

GASTRIC CANCER

Relationship between cell adhesion molecules expression and the biological behavior of gastric carcinoma

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Author contributions: Chu YQ and Zhao ZS contributed equally to this work; Chu YQ, Zhao ZS, Tao HQ, Wang YY, Ye ZY, designed research; Chu YQ, Wang YY, Ma HF, Li SG and Tao HQ performed research; Zhao ZS contributed new reagents/analytic tools; Chu YQ, Wang YY analyzed data; and Chu YQ, Ma HF, and Wang YY wrote the paper.

Supported by The Grant of Zhejiang Province Natural Science Foundation, No. M303843

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Received: August 29, 2007 Revised: January 3, 2008

analysis demonstrated that the mean survival time and 5-year survival rate were lower in the cases with low expressions of syndecan-1 and E-cadherin and high expression of integrin $\beta 3$ ($P < 0.01$, in all cases). COX multivariate analysis showed that the expression level of syndecan-1 could be an independent prognostic index of gastric carcinoma ($P < 0.01$), whereas E-cadherin and integrin $\beta 3$ could not be independent indexes ($P > 0.05$, $P > 0.05$ respectively).

CONCLUSION: The low expression of syndecan-1 and E-cadherin and the high expression of integrin $\beta 3$ are significantly correlated with the invasion and metastasis of gastric carcinoma, and they are highly correlated with each other. Therefore they may serve as important prognostic markers of gastric carcinoma.

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Key words: Cell adhesion molecules; Gastric Carcinoma; Invasion; Metastasis; Prognosis

Peer reviewer: Toru Ishikawa, MD, Department of Gastroenterology, Saiseikai Niigata Second Hospital, Teraji 280-7, Niigata, Niigata 950-1104, Japan

Chu YQ, Ye ZY, Tao HQ, Wang YY, Zhao ZS. Relationship between cell adhesion molecules expression and the biological behavior of gastric carcinoma. *World J Gastroenterol* 2008; 14(13): 1990-1996 Available from: URL: <http://www.wjgnet.com/1007-9327/14/1990.asp> DOI: <http://dx.doi.org/10.3748/wjg.14.1990>

Abstract

AIM: To evaluate the relationship between the expression of cell adhesion molecules (CAMs) and the biological behavior of gastric carcinoma.

METHODS: Expression of syndecan-1, E-cadherin and integrin $\beta 3$ were evaluated by immunohistochemical study in a total of 118 gastric carcinomas and 20 non-tumor gastric mucosas.

RESULTS: The expressions of syndecan-1 and E-cadherin were significantly lower in gastric carcinoma compared to non-tumor gastric mucosa, and the low expression rates were positively correlated to the tumor invasion depth, vessel invasion, lymph node metastasis and distant metastasis ($P < 0.01$ in all cases). However, the expression of integrin $\beta 3$ was significantly higher in gastric carcinoma compared to non-tumor gastric mucosa, and the high expression rates were positively correlated to the tumor invasion depth, vessel invasion, lymph node metastasis and distant metastasis ($P < 0.01$ in all cases). In addition, the three protein expressions were correlated to the tumor growth pattern ($P < 0.01$, $P < 0.01$, and $P < 0.05$ respectively), but not correlated to tumor differentiation ($P > 0.05$, $P > 0.05$ and $P > 0.05$ respectively). Positive correlation was observed between the expressions of syndecan-1 and E-cadherin, but they which were negatively correlated to the expression of integrin $\beta 3$ ($P < 0.01$ in all cases). Univariate

INTRODUCTION

Gastric carcinoma is the most common malignant tumor of the digestive system. Two of the most important causes for the high mortality are invasion and metastasis. However, the mechanism of invasion and metastasis of gastric carcinoma is still not definitely clear at present^[1]. Cell adhesion is one of the important steps in metastasis. Syndecan-1, E-cadherin and integrin $\beta 3$ make up cell adhesion molecules (CAMs) and participate in the adhesion between the cell and the extracellular matrix^[2]. Syndecan-1 is a set of transmembrane heparitin sulfate glycoproteins (HSPGS), which is present at the surface of most epithelia cells and take part in the adhesion between the cell and the extracellular matrix. The expression of syndecan-1 was augmented during epithelial regeneration and rearrangement in the stomach and other tissues^[3,4]. E-cadherin is a calcium dependent intercellular

adhesion molecule and it is present in normal cells to maintain the normal structure of tissues which has special biological characters and is highly related to invasion and metastasis of cancer cells^[3]. Studies show that the reduction or absence of syndecan-1 and E-cadherin expressions could induce the growth, invasion and metastasis of tumors^[5]. Integrin is a heterodimer consisting of a group of α and β polypeptide chains which can be divided into three groups based on the difference of a common β chain ($\beta 1$, $\beta 2$ and $\beta 3$). By identifying the extracellular matrix such as laminin, fibronectin and immunoglobulin superfamily on the cell membrane (I-CAM for example) *etc.*, mediating adhesive reaction of cell-extracellular matrix and cell-cell and receiving and conducting cascade signals, Integrin regulates the survival, apoptosis, movement, proliferation and inflammatory reaction of cells^[6]. To our knowledge, the co-expressions of syndecan-1, E-cadherin and integrin $\beta 3$ in gastric carcinoma and their clinical significances have not been reported before. We thus studied the expressions of CAMs in gastric carcinoma patients to find out the relationship among three of them using the immunochemical S-P method and to explore the correlation in their expression and pathological indexes of gastric carcinoma and survival time.

MATERIALS AND METHODS

Specimen

One hundred and eighteen specimens were collected from gastric carcinoma patients (91 men, 27 women, average age 56.3 years, range 25-79 years). They received the radical operations in our hospital from October 1986 to November 2002. Follow-up period was up to 5 years and the survival period was calculated from the day of surgery to the end of the follow-up or to the day of death. The censored value was zero. Of 118 gastric carcinomas, 70 were highly or moderately differentiated, while 48 were poorly or undifferentiated. According to the tumor, lymph node, and metastasis (TNM) standard stadiation, 47 were in T1-T2 stages and 71 were in T3-T4 stages. Eighty nine cases had vascular invasion and 29 without. Eighty three had lymph node metastasis and 35 without; distant metastases of carcinoma were found in 55 cases, while no distant metastasis in 63 cases. Twenty gastric mucosa specimens were collected 5 cm away from the cutting edges of radical operation as normal controls, which were detected as non-tumor mucosa.

Main reagents

Mouse anti-human syndecan-1, E-cadherin and integrin $\beta 3$ were purchased from ZYMED Company. SP kit was purchased from Maixin Biotect Company, Fuzhou, China. Streptavidin peroxidase staining was performed according to the kit instruction. Normal gastric mucosa was used as a positive control and PBS was used to replace the first antibody as a negative control.

Immunohistochemistry

Immunohistochemistry was made according to the streptavidin peroxidase (SP) methods. The staining step followed the routine process. In order to examine the

specificity of immunostaining, both positive and negative controls were run at the same time in each experiment. The normal gastric mucous was used as the negative control.

Results evaluation

Based on the proportion of positively stained cells in the sections, the criteria of syndecan-1 and E-cadherin were set as follows^[7]: (1) if more than 90% of the tumor cells exhibited intense membranous staining similar to that of normal cells, the result was considered as positive (++) ; (2) if the staining intensity was demonstrably reduced relative to that of normal cells and/or the staining pattern was heterogeneous (10%-90% positive), the result was deemed to be weakly positive (+); (3) if its expression was completely lost or positive in less than 10% of cells, the result was defined as negative (-). In statistical analysis, \pm were classified as the low expression group and ++ were set as the high expression group. In addition, the criteria for integrin $\beta 3$ were classified into four grades^[8]. Briefly, -, no staining in fewer than 10% of tumor cells; +, weak staining in only 10%-50% of tumor cells; ++, moderate staining in 50%-75% of tumor cells; and +++, strong staining of more than 75% of tumor cells. The sections for integrin $\beta 3$ were judged as a high expression group when more than 50% of cancer cells (++ or +++) were stained; others were judged as a low expression group.

Statistical analysis

SPSS 11.5 software package was used in data processing. Non-parameter Spearman rank correlation analysis was used to determine the relationship between the expressions of syndecan-1, E-cadherin and integrin $\beta 3$ and the pathological indexes of the progression of gastric carcinoma. The survival rate was estimated by the Kaplan-Meier method and analyzed by the long-rank test. Fisher's exact test was used to differentiate the rates of different groups. Univariate analysis and Cox-multivariate analysis were used to analyze the effect of the pathologic parameters (differentiation level, invasion depth, vessel invasion and lymph node metastasis), the expression of syndecan-1, E-cadherin and integrin $\beta 3$ on the total survival.

RESULTS

The expressions of syndecan-1, E-cadherin and integrin $\beta 3$ in gastric carcinoma and non-tumor gastric mucosa

Of a total of 118 gastric carcinomas the following was found: syndecan-1 low expression 57.6% (68/118) (Figure 1A) and high expression 42.4% (50/118); E-cadherin low expression 57% (68/118) (Figure 2A) and high expression 42.4% (50/118); and integrin $\beta 3$ low expression 50% (59/118) and high expression 50% (59/118) (Figure 3A). However, of 20 non-tumor gastric mucosa, syndecan-1 high expression (Figure 1B) 90% (18/20) and low expression 10% (2/20); E-cadherin high expression 85% (7/20) (Figure 2B) and low expression 15% (3/20); and integrin $\beta 3$ high expression 15% (3/20) (Figure 3B) and low expression 85% (17/20). Compared to normal tissues, the gastric carcinoma tissues showed lower syndecan-1 expression ($\chi^2 = 15.5$, $P < 0.01$), lower E-cadherin expression rate and density with

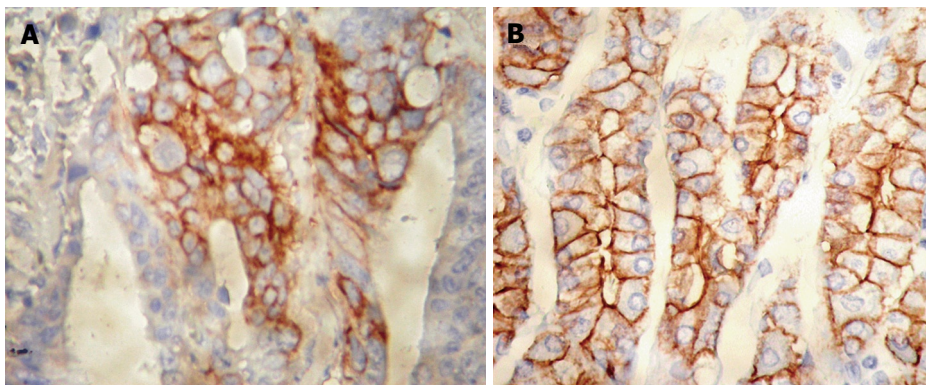


Figure 1 Syndecan-1 expression. **A:** Syndecan-1 was negatively (+) expressed in gastric carcinoma. *Sp method.* ($\times 250$); **B:** Syndecan-1 was highly expressed (++) in non-tumor gastric mucosa ($\times 250$).

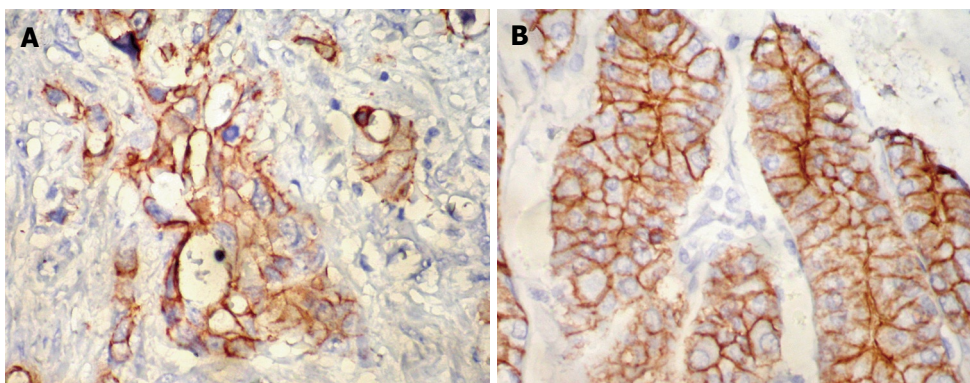


Figure 2 E-cadherin expressions. **A:** E-cadherin was negatively (+) expressed in gastric carcinoma (Magnification $\times 250$); **B:** E-cadherin was highly expressed (++) in non-tumor gastric mucosa ($\times 250$).

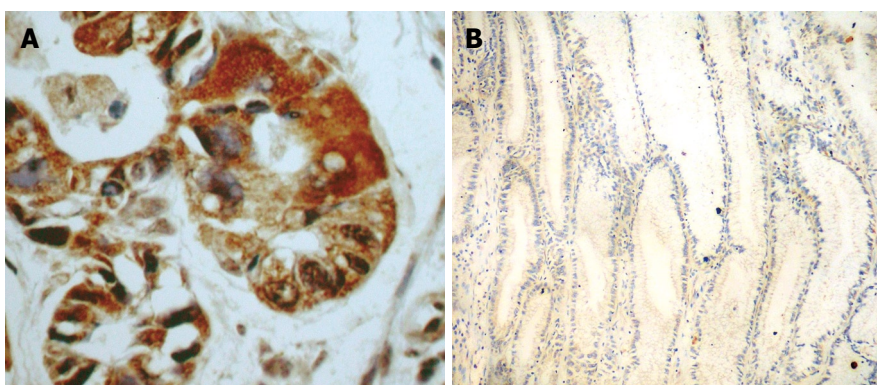


Figure 3 Integrin $\beta 3$ expression. **A:** Integrin $\beta 3$ was highly expressed (++++) in gastric carcinoma ($\times 250$); **B:** Integrin $\beta 3$ was negatively (+) expressed in non-tumor gastric mucosa ($\times 250$).

the increase of invasive depth of cancer cells ($\chi^2 = 12.4$, $P < 0.01$) and higher integrin $\beta 3$ expression ($\chi^2 = 8.5$, $P < 0.01$). There are significant differences in the expressions of these three proteins in gastric carcinoma and non-tumor gastric mucosa.

Relationship between the expression levels of syndecan-1, E-cadherin and integrin $\beta 3$ and the pathological indexes of progression of gastric carcinoma

The low expressions of syndecan-1 and E-cadherin were positively correlated with the gastric carcinoma growth mode ($\chi^2 = 12.47$, $P < 0.01$; $\chi^2 = 15.27$, $P < 0.01$), invasion depth ($\chi^2 = 32.95$, $P < 0.01$; $\chi^2 = 28.73$, $P < 0.01$), vessel invasion ($\chi^2 = 46.22$, $P < 0.01$; $\chi^2 = 40.52$, $P < 0.01$), lymph node metastasis ($\chi^2 = 43.49$, $P < 0.01$; $\chi^2 = 38.28$, $P < 0.01$) and distant metastasis ($\chi^2 = 63.30$, $P < 0.01$; $\chi^2 = 51.98$, $P < 0.01$). Additionally, the gastric carcinoma growing in invasive style had low expressions of syndecan-1 and

E-cadherin which were not correlated to the differentiation level of gastric carcinoma ($\chi^2 = 1.60$, $P > 0.05$). The high expression of integrin $\beta 3$ protein was positively correlated with gastric carcinoma growth modes ($\chi^2 = 5.83$, $P < 0.05$), invasion depth ($\chi^2 = 29.74$, $P < 0.01$), vessel invasion ($\chi^2 = 33.33$, $P < 0.01$), lymph node metastasis ($\chi^2 = 29.61$, $P < 0.01$) and distant metastasis ($\chi^2 = 41.72$, $P < 0.01$). The gastric carcinoma growing in invasive style had high expressions of integrin $\beta 3$ protein, which was not correlated to the differentiation level of gastric carcinoma ($\chi^2 = 0.14$, $P > 0.05$) (Table 1).

Relationship among the expressions of syndecan-1, E-cadherin and integrin $\beta 3$ in gastric carcinoma

There was significant positive correlation between the expression levels of syndecan-1 and E-cadherin. Both of them had negative correlation with integrin $\beta 3$ expression (Table 2).

Table 1 Correlation between expressions of syndecan-1, E-cadherin and integrin $\beta 3$ and pathological parameters in 118 gastric carcinoma patients

| Variable | (n) | Syndecan-1 expression | | | | E-cadherin expression | | | | Integrin $\beta 3$ expression | | | |
|-----------------------------|-----|-----------------------|------|----------|-------|-----------------------|------|----------|-------|-------------------------------|------|----------|-------|
| | | Low | High | χ^2 | P | Low | High | χ^2 | P | Low | High | χ^2 | P |
| Growth mode of tumors | | | | | | | | | | | | | |
| Invasion | 67 | 48 | 19 | 12.47 | 0.000 | 49 | 18 | 15.27 | 0.000 | 27 | 40 | 5.836 | 0.016 |
| Expansion | 51 | 20 | 31 | | | 19 | 32 | | | 32 | 19 | | |
| Histologic differentiations | | | | | | | | | | | | | |
| Well/moderate | 70 | 37 | 33 | 1.60 | 0.205 | 37 | 33 | 1.60 | 0.205 | 36 | 34 | 0.140 | 0.708 |
| Poor | 48 | 31 | 17 | | | 31 | 17 | | | 23 | 25 | | |
| Depth of invasion | | | | | | | | | | | | | |
| T1-T2 | 47 | 12 | 35 | 32.95 | 0.000 | 13 | 34 | 28.73 | 0.000 | 38 | 9 | 29.74 | 0.000 |
| T3-T4 | 71 | 56 | 15 | | | 55 | 16 | | | 21 | 50 | | |
| Vascular invasion | | | | | | | | | | | | | |
| Negative | 29 | 1 | 28 | 46.22 | 0.000 | 2 | 27 | 40.52 | 0.000 | 28 | 1 | 33.33 | 0.000 |
| Positive | 89 | 67 | 22 | | | 66 | 23 | | | 31 | 58 | | |
| Lymphatic metastasis | | | | | | | | | | | | | |
| Negative | 35 | 4 | 31 | 43.49 | 0.000 | 5 | 30 | 38.28 | 0.000 | 31 | 4 | 29.61 | 0.000 |
| Positive | 83 | 64 | 19 | | | 63 | 20 | | | 28 | 55 | | |
| Distant metastasis | | | | | | | | | | | | | |
| Negative | 63 | 15 | 48 | 63.30 | 0.000 | 17 | 46 | 51.98 | 0.000 | 49 | 14 | 41.72 | 0.000 |
| Positive | 55 | 53 | 2 | | | 51 | 4 | | | 10 | 45 | | |

Table 2 Relationship among the expressions of syndecan-1, E-cadherin and integrin $\beta 3$ in gastric carcinoma

| Groups | Syndecan-1 | | | r | P | E-cadherin | | | r | P |
|--------------------|------------|----|----|--------|---|------------|----|----|--------|---|
| | - | + | ++ | | | - | + | ++ | | |
| Syndecan-1 | | | | | | | | | | |
| - | 43 | | | | | 38 | 4 | 1 | | |
| + | | 25 | | | | 11 | 12 | 2 | | |
| ++ | | | 50 | | | 3 | 0 | 47 | | |
| E-cadherin | | | | | | | | | | |
| - | 38 | 11 | 3 | 0.837 | 0 | 52 | | | | |
| + | 4 | 12 | 0 | | | | 16 | | | |
| ++ | 1 | 2 | 47 | | | | | 50 | | |
| Integrin $\beta 3$ | | | | | | | | | | |
| - | 2 | 6 | 48 | -0.792 | 0 | 9 | 1 | 46 | -0.666 | 0 |
| + | 1 | 1 | 1 | | | 2 | 0 | 1 | | |
| ++ | 18 | 8 | 1 | | | 19 | 8 | 2 | | |
| +++ | 22 | 10 | 0 | | | 22 | 7 | 1 | | |

Factors that affect the survival rate of gastric carcinoma

Univariate analysis showed that the patients with high syndecan-1 expression had a 5-year survival rate of 91.66%, while it was 12.8% in those with low syndecan-1 expression. There was significant difference between the rates ($\chi^2 = 53.13, P < 0.01$). The patients with high E-cadherin expression level had a 5-year-survival rate of 93.59%, which was significantly different from that of the patients with low E-cadherin expression with the rate of 12.8%. There was significant difference between the rates ($\chi^2 = 43.36, P < 0.01$). The patients with high integrin $\beta 3$ protein expression had a 5-year-survival rate of 13.85% and the patients with low integrin $\beta 3$ expression had the rate of 72.75%. There was significant difference between the rates ($\chi^2 = 35.11, P < 0.01$). Kaplan-Meier analysis indicated that the patients with low syndecan-1/E-cadherin protein expression level and high integrin $\beta 3$ expression level had poor prognosis (Table 3, Figure 4A-C).

COX-multivariate analysis showed that syndecan-1 expression could be used as a prognostic marker of gastric

Table 3 Relationship between the expressions of syndecan-1, E-cadherin and integrin $\beta 3$ and the prognosis of gastric carcinoma patients

| Groups | n | Mean survival time (mo) | 5-yr survival rate (%) | χ^2 | P |
|-------------------------------|----|-------------------------|------------------------|----------|---|
| Syndecan-1 expression | | | | | |
| Low expression | 68 | 32.10 \pm 4.16 | 12.80 | 53.13 | 0 |
| High expression | 50 | 123.80 \pm 5.56 | 91.66 | | |
| E-cadherin expression | | | | | |
| Low expression | 68 | 33.69 \pm 4.33 | 12.80 | 43.36 | 0 |
| High expression | 50 | 119.78 \pm 5.87 | 93.59 | | |
| Integrin $\beta 3$ expression | | | | | |
| Low expression | 59 | 103.30 \pm 7.73 | 72.75 | 35.11 | 0 |
| High expression | 59 | 33.12 \pm 4.64 | 13.85 | | |

cancer patients ($P < 0.01$). However, E-cadherin and integrin $\beta 3$ could not be used as independent prognosis markers ($P > 0.05$ and $P > 0.05$ respectively). (Syndecan-1: B = 3.447, SE = 0.988, Wald = 12.183, $P < 0.01$; E-cadherin: B = 0.019, SE = 0.686, Wald = 0.001, $P > 0.05$; integrin $\beta 3$: B = 0.098, SE = 0.364, Wald = 27.711, $P > 0.05$).

DISCUSSION

Gastric carcinoma is highly malignant and usually results in a poor prognosis. Although the achievement in early diagnosis and treatment of gastric cancer has improved the patients' outcome, it is still one of the leading causes of mortality in countries such as China and Japan. Currently, about 39% of gastric cancer cases occur in the Chinese population, ranking the leading cause of cancer-mortality in China, particularly in rural areas^[9]. The overall 5-year survival rate for patients who undergo curative surgical resection for gastric carcinoma ranges from 47% to 60.4%^[10]. The typical characteristics of malignant tumor are invasion and metastasis, which are the main cause for their lethality. Tumor progression is considered to be

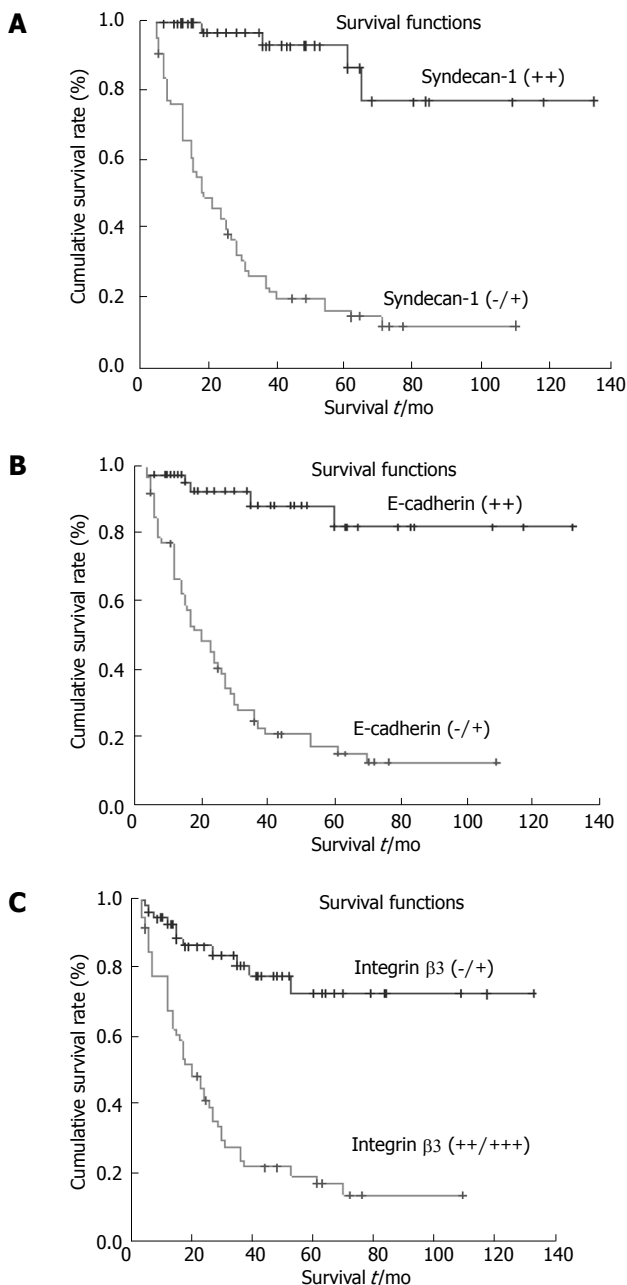


Figure 4 Correlation between syndecan-1, E-cadherin and integrin $\beta 3$ expressions and the survival time. **A:** Survival curves by the Kaplan-Meier method. Long-rank test revealing a significant difference between negative and positive expression of Syndecan-1 ($P < 0.05$); **B:** Survival curves by Kaplan-Meier method. Long-rank test revealing a significant difference between negative and positive expression of E-cadherin ($P < 0.05$); **C:** Survival curves by the Kaplan-Meier method. There was a significant difference in Long-rank test between positive and negative expression of integrin $\beta 3$ ($P < 0.05$).

dynamic, complex, and a multi-step process, where the essential steps are the breakdown of cell-cell adhesion and degradation of basement membrane (BM)^[11]. The cellular and molecular steps required for metastases of neoplastic cells are starting to be elucidated. The metastatic cascade starts with a downregulation of the epithelial bonds which enables tumor cells to leave epithelial structures, to invade the stroma, to enter the blood stream or the lymphatics, to extravasate, and to colonize the target organs. Interestingly, invasive growth and metastases often recapitulate embryonic development and are greatly influenced by

the stromal microenvironment^[12]. Thus, carcinoma cells interact bidirectionally with neighboring fibroblasts, endothelial cells, and lymphocytes through growth factors, chemokines, cell adhesion molecules, and extracellular matrix proteases.

Loss of cell adhesion may contribute to loss of contact inhibition of growth, which is an early step in the neoplastic process. It has been shown that various cell adhesion molecules expressed on carcinoma cells play crucial roles. However, the mechanisms of invasion and metastasis are still under investigation. Until now there is no satisfactory tumor marker for predicting its evolution.

Syndecan-1, E-cadherin and integrin $\beta 3$ make up CAMs together^[2] to participate in adhesion between cell and extracellular matrix. Experimental studies show that changes in cell-cell and cell-matrix adhesion are central to the conversion from premalignant lesions to early invasive carcinoma^[13].

Syndecan-1 (CD138) is a member of the transmembrane heparin sulfate proteoglycan (HSPG) family, taking part in and improving adhesion between cell and extracellular matrix^[14], improving cell proliferation, maintaining the differentiation phenotype of cells and inhibiting the growth of tumor cells^[15]. Wiksten *et al*^[16] reported that abatement or loss of syndecan-1 expression is highly correlated to the focal size, lymphatic metastasis, invasion depth, TNM stage and prognosis of gastric carcinoma. It is reported that the expression of syndecan-1 increases gradually from large intestine adenoma to carcinoma, then to invasive carcinoma^[17,18].

E-cadherin is a calcium dependent transmembrane glycoprotein and has the functions of mediating the adhesion of homogeneous cells among epithelia and of maintaining the integrity and polarity of tissue structures^[19]. The abatement or loss of E-cadherin expression may induce the decrease of adhesion among cells and thus make cancer cells disunite, grow invasively toward peripheral tissues and leave original focal to form metastasis once the necessary conditions are met^[20,21]. Documents indicate that in gastric carcinomas, the reduction in E-cadherin expression activation of E-cadherin gene varies from 17% to 92%^[22,23]. This phenomenon has been confirmed in many kinds of tumors such as lung cancer, breast cancer, large intestine cancer, liver cancer and gastric cancer^[24-27].

Integrins belong to the family of transmembrane glycoprotein hetero-dimer. They mediate adhesion of neighboring cells and participate in the growth and repair of cells and vascular proliferation *etc* as important receptors of extracellular matrix protein^[28]. Molecular biological studies on melanoma, colon and rectal cancer and other carcinomas in the past few years showed that the dissociation from or penetration through BM of tumor cells, caused by the adhesion of $\alpha 3\beta 1$, $\alpha 5\beta 1$, $\beta 3$ and other Integrins on tumor cell surface to extracellular matrix, is the initial step for the invasive growth and remote metastasis of malignant tumor. Moreover the high expression of integrin $\beta 3$ in malignant melanoma and malignant ovarian tumor cells is positively correlated to invasion and metastasis of cancer cells^[29].

Documented data shows that these three proteins, syndecan-1, E-cadherin and integrin $\beta 3$, cooperate with

each other for expressions and functions; moreover their expression levels are correlated with the progression of gastric carcinoma. Experimental studies show that syndecan-1 and E-cadherin are all present in epithelia and both can form immunoprecipitation with transcription regulatory factor β -cadherin and this indicates that they are materially and functionally correlated with each other^[30]. The expression of syndecan-1 and E-cadherin in gastric carcinoma is low and their expression levels are positively correlated^[31]. The abatement or loss of E-cadherin expression is involved in lymph node micro-metastasis of gastric carcinoma^[32]. Sun *et al.*^[33] proposed the following point of view based on different studies: the decrease of *in vitro* syndecan-1 expression inhibits E-cadherin expression, and/or lowers E-cadherin expression at the same time as the beginning of epithelium-stroma transformation and induces effective and timely epithelium-stroma transformation^[33].

Signal conduction mediated by syndecan-1 needs the cooperation of integrin β 3^[34]. Mammary glandular epithelia short of syndecan-1 show rearrangement of integrin β 3 and markedly low expression of E-cadherin at the same time^[35]. Wound healing theory indicates that E-cadherin activates the migration of integrin β 3-transfected cells and constrains them to separate from wound margin. The study of Ohta *et al.* shows that over expression of the homeobox gene HOXD3 promotes the non-expression of E-cadherin and increased expression of integrin β 3, which plays an important role in the quick migration and isolation of tumor cells^[29]. Zhang *et al.*^[11] reported that E-cadherin loss in epithelial tumor progression was not only related to severing cell-cell adhesion but also associated with increased integrins expression, which induced cell-matrix adhesion of these cells^[13].

The results of this study indicate that the expressions of syndecan-1 and E-cadherin in gastric tumor tissues are low and their levels are significantly correlated. This suggests that syndecan-1 and E-cadherin play a positively cooperative role in the genesis and development of gastric carcinoma. They are negatively correlated to the level of integrin β 3 expression and this suggests that Integrins have different effects on the progression of gastric carcinoma. The functional consequence of enhanced cell-matrix adhesion is the initial attachment and retention of these cells at the epithelial-stromal interface, thus providing the appropriate microenvironmental conditions for incipient tumor cell invasion^[13].

Basing on the biological characters of syndecan-1, E-cadherin and Integrins, on relevant documents and on the results of this study, the correlation of CAMs with the progression of gastric carcinoma can be summarized as follows: (1) at the early stage of gastric carcinoma, tumor cells have low E-cadherin and syndecan-1 expression, adhesion between cells is weak and tumor cells are isolated from primary tumor, which is the initial step of invasion and metastasis of gastric carcinoma; (2) the decrease of the expressions of E-cadherin and syndecan-1 reduces adhesion between tumor cells and BM or extracellular matrix mediated by them and this is propitious to local growth and dispersion of tumor. At the same time, various hydrolytic enzymes will be released, after the adhesion of

cancer cells to BM or extracellular matrix, to degrade the BM or extracellular matrix which tumor cells adhere to. Thus cancer cells may enter into the blood circulation. Experimental studies show that Integrins are the main receptors for cells adhesion to extracellular matrix and syndecan-1 increases the combination of them; (3) the increase of Integrin expression, after that cancer cells enter the blood circulation, is in favor of adhesion of tumor cells to endothelia to induce invasive growth and remote metastasis of gastric carcinoma. In these processes, adhesion of tumor cells to endothelia and the BM under endothelia is the key process for the invasion and metastasis.

The pathological indexes and survival analysis results confirm that gastric cancer tissues with low syndecan-1 and E-cadherin protein expressions and high integrin β 3 protein expression have deeper invasion depth, higher occurrences of vascular invasion, lymph node metastasis and remote metastasis, shorter average survival time and lower 5-year survival rate, which is consistent with the study results of Wiksten *et al.*^[16], Trikh *et al.*^[36] and other researchers.

In conclusion, low expressions of syndecan-1 and E-cadherin protein and high expression of integrin β 3 protein are significantly correlated to invasion of gastric carcinoma. As intracellular adhesion molecular complexes, these three proteins are highly correlated with each other. Therefore, the results of co-examination of them can be important indexes for prognosis of gastric carcinoma.

COMMENTS

Background

Cell adhesion is one of the important steps in invasion and metastasis. Syndecan-1, E-cadherin and integrin β 3 make up intercellular adhesion molecules (CAMs) and participate in the adhesion between cell and extracellular matrix. One or two of them in gastric carcinoma has been reported before; however, in order to better understand the coordinated regulation of cell-cell and cell-matrix interactions during malignant transformation, we study the coexpression of E-cadherin, syndecan-1 and integrin β 3 by immunohistochemical study in gastric carcinomas.

Research frontiers

Recent investigations have suggested that frozen tissue-based molecular classifications effectively predict prognosis of gastric cancer, prognostic classification on formalin-fixed tissue is needed. Therefore additional markers are required in the prognosis of patients with gastric cancer.

Innovations and breakthroughs

In this article, we identified that syndecan-1, E-cadherin and integrins were highly correlated with each other as intracellular adhesion molecular complexes. We suggest that the results of co-examination can be important indexes for prognosis of gastric carcinoma.

Applications

The results from the study confirm the correlation between expressions of CAMs and gastric cancer. It suggests that the coexpression of them can be used to identify the prognosis of gastric carcinoma.

Terminology

CAMs are proteins located on the cell surface involved in the binding with other cells or with the extracellular matrix in the process called cell adhesion.

Peer review

This report analyzed that advanced gastric cancer including with/without distant

metastases. Prognostic factor of each stage of gastric cancer about CAMs should be analyzed and author should speculate other factors too.

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