecan-1 on the action of growth factors [2-4]. Although the mechanisms are not yet fully understood, the above-mentioned observations highlight the important role of syndecans in tumor progression and suggest that they may be potential therapeutic targets [34,36,42].

In conclusion, we showed that low levels of tumor and stromal syndecan-1 expression were significantly correlated with adverse histopathological parameters in gastric carcinoma. This suggests that syndecan-1 expression may be helpful for assessing the aggressiveness of gastric carcinomas.

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Conflict of interests

The authors declare no conflict of interests.

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