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Zinc finger protein 139 expression in gastric cancer and its clinical significance

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Abstract

AIM: To investigate the expression of zinc finger protein 139 (ZNF139) in gastric cancer (GC), and to analyze its clinical significance.

METHODS: A total of 108 patients who were diagnosed with GC and underwent surgery between January 2005 and March 2007 were enrolled in this study. Gastric tumor specimens and paired tumor-adjacent tissues were collected and paraffin-embedded, and the clinicopathologic characteristics and prognosis were recorded. The expression of ZNF139, Bcl-2, Bax, and caspase-3 were determined by immunohistochemistry, and apoptosis was assessed by terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling. SPSS 13.0 software was used for data processing and analyses, and significance was determined at $P < 0.05$.

RESULTS: The expression of ZNF139 was stronger in tumors than in tumor-adjacent tissues (66.67% *vs* 44.44%; $P < 0.01$). Overexpression of ZNF139 correlated with tumor differentiation, invasion depth, clinical stage, lymphatic metastasis, and blood vessel invasion (all *P*s < 0.05). Patients with overexpression of ZNF139 had a poorer prognosis ($P < 0.01$), and overexpression of ZNF139 was an independent factor for the prognosis of GC patients by a Cox survival analysis ($P = 0.02$). A negative relationship between ZNF139 and the apoptosis index was observed ($r = -0.686$; $P < 0.01$). The expression of Bcl-2 in GC was stronger than in tumor-adjacent tissues (66.67% *vs* 41.67%), whereas the expression levels of Bax and caspase-3 were lower in primary tumors (54.63% and 47.22%, respectively) than in tumor-adjacent tissues (73.15% and 73.15%, respectively) (all *P*s < 0.05). The expression of ZNF139 negatively correlated with caspase-3 ($r = -0.370$; $P < 0.01$). The expressions of Bcl-2 and Bax were also negatively correlated ($r = -0.231$; $P = 0.02$). The expressions of caspase-3 and Bax protein were positively correlated ($r = 0.217$; $P = 0.024$).

CONCLUSION: ZNF139 is related to clinicopathologic characteristics and prognosis of GC. Furthermore, it is overexpressed and involved in apoptosis in GC tissues by regulating caspase-3.

Key words: Apoptosis; Clinicopathologic characteristics; Gastric cancer; Prognosis; Zinc finger protein 139

Core tip: We investigated the expression of zinc finger protein 139 (ZNF139) in gastric cancer (GC), and analyzed its clinical significance. The results show that ZNF139 is overexpressed in GC tissues, and is related to clinicopathologic characteristics and prognosis of GC. ZNF139 may be involved in apoptosis in GC tissues by regulating caspase-3.

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INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies worldwide. It is particularly prevalent in China, South Korea and Japan. Although the incidence and mortality of GC have decreased over the last several years, GC is still a leading cause of mortality in China. The development of GC is complex and involves multi-factorial, multi-targeted and multi-step processes and the mechanism has not yet been totally elucidated[1-4]. The identification of novel GC related genes is of great significance in the pathogenesis and in determining tumor markers and prognostic factors. Zinc finger protein 139 (ZNF139) is a member of the transcription factor ZNF family. It was reported that the expression of ZNF139 was increased in GC tissues[5]. In a previous study, we also found that ZNF139 was closely related to the differentiation of GC cells[6]. These results indicate that ZNF139 may be involved in the carcinogenesis and development of GC. However, to date, there are no systematic reports on the relationship between ZNF139 and GC.

The aim of this study was to investigate the relationship between ZNF139 and GC. We determined the expression of ZNF139 in GC and tumor-adjacent tissues in 108 patients, and analyzed the relationships between ZNF139 and clinicopathologic features and patient prognosis. In addition, as apoptosis plays an important role in the development of GC[7-10], we analyzed the relationship between ZNF139 and the apoptosis index (AI), as well as with expression of the apoptosis-related proteins Bcl-2, Bax and caspase-3. The involvement of ZNF139 in GC progression *via* regulation of apoptosis was explored.

MATERIALS AND METHODS

Patients

A total of 108 patients with GC admitted to The Fourth Hospital of Hebei Medical University between January 2005 and March 2007, including 79 males and 29 females, aged between 21 and 86 years (median age 61 years) were enrolled. All the patients underwent surgical treatment, and the clinical data as well as follow-up results were available. The diagnosis of GC was confirmed in all cases by surgery and pathologic examination.

Tissue preparation

Tumor and adjacent normal mucosa tissue samples (1.0 cm × 1.0 cm × 0.5 cm) were collected, fixed with 10% neutral formalin, embedded in paraffin and then cut serially into 4-μm-thick sections.

Immunohistochemical detection of ZNF139, Bcl-2, Bax and caspase-3

After antigen retrieval, the streptavidin-perosidase (SP) two-step immunohistochemical method was used to detect the expression of ZNF139, Bcl-2, Bax and caspase-3 in GC tissues and tumor-adjacent tissues, following the kit instructions. Rabbit anti-human ZNF-139 polyclonal antibody was purchased from Sigma-Aldrich (St. Louis, MO, United States), and rabbit anti-human Bcl-2, Bax and caspase-3 polyclonal antibodies were purchased from Santa Cruz Inc. (Dallas, TX, United States). The working concentration of the antibodies was 1:100. ZNF139 was positive if the cell nucleus and/or cytoplasm showed brown particles; Bcl-2, Bax and caspase-3 were positive if brown granules appeared in the cytoplasm. Five visual fields were randomly observed under a light microscope at 400 × magnification, and 100 cells were counted in each field. A secondary scoring method was used. First, the sections were scored based on the staining intensity: 0 for colorless, 1 for pale yellow, 2 for brownish yellow and 3 for tan; then positive cells were scored by percentage: 0 for < 25% positive cells, 1 for between 25% and 50% positive cells, 2 for between 51 and 75% positive cells, and 3 for > 75% positive cells. The sum of staining intensity and the percentage of positive cells was regarded as the expression level, with 0 as negative (-), 1-2 as weakly positive (+), 3-4 as positive (++), and 5-6 as strongly positive (+++).

Determination of AI with the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling assay

The terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) kit was obtained from Jiangsu Biyuntian Co. (China) and the assay was performed according to the kit instructions. Apoptosis was present if the nuclei underwent pyknosis, shrank to a round or oval shape and were brown or tan, and crescent-shaped chromosomes were observed along the nuclear membrane. Five visual fields at 400 × magnification were examined under a light microscope, and the mean percentage of apoptotic cells from 100 cells counted in each field was calculated and scored as follows: AI < 5% (-), 5%-10% (+), 10%-15% (++) and ≥ 15% (+++).

Statistical analysis

The χ^2 and Wilcoxon signed rank tests and Spearman's correlation were used to analyze the data. In the analysis of prognosis, the Kaplan-Meier method was employed to calculate survival rate, and the Cox proportional hazards regression model was used for multivariate analysis. All data were processed using SPSS 13.0 statistical software (SPSS Inc., Chicago, IL, United States). A $P < 0.05$ was considered statistically significant.

RESULTS

Expression of ZNF139, Bcl-2, Bax, and caspase-3 in GC

ZNF139 was mainly expressed in the cell nucleus and cytoplasm. Staining of positive cells in the area with tumor necrosis was strong, and a general diffuse distribution was observed (Figure 1). The positive expression rate of ZNF139 in GC tissue was 66.67% (72/108), which was significantly higher than in tumor-adjacent tissues (44.44%; 48/108) (P = 0.002). The positive expression rate of Bcl-2 protein in GC tissues was 66.67% (72/108), which was significantly higher than in tumor-adjacent tissues (41.67%; 51/108) (P < 0.001). The positive expression rate of Bax in GC tissues was 54.63% (59/108), which was significantly lower than in tumor-adjacent tissues (73.15%; 79/108) (P = 0.007). The positive expression rate of caspase-3 protein in GC tissue was 47.22% (51/108), which was significantly lower than in tumor-adjacent tissues (73.15%; 79/108) (P < 0.001).

Relationship between ZNF139 expression and clinicopathologic characteristics of GC

There were no correlations between the expression of ZNF139 and gender or age (both Ps > 0.05). The expression of ZNF139 was correlated with the degree of histologic differentiation of the tumor, invasion depth, clinical stage, lymphatic metastasis, and blood vessel invasion; ZNF139 expression was increased when the degree of tumor differentiation was reduced (P = 0.039). The positive expression rate of ZNF139 in GC stage Ⅰ-Ⅱ tissues was 48.84% (21/43), which was significantly lower than in stage Ⅲ (78.46%, 51/65) (P = 0.002). ZNF139 expression in patients with tumor invasion that was limited to stages T1/T2 (8/20) was significantly lower than in patients with tumor invasion of stages T3/T4 (72.73%; 64/88) (P = 0.008). The positive expression rate of ZNF139 in GC patients without lymph node metastasis was significantly lower than in the patients with lymph node metastasis (P = 0.005) (Table 1).

Significance of ZNF139 expression in the prognosis of GC

Kaplan-Meier analysis was used to analyze the relationship between ZNF139 expression and prognosis, and the survival curve is shown in Figure 2. Survival rate in patients with positive expression of ZNF139 was lower than in patients with negative expression (P < 0.001). To determine the independent risk factors affecting the prognosis of GC, Cox risk regression analysis was performed using eight indicators as follows: ZNF139 expression, gender, age, degree of tumor differentiation, clinical stage, depth of tumor invasion, lymph node metastasis, and neurovascular invasion. The results show that positive ZNF139 expression, lymph node metastasis, neurovascular invasion and clinical stage are independent risk factors affecting the prognosis of patients with GC (all Ps < 0.05) (Table 2).

Relationship between ZNF139 expression and AI of GC cells

Spearman correlation analysis was used to evaluate the AI and ZNF139 expression in GC, and the results show that the AI is negatively correlated with ZNF139 expression (r = -0.686; P < 0.001) (Figure 3).

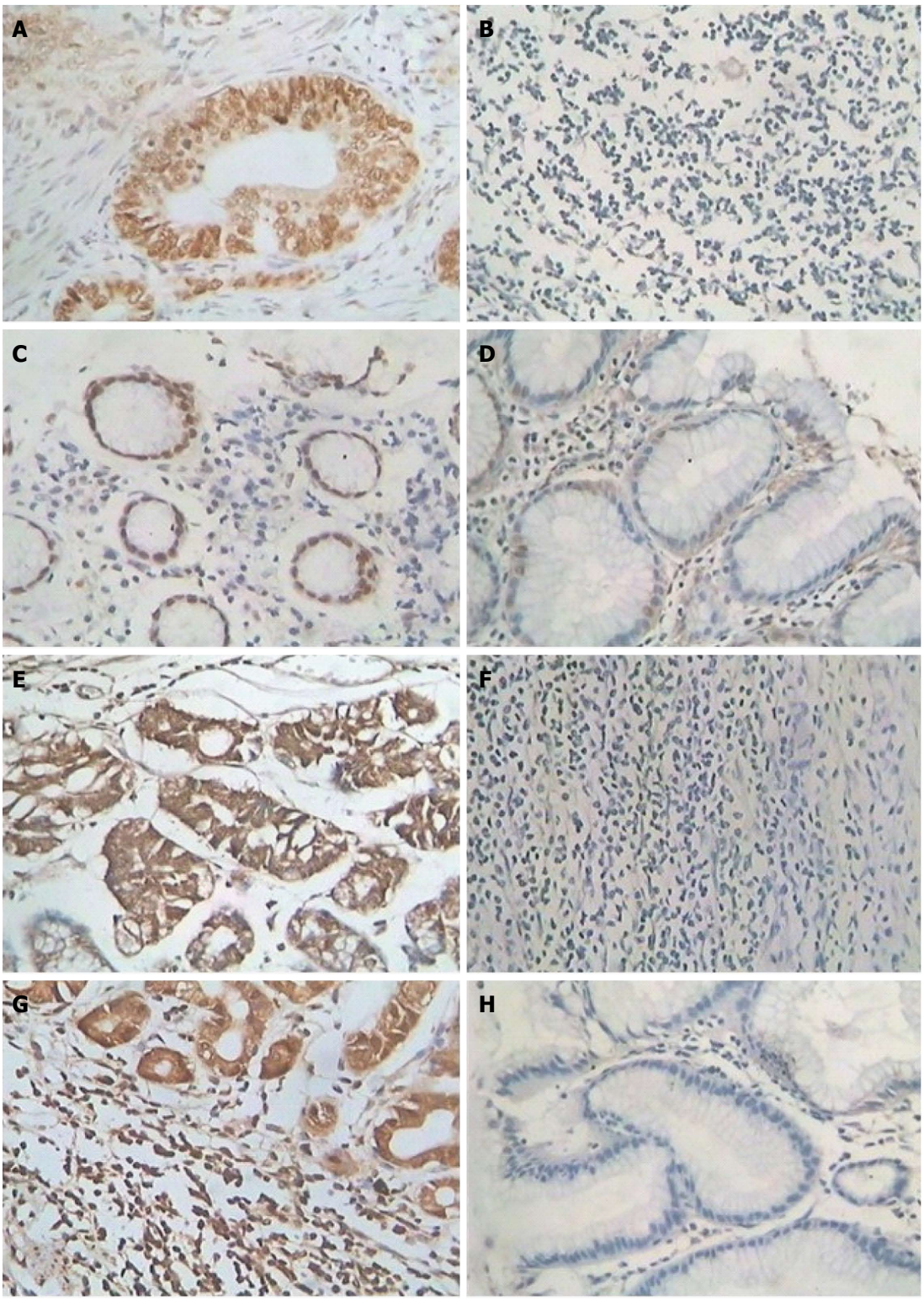
Relationship between expression of ZNF139 and Bcl-2, Bax, and caspase-3 in GC

Spearman correlation analysis show that ZNF139 protein expression is negatively correlated with caspase-3 expression (r = -0.370; P < 0.001), and not correlated with Bcl-2 or Bax. The expressions of Bcl-2 and Bax protein were negatively correlated (r = -0.231; P = 0.016). In addition, the expressions of caspase-3 and Bax protein were positively correlated (r = 0.217; P = 0.024), and caspase-3 showed no significant correlation with Bcl-2 protein.

DISCUSSION

The C terminus of proteins in the zinc finger family contains a C_2H_2 zinc finger motif that can be specifically bound to the regulatory region of target genes or proteins; SCAN and KRAB domains contained in the N terminus can regulate target genes or protein activity by combining the auxiliary effectors[11-14]. Several studies have recently found that many members of the zinc finger protein family are involved in carcinogenesis and the development of tumors. Therefore, research on the transcriptional regulatory function of zinc finger proteins has attracted more attention and has become a research hot spot[15-17]. The ZNF139 gene, located on chromosome 7q21.3-q22.1, was discovered in 1995 and might be involved in gene rearrangement in malignancies in the hematologic system, and absence of its expression is closely related to congenital split-hand/split-foot malformation[11,18]. van Dekken *et al*[5] found that ZNF139 expression was strongly positive in adenocarcinoma tissues at the gastroesophageal junction, and the expression was also high in normal gastric mucosa of adjacent cancer tissues at proliferation, which suggest that it may possibly participate in the genesis of GC through cell cycle regulation. In our previous study, we found that expression of ZNF139 was closely related to GC, suggesting that ZNF139 might be involved in gastric carcinogenesis and development[6]. Another previous study showed that ZNF139 was involved in GC multidrug resistance by simultaneously promoting the expression of MDR1/P-gp, MRP1 and Bcl-2 and inhibiting Bax[19]. The present study shows that ZNF139 expression in GC tissues is significantly higher than in tumor-adjacent tissues, which indicates that ZNF139 may be involved in gastric carcinogenesis and development. Thus, further studies on ZNF139 may help to elucidate the pathogenesis of GC.

In present study, we analyzed the relationship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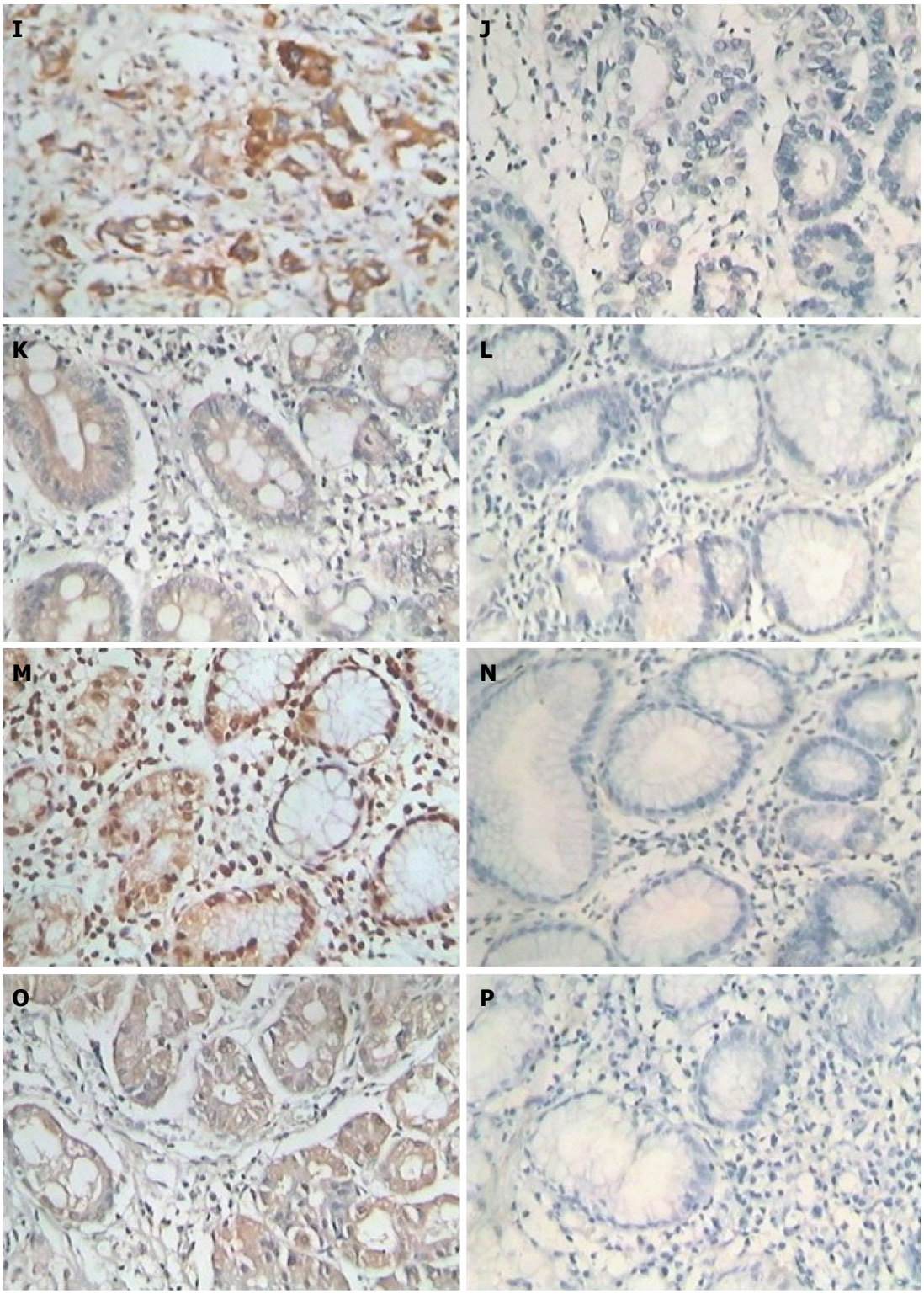

Figure 1 Immunohistochemistry for zinc finger protein 139, Bcl-2, Bax and caspase-3 in gastric cancer and tumor-adjacent tissues. A: Positive ZNF139 expression in GC; B: Negative ZNF139 expression in GC; C: Positive ZNF139 expression in tumor-adjacent tissues; D: Negative ZNF139 expression in tumor-adjacent tissues; E: Positive Bcl-2 expression in GC; F: Negative Bcl-2 expression in GC; G: Positive Bcl-2 expression in tumor-adjacent tissues; H: Negative Bcl-2 expression in tumor-adjacent tissues; I: Positive Bax expression in GC; J: Negative Bax expression in GC; K: Positive Bax expression in tumor-adjacent tissues; L: Negative Bax expression in tumor-adjacent tissues; M: Positive caspase-3 expression in GC; N: Negative caspase-3 expression in GC; O: Positive caspase-3 expression in tumor-adjacent tissues; P: Negative caspase-3 expression in tumor-adjacent tissues; (magnification × 400). ZNF139: Zinc finger protein 139; GC: Gastric cancer.

between the expression of ZNF139 in GC tissues and clinicopathologic features in patients. It was found that ZNF139 protein expression in GC was closely related to the degree of histologic differentiation, clinical stage, depth of invasion, lymph node metastasis, and neurovascular invasion. That is, the lower the degree

Table 1 Zinc finger protein 139 expression in 108 gastric carcinoma patients according to clinicopathologic features

Clinical feature	Zinc finger protein 139		*P* value
	Positive (*n*)	Negative (*n*)	
Sex			0.655
Male	53	25	
Female	19	11	
Age (yr)			0.539
⩾ 60	43	19	
< 60	29	17	
Tumor differentiation			0.039
High/moderate	39	27	
Poor/undifferentiated	33	9	
Depth of invasion			0.008
T1/T2	8	12	
T3/T4	64	24	
Lymphatic metastasis			0.005
Positive	53	16	
Negative	19	20	
Nerve or blood vessel invasion			0.033
Invaded	29	7	
Not invaded	43	29	
Tumor-node-metastasis stage			0.002
Ⅰ-Ⅱ	21	22	
Ⅲ	51	14	

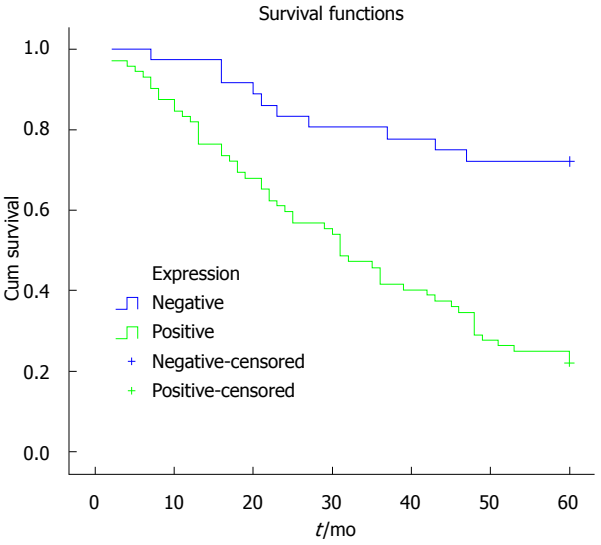

Figure 2 Kaplan-Meier survival curves of 108 patients with gastric cancer in relation to zinc finger protein 139 expression.

of tumor differentiation, the later the clinical stage, the deeper the invasion. In addition, lymph node metastases and neurovascular invasion contributed to higher ZNF139 expression, indicating that ZNF139 is related to the development of GC and the degree of malignancy; this gene was further enhanced during tumor progression and might contribute to the progress of GC. The prognostic analysis showed that the five-year survival rate in patients with positive ZNF139 expression was significantly lower than in patients with negative expression, and ZNF139 was an independent risk factor affecting the prognosis of GC patients. These results show that ZNF139 may play an important role as an

Table 2 Results of Cox risk analysis model of gastric cancer

	B	SE	Wald	*df*	*P* value	Exp(B)	95%CI for Exp(B)	
							Lower	Upper
ZNF139 expression	0.822	0.353	5.414	1	0.02	2.276	1.138	4.551
Lymphatic metastasis	1.396	0.645	4.679	1	0.031	4.038	1.14	14.301
Neurovascular invasion	0.573	0.257	4.965	1	0.026	1.774	1.072	2.939
TNM stage	1.155	0.554	4.351	1	0.037	3.175	1.072	9.401

TNM: Tumor node metastasis; ZNF139: Zinc finger protein 139.

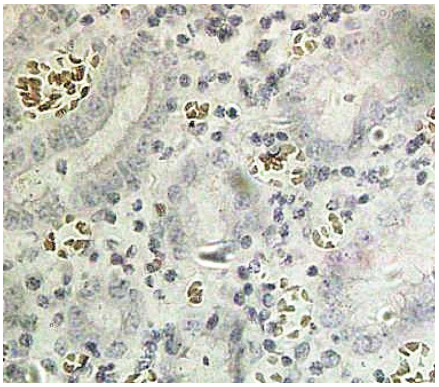

Figure 3 Apoptosis of gastric cancer cells. Photomicrograph showing terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling in gastric cancer cells (× 400).

oncogene in the development of GC, and may contribute to the diagnosis and treatment of GC as a new tumor marker and a predictor of prognosis.

To determine the mechanisms of ZNF139's involvement in GC progression, we analyzed the relationship between ZNF139 and tumor cell apoptosis. Apoptosis of tumor cells can be assessed using the TUNEL assay to calculate the AI[20,21], a method used in the present study to examine the relationship between ZNF139 expression and apoptosis. The results show that ZNF139 protein is negatively correlated with the AI, suggesting that positive ZNF139 expression may inhibit tumor cell apoptosis. Further investigation demonstrated that ZNF139 expression is negatively correlated with the apoptosis-related protein caspase-3, but not with Bcl-2 or Bax. Bcl-2 and Bax are important genes in the regulation of tumor cell apoptosis through a mitochondrial pathway, whereas activation of caspase-3 can directly promote apoptosis[22-27]. These results suggest that ZNF139, as a nuclear transcription factor, may directly regulate the expression and inhibit activity of caspase-3, thus prevent apoptosis and contribute to the progression of GC. However, the exact mechanism requires further study.

This study shows that ZNF139 is upregulated in GC and related to some of the clinicopathologic features, and thus may be involved in gastric carcinogenesis and progression. ZNF139 may be used as a prognostic

factor as GC patients with strong ZNF139 expression had a poor prognosis. These effects of ZNF139 may be related to the regulation of caspase-3 expression, and thus participate in the regulation of apoptosis in GC. However, identification of the detailed mechanisms of ZNF139 in GC cells requires further investigation. Our findings suggest that ZNF139 may play an important role as an oncogene in the development of GC and further research on ZNF139 may lead to clarification of the development of GC and thus treatment.

COMMENTS

Background

Previous research showed that zinc finger protein 139 (ZNF139) was overexpressed in gastric cancer (GC) cells, which was related to the differentiation of GC. However, there is no research on the relationship between ZNF139 and the clinicopathologic characteristics and prognosis of GC.

Research frontiers

A number of oncogenes are involved in the carcinogenesis and development of GC, and, to date, researchers have not identified an oncogene that could be a prognostic factor. In the present study, the clinical value of ZNF139 in GC was explored.

Innovations and breakthroughs

There are many reports on the effect of new genes in GC. In the present study, authors found that ZNF139 was closely related to the clinicopathologic characteristics and prognosis of GC, thus, ZNF139 may play an important role in GC.

Applications

ZNF139 can be used as a tumor marker and prognostic factor to evaluate the prognosis of patients with GC. In addition, ZNF139 may regulate apoptosis of GC cells, and the *ZNF139* gene may be a target in gene therapy of GC.

Terminology

A zinc finger is a small structural protein motif that is characterized by the coordination of one or more zinc ions in order to stabilize the fold. Originally coined to describe the finger-like appearance of a hypothesized structure from *Xenopus laevis* transcription factor IIIA, the zinc finger has been found in a wide variety of different protein structures. Immunohistochemistry refers to the process of detecting antigens (*i.e.*, proteins) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biologic tissues. The apoptosis index describes the proportion of apoptotic cells in the total cell population.

Peer review

In this study, the relationships between ZNF139 and the clinicopathologic characteristics and prognosis of GC were investigated. The authors propose that ZNF139 may regulate apoptosis of GC cells by regulating caspase-3. It is a new discovery regarding the mechanism of carcinogenesis and development of GC. Tests evaluating ZNF139 may be applied to evaluate the prognosis of GC patients.

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