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Clinical Significance of SPARC Gene Expression in Patients With Gastric Cancer

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Purpose: *Secreted protein acidic and rich in cysteine (SPARC)* is one of the first known matricellular proteins that modulates interactions between cells and extracellular matrix. Recent studies investigated the clinical significance of SPARC gene expression in the development, progression, and metastasis of cancer. The present study examined the relations of the relative expression of the SPARC gene to clinicopathological factors and overall survival in patients with gastric cancer.

Methods: We studied surgical specimens of cancer tissue and adjacent normal mucosa obtained from 227 patients with previously untreated gastric cancer. The relative expression levels of *SPARC* mRNA in cancer tissue and in adjacent normal mucosa were measured by quantitative real-time, reverse-transcription polymerase chain reaction.

Results: The relative expression level of the *SPARC* gene was higher in cancer tissue than in adjacent normal mucosa. High expression levels of the *SPARC* gene were related to serosal invasion ($P = 0.046$). Overall survival at 5 years differed significantly between patients with high *SPARC* gene expression and those with low expression ($P = 0.006$).

Conclusions: Overexpression of the *SPARC* gene may be a useful independent predictor of outcomes in patients with gastric cancer.
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KEY WORDS: SPARC; gastric cancer; prognostic factor

INTRODUCTION

Gastric cancer is the fourth most prevalent cancer worldwide and the second leading cause of cancer-related death [1]. In Japan, mortality rates may have declined because of the introduction of screening by photofluorography [2], which may have also contributed to the persistently high incidence rates in the country. The outcomes of gastric cancer have been improved recently owing to gastrectomy with D2 dissection and advances in chemotherapy [3,4]. However, recurrence rates after curative resection of advanced gastric cancer remain high, and unresectable gastric cancer still carries a poor prognosis [5,6].

Secreted protein acidic and rich in cysteine (SPARC, also known as osteonectin or BM-40) belongs to the matricellular family of proteins, which are secreted by endothelial cells. Initially discovered as a component of bone, SPARC is also expressed in epithelia with high rates of turnover [7]. SPARC is a nonstructural component of extracellular matrices that modulates cell–matrix interactions, particularly during tissue development, remodeling, and repair [8]. SPARC is expressed in many cell types, and its expression increases during embryogenesis, the development of adult bone tissue, wound healing, and tissue remodeling [7]. Recent studies have revealed other biologic functions of SPARC, including cell proliferation, migration, de-adhesion, differentiation, and angiogenesis [9]. Many types of cancers are characterized by up-regulated expression of SPARC [10]. Overexpression of SPARC in tumors and the surrounding stroma has been documented in several types of solids tumors, such as breast cancer [11], hepatocellular carcinoma [12], prostate cancer [13], colorectal cancer [14,15], ovarian cancer [16,17], gastric cancer [18], melanoma [19], and glioblastomas [20]. Recent studies have also shown that SPARC is associated with clinicopathological factors such as histological differentiation, tumor size, depth of invasion, lymph node metastasis, distant metastasis, and TNM stage [21,22].

The functions of SPARC in GC cells remain poorly understood. Yin et al. showed overexpression of the SPARC gene in human GC cell lines on quantitative RT-PCR and Western blot analysis. Wang et al. [22,23] reported that positive immunohistochemical expression of SPARC in tumor cells was related to clinicopathological factors in 43 patients with GC. Zhao et al. [21] demonstrated that high SPARC immunohistochemical expression was significantly associated with poorer 5-year survival than was low SPARC expression in 436 patients with GC.

In this study, we measured expression levels of the *SPARC* gene in paired specimens of cancer tissue and adjacent normal mucosa obtained from 227 patients with gastric cancer by quantitative RT-PCR. Our objective was to evaluate the relative expression of the *SPARC* gene and to determine whether such expression correlates with clinicopathological factors and outcomes in patients with GC.

The authors declare that they have no conflicts of interest related to the contents of this manuscript.

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MATERIALS AND METHODS

Patients and Samples

We studied surgical specimens of cancer tissue and adjacent normal mucosa obtained from 227 patients with untreated gastric cancer. The patients underwent surgery at the Department of Surgery, Yokohama City University, and at the Gastroenterological Center, Yokohama City Medical Center between 2002 and 2010. Informed consent was obtained from each patient, and the Ethics Committees of Yokohama City Medical Center and Yokohama City University approved the protocol before initiation of the study. Each tissue sample was embedded in O.C. T. compound (Sakura Finetechnical Co., Ltd., Tokyo) and immediately stored at −80°C until use. No patient had any other malignancies. Tissue specimens were stained with hematoxylin and eosin and examined histopathologically. Sections that consisted of >80% carcinoma cells were used to prepare total RNA.

Quantitative Real-Time, Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR)

Total RNA isolated from gastric cancer tissue and adjacent normal mucosa was prepared with the use of Trizol (Gibco, Life Tech, Gaithersburg, MD). Complementary DNA (cDNA) was synthesized from 2 μg of total RNA with an iScript cDNA Synthesis Kit (Bio-Rad Laboratories, Hercules, CA). After synthesis, the cDNA was diluted 1:4 with water and stored at -20°C until use. Quantitative RT-PCR was performed with iQ SYBR-Green Supermix (Bio-Rad Laboratories). PCR reactions were carried out in a total volume of 15 μl, containing cDNA derived from 75 ng of RNA, 0.27 μM of each primer, 7.5 μl of iQ SYBR-Green Supermix containing dATP, dCTP, dGTP, and dTTP at concentrations of 400 μM each, and 50 units/ml of iTag DNA polymerase. The PCR consisted of 10 min at 94°C, followed by 50 cycles of denaturation of the cDNA for 30 sec at 94°C, annealing for 30 sec at an appropriate temperature (Table I), and a primer extension for 1 min at 72°C followed by 72°C for 10 min. The PCR primer sequences of *SPARC* and *ß-actin*, used as an internal control, are shown in Table I.

Statistical Analysis

Gene expression levels of gastric cancer were compared with those of adjacent normal mucosa with the use of the Wilcoxon test. Relations between gene expression and potential explanatory variables, including age, gender, tumor size, histological type, depth of invasion, lymph node metastasis, lymphatic invasion, venous invasion, and distant metastasis, were evaluated with the χ^2 test. The postoperative survival rate was analyzed by the Kaplan–Meier method, and differences in survival rates were assessed with the log-rank test. A Cox proportional-hazards model was used to perform univariate and multivariate analyses. *P*-values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the Dr. SPSS II program, version 11.0.1J for Windows (SPSS, Inc., Chicago, IL).

TABLE I. PCR Primers and Conditions

Gene	Primer	Annealing temperature (°C)	Product size (bp)
SPARC	5′-GCTGGATGAGAACAACAC-3′ 5′-AAGAAGTGGCAGGAAGAG-3′	55.0	126
β-actin	5′-AGTTGCGTTACACCCTTTCTTGAC-3′ 5′-GCTCGCTCCAACCGACTGC-3′	60.0	171

RESULTS

Comparison of *SPARC* mRNA Expression Between Gastric Cancer Tissue and Adjacent Normal Mucosa

SPARC gene expression levels were higher in cancer tissue (8.32 ± 12.40) than in adjacent normal mucosa (3.79 ± 7.60; $P = 0.001$; Fig. 1).

Relations of *SPARC* Gene Expression Levels to Clinicopathological Features

Expression levels of the *SPARC* genes were categorized as low or high as compared with the median value. Relations between the expression of these genes and clinicopathological features were then examined. High expression levels of the *SPARC* gene were related to serosal invasion ($P = 0.046$), but not to any other clinicopathological variable (Table II).

Relations of *SPARC* Gene Expression Levels to Survival

The 5-year overall survival rate was 58.6% in the study group as a whole and was significantly higher in patients with low *SPARC* expression (70.7%) than in those with high *SPARC* expression (44.2%; $P = 0.002$ by the log-rank test; Fig. 2). The median follow-up period was 1,145 days.

Univariate and Multivariate Analyses of the Relations of Clinicopathological Factors and *SPARC* Gene Expression Levels to Outcomes

Univariate Cox regression analysis showed that male sex, serosal invasion, lymph node metastasis, lymphatic/venous invasion, distant metastasis, and *SPARC* gene expression level were related to overall survival (Table III). On multivariate Cox regression analysis, a higher level of *SPARC* gene expression was independently related to poorer 5-year overall survival ($P = 0.006$, Table IV).

DISCUSSION

In this study, we examined expression levels of *SPARC* mRNA in gastric cancer and adjacent normal mucosa. We also studied the relations

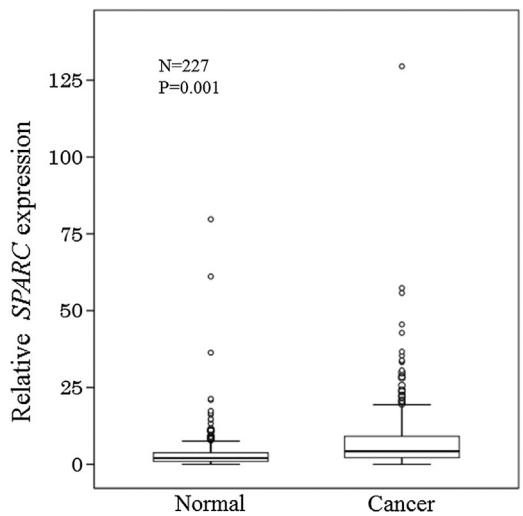

Fig. 1. Comparison of SPARC expression between gastric cancer tissue and adjacent normal mucosa. SPARC gene expression was significantly higher in cancer tissue than in adjacent normal mucosa ($P = 0.001$).

TABLE II. Relation Between *SPARC* Gene Expression and Clinicopathological Features

Variable/category	*SPARC* expression		*P*-value
	Low (n = 113)	High (n = 114)	
Age	67.9 ± 11.1	67.7 ± 9.3	0.926
Gender			
Male	78	79	1.000
Female	35	35	
Tumor size			
<6 cm	53	60	0.427
≧6 cm	60	54	
Histological type			
Differentiated	59	63	0.690
Undifferentiated	54	51	
Serosal invasion			
Absent	68	53	0.046
Present	45	61	
Lymph node metastasis			
Absent	36	29	0.307
Present	77	85	
Lymphatic invasion			
Absent	42	31	0.119
Present	71	83	
Venous invasion			
Absent	47	40	0.341
Present	66	74	
Distant metastasis			
Absent	80	80	1.000
Present	33	34	
TNM stage			
Stage I	20	10	0.248
Stage II	27	33	
Stage III	35	37	
Stage IV	31	34	

TABLE III. Univariate Analysis of Clinicopathological Factors for 5-Year Overall Survival

Variable/category	n	Hazard ratio	95% CI	*P*-value
Age				
<65	86	1		
≧65	141	1.378	0.873–2.177	0.169
Gender				
Male	157	1		
Female	70	0.429	0.245–0.751	0.003
Tumor size				
<6 cm	113	1		
>6 cm	114	1.123	0.728–1.733	0.601
Histological type				
Differentiated	122	1		
Undifferentiated	105	1.092	0.708–1.685	0.690
Serosal invasion				
Absent	121	1		
Present	106	2.759	1.751–4.347	0.001
Lymph node metastasis				
Absent	65	1		
Present	162	4.022	2.064–7.837	0.001
Lymphatic invasion				
Absent	73	1		
Present	154	3.515	1.900–6.504	0.001
Venous invasion				
Absent	87	1		
Present	140	2.606	1.544–4,399	0.001
Distant metastasis				
Absent	183	1		
Present	44	3.187	2.037–4.986	0.001
SPARC				
Low	113	1		
High	114	1.960	1.249–3.077	0.003

of the relative expression of the *SPARC* gene to clinicopathological factors and outcomes in patients with gastric cancer.

We first compared mRNA expression levels between gastric cancer tissue and adjacent normal mucosa. Previous studies reported that the expression level of *SPARC* mRNA is up-regulated in gastric cancer tissue as compared with matched normal tissue [23–25]. SPARC expression in stromal cells surrounding gastric cancer cells nests is significantly higher than that in normal mucosa tissues [22,25]. SPARC has also been reported to be overexpressed in breast cancers as well as gliomas and melanomas, suggesting its role as an oncogene [26–29]. In our study, the expression level of *SPARC* mRNA was up-regulated in gastric cancer tissues as compared with matched normal tissues.

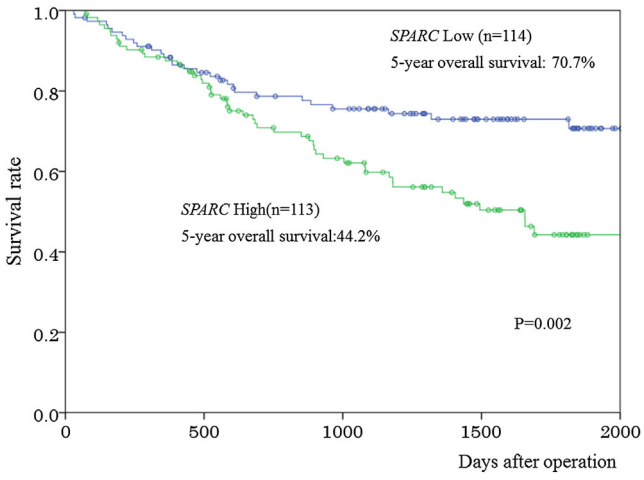

Fig. 2. Postoperative survival of patients with gastric cancer. Comparison of postoperative survival according to SPARC gene expression. In the study group as a whole, the 5-year overall survival rate was significantly higher in patients with low SPARC expression (70.7%) than in those with high SPARC expression (44.2%; $P = 0.002$).

Next, we examined whether the expression level of *SPARC* was related to clinicopathological factors. Our results showed that high expression levels of the *SPARC* gene were related to serosal invasion. Wang et al. [23] reported SPARC expression in tumor cell nests was statistically significant difference with differentiation degree, Lauren classification, lymph node metastases, and TNM stage. Zhao et al. showed that positive expression of SPARC correlated with tumor size, degree of differentiation, depth of invasion, vascular invasion, lymph node and distant metastases, and TNM stage [21,22]. On the other hand, Junnila et al. [25] found no relation between *SPARC* expression and clinicopathological features.

TABLE IV. Multivariate Analysis of Clinicopathological Factors for 5-Year Overall Survival

Variable/category	Hazard ratio	95% CI	*P*-value
Gender (male/female)	1.607	0.906–2.849	0.104
Serosal invasion (present/absent)	1.394	0.855–2.272	0.183
Lymph node metastasis (present/absent)	1.730	0.754–3.968	0.196
Lymphatic invasion (present/absent)	1.520	0.716–3.228	0.276
Venous invasion (present/absent)	1.477	0.860–2.537	0.158
Distant metastasis (present/absent)	3.797	2.380–6.058	0.001
SPARC (high/low)	1.908	1.199–3.037	0.006

We then examined the relation between *SPARC* gene expression levels and outcomes of gastric cancer. Our results showed that high *SPARC* expression was associated with poorer 5-year overall survival than was low *SPARC* expression. On univariate and multivariate Cox regression analyses, a higher *SPARC* gene expression level was a significant independent predictor of poorer 5-year overall survival in patients with gastric cancer. Our results are consistent with those of Hsiao et al. [11], who reported that positive immunohistochemical expression of SPARC significantly correlated with poor long-term survival in 286 patients with breast cancer. Chen et al. [17] also showed that high SPARC expression was associated with significantly poorer outcomes than was low SPARC expression in 140 women with ovarian cancer. Zhao et al. [21] demonstrated that high SPARC immunohistochemical expression was significantly associated with poorer 5-year survival than was low SPARC expression in 436 patients with gastric cancer. In contrast, however, Chew et al. [30] and Liang et al. [31] reported that low expression of SPARC correlates with poorer long-term survival in 120 and 114 patients with colorectal cancer, respectively.

Previous studies have suggested that SPARC plays a crucial role in tumor invasion and metastasis. SPARC is expressed in tumor cells and their surrounding stroma [22,23,32]. SPARC can bind to extracellular matrix components such as collagens, laminin, fibronectin, and vitronectin [33] and mediate cell matrix interactions. SPARC regulates cell-ECM communications that manipulate cell adhesion and migration [7]. High expression of SPARC was found in reaction stroma associated with invasive differentiated adenocarcinomas [24]. Yin et al. [34] reported that knockdown of SPARC expression by siRNA decreases proliferation and invasion in gastric cancer cell lines. Porte et al. analyzed the relative abundance of SPARC transcripts by Northern blot in normal colorectal mucosa, primary colorectal adenocarcinoma, and liver metastases. SPARC mRNA was detected in 83% of primary adenocarcinomas and 95% of liver metastases, and SPARC mRNA levels were higher in Dukes' stage B, C, D disease and liver metastases than in normal mucosa and control liver tissue. Dissemination of cancer cells, either locally or at distant metastatic sites, requires that malignant cells acquire the ability to invade the basement membrane and adhere to other matrices, suggesting that SPARC may play a key role in the initial steps of tumor invasion and metastasis [35]. Lane et al. [36] showed that SPARC mRNA and protein are synthesized by endothelial cells during angiogenesis in vivo and reported that SPARC is expressed by endothelial cells during vascular remodeling, releasing bioactive peptides that could regulate angiogenesis. Thus, SPARC appears to regulate multiple biological processes, including cell proliferation, invasion, adhesion, migration, and angiogenesis [37,38]. Further molecular investigations are required to clarify the role of SPARC as a prognostic factor and to explain its pleiotropic functions.

In conclusion, our results suggest that overexpression of the *SPARC* gene correlates with tumor invasion depth and survival in gastric cancer. Overexpression of the *SPARC* gene may thus be a useful independent predictor of outcomes in patients with gastric cancer.

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