Overexpression of stromal interaction molecule 1 may promote epithelial-mesenchymal transition and indicate poor prognosis in gastric cancer

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Abstract. The aim of the present study was to investigate the prognostic significance of stromal interaction molecule 1 (STIM1) expression in gastric cancer (GC) and examine the association between STIM1 and epithelial-mesenchymal transition (EMT). Immunohistochemical staining was performed to detect STIM1, E-cadherin, β-catenin and matrix metalloproteinase-9 (MMP-9) in 170 GC and 35 adjacent healthy gastric tissue samples. Positive staining of STIM1, E-cadherin, β-catenin and MMP-9 in GC tissues was significantly greater compared with adjacent healthy tissues (P<0.05). Clinicopathological analysis revealed that STIM1 expression was significantly associated with LNM (P<0.001) and tumor-node-metastasis stage (P=0.01). The overall survival rate was significantly reduced in STIM1-positive compared with STIM1-negative patients (P=0.043). Cox regression analysis indicated that STIM1 expression was significantly associated with abnormal cytoplasmic and nuclear expression of E-cadherin and β-catenin in GC cells, which suggested that STIM1 may promote EMT in GC.

Introduction

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer-associated mortality worldwide (1). As 5-year survival rates of GC remain <30% (2,3), further understanding of GC is urgently required.

Epithelial-mesenchymal transition (EMT) is an essential early step in tumor metastasis (4). During EMT, tumor cells lose their epithelial characteristics and obtain mesenchymal traits (5-8). It has been demonstrated that EMT is correlated with poor tumor staging, an increased risk of cancer recurrence and decreased survival in various cancer types, including breast (9,10), colorectal (11), bladder (12,13), lung (14) and GC (15).

Stromal interaction molecule 1 (STIM1) is responsible for the activation of store-operated Ca²⁺ entry (16). Previous studies have reported that STIM1 is important in the growth and migration of cancer cells, and for angiogenesis and progression of cancer (17-20). Furthermore, STIM1 is a key molecule in the process of EMT in various cancer types. Ectopic STIM1 expression induced EMT in colorectal cancer cells (20), and STIM1 silencing reversed EMT initiated by downregulation of the POU class 5 homeobox 1 transcription factor in breast cancer cells (19). Casas-Rua et al (21) demonstrated that STIM1 overexpression increased migration and EMT in endometrial adenocarcinoma cells. However, the role of STIM1 in GC progression and metastasis and its association with EMT remains to be elucidated.

In the present study, immunohistochemistry was performed to detect STIM1, E-cadherin, β-catenin and matrix metalloproteinase-9 (MMP-9) in 170 GC and 35 adjacent healthy gastric tissue samples. STIM1 was overexpressed in GC samples and associated with poor survival of GC patients. STIM1 expression was significantly associated with abnormal cytoplasmic and nuclear expression of E-cadherin and β-catenin in GC cells, which suggested that STIM1 may promote EMT in GC.

Materials and methods

Patients and tissue samples. GC and adjacent healthy tissue samples were obtained from 170 GC patients with histologically confirmed gastric adenocarcinoma between June
and sections were counterstained with hematoxylin. Finally, sections were dehydrated, cleared, covered with coverslips and sealed with neutral gum.

All slides were assessed by two pathologists who were blinded to the patient details. The intensity of STIM1 staining was graded on a 0–3 scale: 0, no staining; 1, weak immunoreactivity; 2, moderate immunoreactivity; 3, strong immunoreactivity. The percentage of immunoreactivity was scored on a 0–3 scale: 0, no positive cells; 1, 0–25% positive cells; 2, 26–50% positive cells; 3, >50% positive cells (24).

E-cadherin, β-catenin and MMP-9 staining were classified as abnormal according to the degree of cytoplasmic and nuclear staining and the proportion of positive cells. Abnormal staining intensity was graded on a 0–3 scale: 0, no staining; 1, weak immunoreactivity; 2, moderate immunoreactivity; 3, strong immunoreactivity. The percentage of abnormal immunoreactivity was scored on a 0–4 scale: 0, 0–20% positive cells; 1, 21–40% positive cells; 2, 41–60% positive cells; 3, 61–80% positive cells; 4, >80% positive cells (25).

Statistical analysis. All data were processed with SPSS software version 19.0 (IBM SPSS, Armonk, NY, USA). P<0.05 was considered to indicate a statistically significant difference. The chi-square test was used to analyze the association between STIM1 expression and patient characteristics. A binary logistical regression model was applied to identify factors associated with STIM1 positive expression. Cohen’s kappa statistic was used to determine the association between STIM1 expression and abnormal E-cadherin and β-catenin expression. The Kaplan-Meier method was used to calculate patient survival rate, and the Cox proportional hazards models were employed to identify independent factors associated with patient survival. In this model, X1, Age; X2, Sex; X3, Tumor location; X4, Tumor differentiation; X5, Tumor size; X6, Lymphatic metastasis; X7, Tumor-node-metastasis; and X8, STIM1 expression were used as independent variables; and Y, Survival as a dependent variable.

Results

STIM1 expression and its association with clinicopathological characteristics of GC patients. STIM1 expression in GC tissues was predominantly cytoplasmic (Fig. 1A). The STIM1 positive expression rate in GC tissues was 43.5% (74/170), which was significantly greater compared with adjacent healthy tissues (8.60%; 3/35; χ²=15.12; P<0.001; Table II; Fig. 1B). The STIM1 expression rate in GC patients with LNM was significantly greater compared with patients without LNM (P<0.001). STIM1 expression in stage I-II GC tissues was 33.5% (17/57), which was significantly reduced compared with stage III-IV tumors (66.3%; 57/113; P=0.01; Table I). However, STIM1 expression in GC tissues did not correlate with sex, age, the degree of histologic differentiation, location of the tumor or tumor size (P>0.05). Cox risk regression analysis indicated that lymphatic metastasis was the only independent risk factor for STIM1 expression in GC patients (Table III).
Table I. Association of STIM1, E-cadherin, β-cadherin and MMP-9 expression with characteristics of 170 gastric cancer patients.

| Characteristic       | STIM1                 | E-Cadherin          | β-cadherin          | MMP-9                 |
|----------------------|-----------------------|---------------------|---------------------|-----------------------|
|                      | Positive (74) | Negative (96) | χ² | P-value | Positive (89) | Negative (81) | χ² | P-value | Positive (105) | Negative (65) | χ² | P-value | Positive (88) | Negative (82) | χ² | P-value |
| Sex                  |                       |                     |                 |                     |                       |                     |       |                     |                       |                     |       |                     |                       |                     |       |                     |
| Male (127)           | 54 (42.5)             | 73 (57.5)           | 0.208            | 0.648               | 63 (49.6)              | 64 (50.4)           | 1.52 | 0.218               | 76 (59.8)              | 51 (40.2)           | 0.79 | 0.375               | 68 (53.5)              | 59 (46.5)           | 0.64 | 0.43               |
| Female (43)          | 20 (46.5)             | 23 (53.5)           |                 |                     | 26 (60.5)              | 17 (39.5)           |       |                     | 29 (67.4)              | 14 (32.6)           |       |                     | 20 (46.5)              | 23 (53.5)           |       |                     |
| Age (years)          |                       |                     |                 |                     |                       |                     |       |                     |                       |                     |       |                     |                       |                     |       |                     |
| ≤60 (96)             | 45 (46.9)             | 51 (53.1)           | 1.004            | 0.316               | 48 (50.0)              | 48 (50.0)           | 0.49 | 0.484               | 55 (57.3)              | 41 (42.7)           | 1.87 | 0.171               | 45 (46.9)              | 51 (53.1)           | 2.11 | 0.15               |
| >60 (74)             | 29 (39.2)             | 45 (60.8)           |                 |                     | 41 (55.4)              | 33 (44.6)           |       |                     | 50 (67.6)              | 24 (32.4)           |       |                     | 43 (58.1)              | 31 (41.9)           |       |                     |
| Tumor location       |                       |                     |                 |                     |                       |                     |       |                     |                       |                     |       |                     |                       |                     |       |                     |
| Cardia (92)          | 43 (46.7)             | 49 (79.0)           | 1.010            | 0.603               | 44 (47.8)              | 48 (52.2)           | 1.70 | 0.428               | 58 (63.0)              | 34 (37.0)           | 0.20 | 0.904               | 49 (53.3)              | 43 (46.7)           | 5.37 | 0.07               |
| Body (11)            | 5 (45.5)              | 6 (54.5)            |                 |                     | 6 (54.5)               | 5 (45.5)            |       |                     | 7 (63.6)               | 4 (36.4)            |       |                     | 2 (18.2)               | 9 (81.8)            |       |                     |
| Antrum (67)          | 26 (38.8)             | 41 (61.2)           |                 |                     | 39 (58.2)              | 28 (41.8)           |       |                     | 40 (59.7)              | 27 (40.3)           |       |                     | 37 (55.2)              | 30 (44.8)           |       |                     |
| Tumor differentiation|                       |                     |                 |                     |                       |                     |       |                     |                       |                     |       |                     |                       |                     |       |                     |
| Poor/undifferentiated(79) | 32 (40.5)          | 47 (59.5)           | 0.549            | 0.459               | 37 (46.8)              | 42 (53.2)           | 1.80 | 0.180               | 54 (68.4)              | 25 (31.6)           | 2.71 | 0.099               | 45 (57.0)              | 34 (43.0)           | 1.60 | 0.21               |
| High/moderate (91)   | 42 (46.2)             | 49 (53.8)           |                 |                     | 52 (57.1)              | 39 (42.9)           |       |                     | 51 (56.0)              | 40 (44.0)           |       |                     | 43 (47.3)              | 48 (52.7)           |       |                     |
| Tumor size           |                       |                     |                 |                     |                       |                     |       |                     |                       |                     |       |                     |                       |                     |       |                     |
| <5 cm (74)           | 34 (45.9)             | 40 (54.1)           | 0.311            | 0.577               | 36 (48.6)              | 38 (51.4)           | 0.72 | 0.399               | 48 (64.9)              | 26 (35.1)           | 25.84b <0.001         | 32 (43.2)              | 42 (56.8)           | 3.81 | 0.05               |
| ≥5 cm (96)           | 40 (41.7)             | 56 (58.3)           |                 |                     | 53 (55.2)              | 43 (44.8)           |       |                     | 57 (59.3)              | 39 (40.6)           |       |                     | 56 (58.3)              | 40 (41.7)           |       |                     |
| Lymphatic metastasis |                       |                     |                 |                     |                       |                     |       |                     |                       |                     |       |                     |                       |                     |       |                     |
| Negative (64)        | 10 (15.6)             | 54 (84.4)           | 32.513b <0.001   |                     | 22 (34.4)              | 42 (65.6)           | 13.30b <0.001       | 16 (25.0)              | 48 (75.0)           | 58.75b <0.001         | 16 (25.0)              | 48 (75.0)           | 29.45b <0.001        |                     |
| Positive (106)       | 64 (60.4)             | 42 (39.6)           |                 |                     | 67 (63.2)              | 39 (36.8)           |       |                     | 89 (84.0)              | 17 (16.0)           |       |                     | 72 (67.9)              | 34 (32.1)           |       |                     |
| Tumor-node-metastasis stage |                    |                     |                 |                     |                       |                     |       |                     |                       |                     |       |                     |                       |                     |       |                     |
| I-II (57)            | 17 (29.8)             | 40 (70.2)           | 6.552a <0.05     | 0.010               | 18 (31.6)              | 39 (68.4)           | 14.84b <0.001       | 20 (35.1)              | 37 (64.9)           | 25.84b <0.001         | 27 (47.4)              | 30 (52.6)           | 0.66 | 0.42               |
| III-IV (113)         | 57 (50.4)             | 56 (49.6)           |                 |                     | 71 (62.8)              | 42 (37.2)           |       |                     | 85 (75.2)              | 28 (24.8)           |       |                     | 61 (54.0)              | 52 (46.0)           |       |                     |

Data are expressed as no. (%). *P<0.05; **P<0.01. STIM1, stromal interaction molecule 1; MMP-9, matrix metalloproteinase-9.
E-cadherin, β-catenin and MMP-9 expression, and their association with clinicopathological features of GC patients.

In the present study, E-cadherin (Fig. 1C and D) and β-catenin (Fig. 1E and F) were abnormally expressed in the cytoplasm or nucleus of GC cells. The positive expressions of E-cadherin and β-catenin were observed in 61.8% (105/170) and 52.4% (89/170), respectively, of GC tissue samples, and in 11.4% (4/35) and 20.0% (7/35), respectively, of adjacent healthy gastric tissues. Differences in the rates of abnormal E-cadherin and β-catenin expression between GC tissues and adjacent healthy gastric tissues were significant (P<0.001; Table II). MMP-9 expression in GC tissues was additionally predominantly cytoplasmic (Fig. 1G). Greater expression of MMP-9 was observed in GC tissues compared with adjacent healthy gastric tissues (P<0.05; Table II; Fig. 1H). In addition, expression of E-cadherin was positively associated with LNM and a more advanced clinical stage (P<0.001; Table I). β-catenin expression correlated significantly with tumor size, LNM and the clinical stage of GC tissues (P<0.001; Table I); however, there was no correlation between β-catenin expression and other clinicopathological parameters (P>0.05; Table I). Expression of MMP-9 was positively associated with LNM (P<0.001; Table I); however, there was no correlation between MMP-9 expression and other clinicopathological parameters (P>0.05; Table I).

Associations between STIM1, E-cadherin, β-catenin and MMP-9 expression in GC tissues. Potential associations between STIM1, E-cadherin and β-catenin expression patterns in GC were evaluated. Of STIM1-positive tumors, 78.4% (58/74) were E-cadherin positive and 90.5% (67/74) were positive for β-catenin. Chi-square tests revealed that STIM1 expression correlated significantly with abnormal E-cadherin expression ($\chi^2=34.555; P<0.001; \kappa=0.447$) and with abnormal β-catenin expression ($\chi^2=45.947; P<0.001; \kappa=0.486$; Table IV), whereas no correlation was observed between STIM1 and MMP-9 ($\chi^2=1.420; P=0.233; \kappa=-0.616$; Table IV). Furthermore, 79.8% (71/89) of E-cadherin-positive tumors were additionally positive for β-catenin, and this association was statistically significant (P<0.05; Table V).

Association between STIM1 expression and survival. Using Kaplan-Meier analysis, it was demonstrated that the overall survival rate was significantly reduced in patients with STIM1-expressing GC tumors compared with patients with GC tumors without STIM1 expression (P=0.043; Fig. 2). Factors that significantly correlated with patient survival rate, including STIM1 expression, LNM and a high TNM stage, were identified by univariate analysis (Table VI). Cox risk regression analysis indicated that STIM1 expression and LNM were independent prognostic factors for GC patients (Table VII).

Discussion

Various studies have demonstrated that STIM1 protein is involved in adhesion, invasion, metastasis and proliferation of cancer cells (17,18,26-29). STIM1 expression has been reported to correlate with lymphatic invasion in colon adenocarcinomas (30). Ectopic STIM1 overexpression in colorectal

### Table II. STIM1, E-cadherin, β-catenin and MMP-9 expression in GC tissues and adjacent healthy gastric tissues.

| Tissue          | STIM1  | E-cadherin | β-catenin | MMP-9  |
|-----------------|--------|------------|-----------|--------|
| GC              | Positive: 74 (43.5) | 96 (56.5) | 105 (61.8) | 65 (38.2) |
| Adjacent healthy gastric | 3 (14.4) | 32 (91.4) | 15 (12.5) | 9 (26.0) |

Data are expressed as no. (%).

$\chi^2$-test: $P<0.05$; $P<0.01$. STIM1, stromal interaction molecule 1; MMP-9, matrix metalloproteinase-9; GC, gastric cancer.
Figure 1. Immunohistochemical staining of STIM1, E-cadherin, β-catenin and MMP-9 in GC and adjacent healthy gastric tissues. STIM1 expression was detected in (A) GC tissues, but not in (B) adjacent healthy gastric tissues. E-cadherin expression was abnormal in (C) GC tissues and normal in (D) adjacent healthy gastric tissues. β-catenin expression was abnormal in (E) GC tissues and normal in (F) adjacent healthy gastric tissues. MMP-9 expression was detected in (G) GC tissues, but not in (H) adjacent healthy gastric tissues. Original magnification, x200. STIM1, stromal interaction molecule 1; MMP-9, matrix metalloproteinase-9; GC, gastric cancer.

Table III. Multivariate analysis of factors associated with stromal interaction molecule 1 expression in gastric carcinoma.

| Parameter                  | B     | SE   | Wald  | df | Sig. | Exp (B) | 95.0% CI         |
|----------------------------|-------|------|-------|----|------|---------|-----------------|
| Sex                        | 0.690 | 0.429| 2.584 | 1  | 0.108| 1.994   | 0.860 - 4.626   |
| Age                        | -0.403| 0.359| 1.256 | 1  | 0.262| 0.669   | 0.331 - 1.352   |
| Tumor location             | -0.028| 0.190| 0.023 | 1  | 0.881| 0.972   | 0.670 - 1.410   |
| Tumor differentiation      | 0.162 | 0.358| 0.205 | 1  | 0.651| 1.176   | 0.583 - 2.371   |
| Tumor size                 | -0.126| 0.361| 0.121 | 1  | 0.728| 0.882   | 0.434 - 1.790   |
| Lymphatic metastasis       | 2.171 | 0.446| 23.734| 1  | 0.000| 8.767   | 3.660 - 20.998  |
| Tumor-node-metastasis      | 0.238 | 0.411| 0.336 | 1  | 0.562| 1.269   | 0.567 - 2.840   |
| Constant                   | -2.666| 1.154| 5.335 | 1  | 0.021| 0.070   |                 |

CI, confidence interval; B, regression coefficient; SE, standard error; Wald, the statistic value of the regression; df, degree of freedom; Sig, significance; Exp (B), odds ratio.
cancer was revealed to significantly associate with tumor size, depth of invasion and LNM status, and to promote colorectal cancer cell motility (24). It has been reported that STIM1 is upregulated during hepatocarcinoma growth (31), and STIM1 has been suggested to be critical for breast cancer cell migration and metastasis (18). However, certain studies have demonstrated that STIM1 protein serves an opposing role in various cancers. For example, in vitro overexpression of STIM1 in G401 rhabdomyosarcoma cells resulted in morphological alterations and, ultimately, cell death (32,33). Suyama et al (34) revealed that STIM1 has an antimetastatic function. Weidinger et al (35) reported that patients with loss‑of‑function mutations in the STIM1 gene were immuno‑deficient and prone to developing virus‑associated tumors. The present study demonstrated that STIM1 was highly expressed in GC compared with adjacent healthy tissues, and that STIM1 expression was associated with LNM, TNM stage and poor overall survival rate. Furthermore, LNM was the only independent risk factor for STIM1 expression in GC patients. The results of the present study indicated that STIM1 may serve an important role in the initiation and development of GC, and may contribute to the diagnosis and treatment of GC as a prognostic marker. These results therefore provide novel information on the function of STIM1 in GC progression.

The molecular mechanisms underlying the effect of STIM1 on the process of EMT in GC remain to be fully elucidated. A previous study by Hu et al (19) suggested that STIM1 may be involved in EMT, which is a critical step in immune evasion
and metastasis of tumor cells. In addition, STIM1 overexpression has been reported to induce EMT in colorectal cancer cells, whereas STIM1 silencing had the opposite effect (20). Casas-Rua et al. (21) demonstrated that STIM1 phosphorylation at extracellular signal-regulated kinase 1/2 target sites mediates EMT triggered by epidermal growth factor in Ishikawa
cells. However, the role of STIM1 in cancer cell progression and metastasis and its association with EMT in GC remain to be investigated. In the present study, the association between the expression of STIM1, E-cadherin, β-catenin and MMP-9 proteins in GC tissues was analyzed by immunohistochemical staining. The results of the present study revealed that STIM1 overexpression in GC tissues correlated significantly with abnormal E-cadherin and β-catenin expression in the cytoplasm and nucleus, whereas no association was observed between STIM1 and MMP-9 expression. Therefore, STIM1 may increase GC motility and invasiveness by promoting EMT via E-cadherin and β-catenin; however, MMP-9 does not appear to be involved in this process.

In conclusion, the results of the present study demonstrated that STIM1 is significantly upregulated in GC and that STIM1 overexpression is associated with a poor prognosis in GC patients with LNM and an advanced TNM stage. Therefore, STIM1 may be a useful prognostic marker for GC.

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