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
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).
null
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**

<table>
<thead>
<tr>
<th>Clinicopathological parameters</th>
<th>Epithelial syndecan-1 (%)</th>
<th>( p ) value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0(&lt;10 ) 10-50 ( &gt;50 )</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
<td>13</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>(&lt;65 )</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>(&gt;65 )</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>Lauren classification</td>
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<tr>
<td>Intestinal type</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td>Diffuse/mixed type</td>
<td>35</td>
<td>13</td>
</tr>
<tr>
<td>Grade of differentiation</td>
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</tr>
<tr>
<td>G1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>G2/G3</td>
<td>67</td>
<td>19</td>
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<tr>
<td>Lymph node metastases</td>
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</tr>
<tr>
<td>Yes</td>
<td>54</td>
<td>15</td>
</tr>
<tr>
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<td>15</td>
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</tr>
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<tr>
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<td>8</td>
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<tr>
<td>Nerves invasion</td>
<td></td>
<td>NS</td>
</tr>
<tr>
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<td>12</td>
</tr>
<tr>
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<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Tumor size, cm</td>
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</tr>
<tr>
<td>(&lt;5 )</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>(&gt;5 )</td>
<td>40</td>
<td>12</td>
</tr>
</tbody>
</table>

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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