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RESEARCH

Abnormal Expression of Adhesion Protein Bves is Associated with Gastric Cancer Progression and Poor Survival

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Abstract Although many molecular and biological studies have shown risk factors for gastric cancer, the available knowledge is still insufficient to unveil the exact mechanism of gastric cancer. To investigate the relationships between Bves expression and the clinicopathologic features of gastric cancer and whether Bves can act as prognostic indicators in gastric cancer. Tissues were obtained from the gastrectomy specimens of 306 human gastric cancer and 78 noncancerous gastric tissue at the Department of Surgery and Pathology, the Second Affiliated Hospital of Kunming Medical University from February 1996 to March 2007. The method of immunohistochemistry was used to investigate the expression of Bves in them. The relationship between Bves expression and the survival times of the patients was retrospectively analysed. Reduced expression of Bves frequently occurred in gastric cancer tissue. Low expression of Bves correlated with histologic differentiation, depth of invasion, regional lymph nodes and distant metastasis, and TNM stages ($P<0.05$). Bves expression did not correlate with age, gender, location of tumor, size of tumor and histologic type ($P>0.05$); Further multivariate analysis revealed that lymph node metastasis ($P<0.0001$), distant metastasis ($P<0.0001$), surgical treatment ($P<0.0001$), and the expression of Bves ($P<0.0001$) were independent prognostic factors in patients with gastric cancer; The Kaplan-Meier plot showed that survival times of patients with low Bves expression was significantly lower than those in patients with high Bves expression. Besides, low Bves expression had a much more significant effect on the survival of those patients with early stage tumors ($\chi 2=131.216, P<0.0001$), highlighted by a >51.3% reduction in 3-year survival compared with that of patients with high Bves expression. In late stages, the difference was also significant ($\chi 2=5.818, P=0.016$), with a 34.8% reduction in 3-year survival. Reduced expression of Bves in gastric cancer is associated with tumor progression and the patient's poor survival. This study showed that the studied protein has further provided a basis for the development of potential biomarker for gastric cancer prognosis.

Keywords Gastric cancer · Bves · Cell adhesion molecules · Metastasis · Prognosis

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Introduction

According to NCCN Clinical Practice Guidelines in 2010, the incidence of gastric cancer has been declining globally since World War II [1]. By some estimates, it is the fourth most common cancer after lung, breast, and colorectal cancer and the second leading cause of cancer-related deaths. In 2009, 21,130 new diagnoses of gastric cancer were estimated in the United States and 10,620 deaths expected [2]. Although a marked decrease in gastric cancer mortality rate world widely, there is a higher prevalence of gastric cancer in the China than in other countries [3]. Undoubtedly, the problem of gastric cancer has become a

key public health issue in China [4]. In contrast to the incidence trends in the West, more new cases are diagnosed each year in China [5–8]. However, gastric cancer is often diagnosed at an advanced stage.

The Popeye domain containing (popdc) gene family consists of Bves, Popdc2 and Popdc3, of which Bves is the prototypical member. It was discovered in 1999 by two independent laboratories using screens to identify novel genes that were highly expressed in the developing heart [9, 10]. Work by many researchers has illuminated that Bves is highly conserved and has been identified in a wide variety of vertebrate and invertebrates [11, 12]. Further studies identified that both mRNA and protein of Bves are highly expressed in striated and smooth muscle and in various forms of epithelial cell types in the embryo and adult [13, 14]. Given the definitive role Bves plays in cell-cell adhesion and in maintaining epithelial integrity, it is highly expected that loss of Bves function could result in abnormal cell behavior and disease [15–17]. However, although several studies have shown that abnormal expression of Bves might play important roles in the process of tumorigenesis including lung cancer [18], gastric cancer [19] and uveal melanoma [20], its biochemical mechanism and potential function in cancer is unknown.

The present study was carried out to investigate the alterations in the expression of Bves in surgical specimens of gastric cancer, to explore the possible correlation between Bves expression and clinicopathologic variables, to correlate expression of Bves with lymph node metastasis and distant metastasis. In addition, we also analyzed the prognostic significance of Bves expression and assessed the impact of expression of the studied protein on patients survival.

Methodology

Patients and Tissue Samples

Gastric cancer tissues were collected from gastrectomy specimens of 306 patients (median age, 58.2 y; range, 27–96 y; 199 male, 107 female) from the Department of Surgery and Pathology, the Second Affiliated Hospital of Kunming Medical University from February 1996 to March 2007. Seventy-eight noncancerous human gastric tissues were obtained from gastrectomies of adjacent gastric cancer margins greater than 5 cm. All tissue samples were approved by the hospital's ethics committee and they were arranged in tissue array blocks. Tissue had been formalin-fixed, paraffin-embedded, and clinically and histopathologically diagnosed at the Departments of Gastrointestinal Surgery and Pathology. All patients had follow-up records for over 5 y. The follow-up deadline was April 2011. The survival time was counted from the date of surgery to the follow-up deadline or date of death, which was mostly caused by recurrence or metastasis. There were 19, 124, and 163 cases from the cardia, body, and antrum, respectively. According to TNM-7th edition 2009 (UICC/AJCC) and Japanese Classification 2010 in Gastric Cancer [21, 22], there were 8 papillary adenocarcinomas, 209 tubular adenocarcinomas, 52 mucinous adenocarcinomas, 37 signet ring cell carcinomas, and 17 highly differentiated adenocarcinomas; 100 were classified as well or moderately differentiated adenocarcinomas, 185 as poorly differentiated adenocarcinomas, and 4 as undifferentiated adenocarcinomas. Seventy-three cases were categorized as stage I, 109 were stage II, 92 were stage III, and 32 were stage IV. In total, 216 patients (70.6%) underwent a potentially curative resection (R0 resection), 74 patients (24.2%) had residual microscopic disease (R1 resection), and 16 patients (5.2%) had residual macroscopic disease (R2 resection). Nineteen patients (15.3%) with advanced stage disease after operation received postoperative chemotherapy but no radiation treatment was administered to any of the patients included in our study.

Immunohistochemistry

Immunohistochemical analysis was undertaken to study altered protein expression in 78 noncancerous human gastric tissue controls and 306 human gastric cancer tissues. According to protocol for immunohistochemistry on paraffin-embedded tissue sections, slides were baked at 60°C for 2 h followed by deparaffinization with xylene and rehydrated. The sections were submerged into EDTA antigenic retrieval buffer and microwaved for antigenic retrieval, after which they were treated with 3% hydrogen peroxide in methanol to block endogenous peroxidase activity, followed by incubation with 1% bovine serum albumin to block nonspecific binding. Sections were incubated with Rabbit anti-Bves Polyclonal Antibody (ProteinTech Group, Chicago IL) overnight at 4°C. Normal goat serum was used as a negative control. After rinsing 2× 5 min with TBST, tissue sections were treated with secondary antibody in TBS for 1 h at room temperature. Develop with chromogen (DAB) at room temperature, watching under microscope. After that, all tissue sections were then counterstained with hematoxylin, were dehydrated, and were mounted. The cell membrane and cytoplasm with Bves was stained as buffy, whereas weak expression was associated with stroma .

Assessment of Bves Staining in the Tissue Sections

The degree of immunostaining was reviewed and scored independently by at least two observers based on the

proportion of positively stained tumor cells and intensity of staining. Tumor cell proportion was scored as follows: 0 (≤5% positive tumor cells), 1 (6–25% positive tumor cells), 2 (26–50% positive tumor cells), and 3 (>51% positive tumor cells). Staining intensity was graded according to the following criteria: 0 (no staining), 1 (weak staining, light yellow), 2 (moderate staining, yellow brown), and 3 (strong staining, brown). Staining index was calculated as the product of staining intensity score and the proportion of positive tumor cells. Using this method of assessment, we evaluated Bves expression in benign gastric epithelia and malignant lesions by determining the staining index with scores of 0, 1, 2, 3, 4, 6, or 9. The cutoff value for high and low expression level was chosen based on a measure of heterogeneity using the log-rank test with respect to overall survival. An optimal cutoff value was identified as follows: a staining index score of ≥4 was used to define tumors with high Bves expression, and a staining index score of ≤3 was used to indicate low expression.

Statistical Analysis

All statistical analyses were done using the SPSS17.0 software. Measurement data were analyzed using the Student's *t* test, whereas categorical data were studied using $\chi 2$ or Fisher exact tests. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test was used to compute differences between the curves. Multivariate analysis using the Cox proportional hazards regression model was done to assess the prognostic values of protein expression. Correlation coefficients between protein expression and clinicopathologic findings were estimated using the Pearson correlation method. Statistical significance was set at $P<0.05$.

Results

Expression of Bves in Gastric Cancer and Clinicopathologic Features

Bves was detected in 63 (80.77%) of 78 human nontumor mucosa. High expression of Bves protein was detected in 109(35.62%) of 306 human gastric cancer cases, and low expression was detected in 197 (64.38%). Bves staining was detected in the majority of normal cells, especially in membrane and cytoplasm. We also found Bves expression in intestinal metaplasia. However, Bves was mainly localized in the cytoplasm of primary cancer. The differences of Bves expression between gastric cancer and noncancerous mucosa were also statistically significant

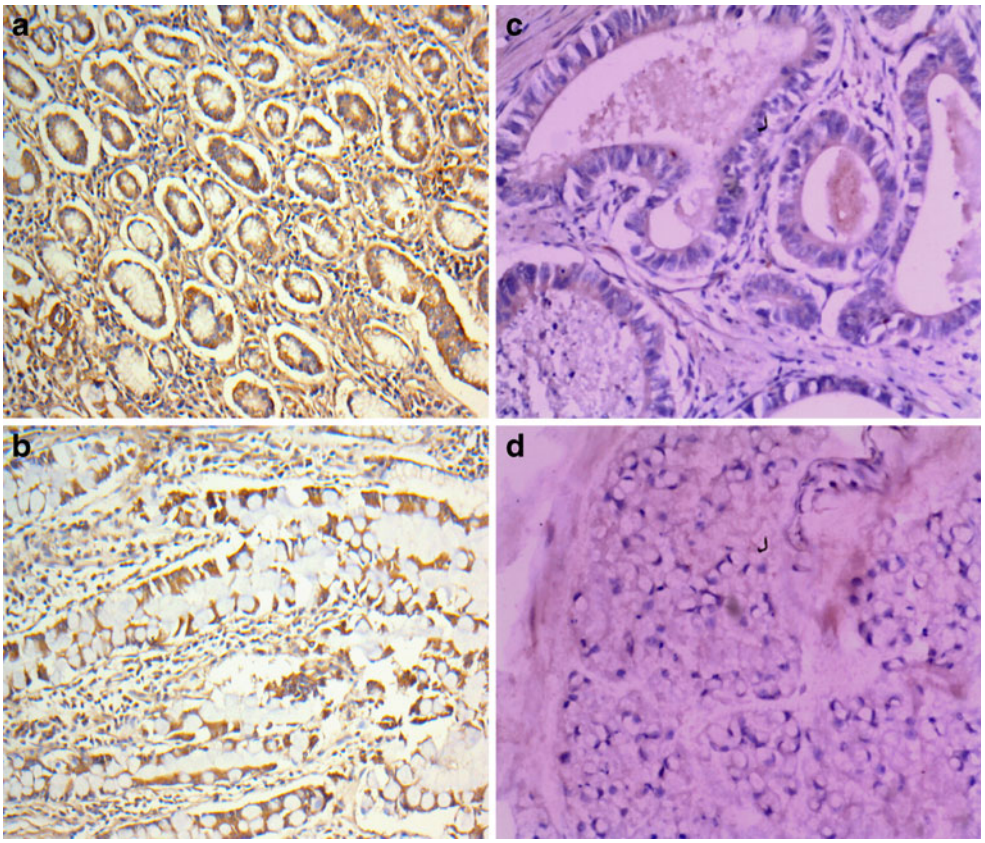

Fig. 1 Reduced expression of Bves frequently occured in gastric cancer tissue

($\chi 2=51.235$, $P<0.0001$; Fig. 1). Low expression of Bves correlated with histologic differentiation, depth of invasion, regional lymph nodes and distant metastasis, and TNM stages ($P<0.05$). Bves expression did not correlate with age, gender, location of tumor, size of tumor and histologic type ($P>0.05$). (Table 1).

Table 1 Relationship of Bves expression with pathologic parameters of gastric cancer

Clinical parameters	n	Bves		X^2	P
		Low	High		
Age					
<50	105	61(58.1%)	44(41.9%)		
≥50	201	136(67.7%)	65(32.3%)	2.752	0.097
Gender					
Male	199	128(64.3%)	71(35.7%)		
Female	107	69(64.5%)	38(35.5%)	0.001	0.977
Location					
Proximal	19	13(68.4%)	6(31.6%)		
Middle	124	80(64.5%)	44(35.5%)		
Distal	163	104(63.8%)	59(36.2%)	0.160	0.923
Size					
<5 cm	154	104(67.5%)	50(32.5%)		
≥5 cm	152	93(61.2%)	59(38.8%)	1.344	0.246
Histology					
Papillary adenocarcinoma	8	4(50%)	4(50%)		
Tubular adenocarcinoma	209	127(60.8%)	82(39.2%)		
Mucinous adenocarcinoma	52	37(71.2%)	15(28.8%)		
Signet ring cell carcinoma	37	29(78.4%)	8(21.6%)	6.116	0.106
Histologic differentiation					
Well	17	9(52.9%)	8(47.1%)		
Moderately	100	52(52%)	48(48%)		
Poorly	185	134(72.4%)	51(27.6%)		
Others	4	4(100%)	0(0%)	12.386	0.002
Invasion depth					
T1	24	3(12.5%)	21(87.5%)		
T2	63	27(42.9%)	36(57.1%)		
T3	181	131(72.4%)	50(27.6%)		
T4a	30	2(6.7%)	28(93.3%)		
T4b	8	2(25.0%)	6(75.0%)	61.211	<0.0001
Regional lymph nodes					
N0	163	63(38.7%)	100(61.3%)		
N1	41	39(95.1%)	2(4.9%)		
N2	54	50(92.6%)	4(7.4%)		
N3a	19	12(63.2%)	7(36.8%)		
N3b	28	17(60.7%)	11(39.3%)	100.767	<0.0001
Distant metastasis					
M0	274	167(60.9%)	107(39.1%)		
M1	32	30(93.8%)	2(6.2%)	13.433	<0.0001
TNM stages					
I	73	17(23.3%)	56(76.7%)		
II	109	65(59.6%)	44(40.4%)		
III	92	85(92.4%)	7(7.6%)		
IV	32	30(93.8%)	2(6.3%)	98.577	<0.0001

Correlation between Bves Expression and Patient Prognosis

The factors with possible prognostic effects in gastric carcinoma were analyzed by Cox regression analysis. The following 9 criteria were selected for evaluation: the patient's age, histologic type, histologic differentiation, depth of invasion, lymph node metastasis, distant metastasis, surgical resection, adjuvant chemotherapy and Bves expression (at least factors with an univariate $p<0.2$ have been included in Cox regression analysis). Invasion depth and distant metastases are the components of TNM staging. Therefore, TNM staging could be omitted from the multivariate analysis. The study revealed that lymph node metastasis ($P<0.0001$), distant metastasis ($P<0.0001$), surgical treatment ($P<0.0001$), and the expression of Bves ($P<0.0001$) were independent prognostic factors in patients with gastric carcinoma. However, the patient's age, histologic type, histologic differentiation, invasion depth, and adjuvant chemotherapy had no prognostic value (Table 2).

The Kaplan-Meier plot showed that survival times of patients with low Bves expression was significantly lower than those in patients with high Bves expression. The survival estimates showed a dramatical difference in median survival between the high and low Bves expression: the former averaged 55 months (95% confidence interval 52.34–57.66), whereas the latter 21 months (95% confidence interval 19.17–22.83). For patients with low Bves protein expression, 1,3-y survival rate was 78.68%,12.18%, respectively, that was significantly lower than in patients with high Bves expression 81.65%,73.4%, respectively ($\chi 2=178.269$,$P<0.0001$). From this result, we concluded that decreased expression of Bves is a prognostic indicator of poor survival for patients with gastric cancer (Fig. 2 and Table 3). Additionally, we further compared the survival times between the patients who differed in Bves expression respectively in early TNM stage (stages I and II) or late stages (stages III and IV). The results showed that low Bves expression had a much more significant effect on the survival of those patients with early stage tumors ($\chi 2=131.216$,$P<0.0001$), highlighted by a >51.3% reduction in 3-year survival compared with that of patients with high Bves expression. In late stages, the difference was also significant ($\chi 2=5.818$, $P=0.016$), with a 34.8% reduction in 3-year survival. More importantly, these data suggested Bves expression as an independent prognostic variable for gastric cancer in early stage and late stage (Table 3).

Table 2 Multivariate analysis for disease-related deaths (Cox regression model)

Variables	*P* value
Age (years) (<50 vs. ≥50)	0.752
Histologic type	0.956
Histologic differentiation	0.072
Invasion depth	0.608
Lymph node metastasis	<0.0001
Distant metastasis (No vs. Yes)	<0.0001
R classification (R0 1 vs. R1-2)	<0.0001
Adjuvant chemotherapy (No vs. Yes)	0.711
Bves expression (Low vs. High)	<0.0001

Discussion

Several studies have identified a correlation between Bves expression and tumorigenesis or high metastatic potential in non-small cell lung cancer(NSCLC), gastric cancer and uveal melanoma. Feng et al. [18] used MethyLight assays to analyze DNA methylation status of 27 genes on 49 paired cancerous and noncancerous tissue samples from NSCLC patients who underwent surgical resection. They found that Bves were found to be methylated significantly more frequently in tumor tissues than in noncancerous tissues. Methylation of BVES was present in 80% of NSCLC tissues but only in 14% of noncancerous tissues. And this is the first report of a modification of Bves in cancer.

After that, Kim et al. [19] carried out the first detailed investigation and determined that frequent silencing of BVES was associated with promoter hypermethylation in gastric cancer. Their research revealed that expression of BVES was down regulated in 73% of the gastric cancer cell

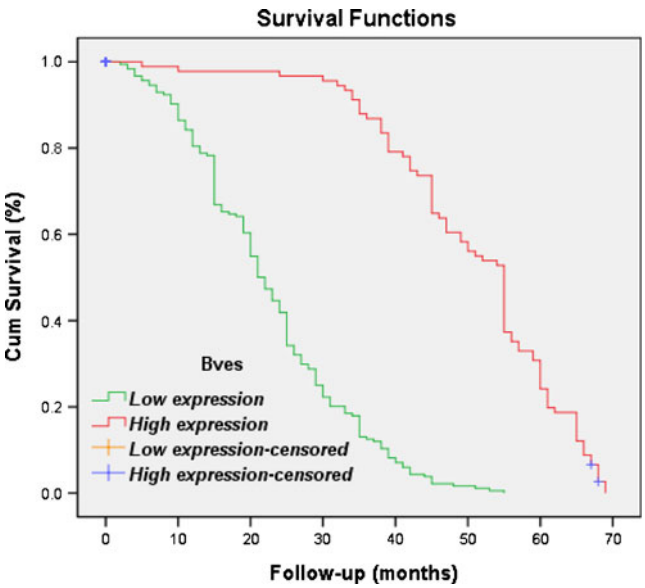

Fig. 2 Survival times of low Bves expression was significantly lower than those in patients with high Bves expression in gastric caner

Table 3 Survival estimates (and 95% confidence intervals) for disease-related deaths

Group	Median survial(months)	1-year survival rate	3-year survival rate	Chi-Square	P
Low	21.00(19.17–22.83)	155(78.68%)	24(12.18%)		
High	55.00(52.34–57.66)	89(81.65%)	80(73.4%)	178.269	<0.0001
Stage I–II and Low	27.5(22.00–35.00)	78(95.12%)	26(31.7%)		
Stage I–II and High	51.5(23.00–59.00)	84(84%)	83(83%)	131.216	<0.0001
Stage III–IV and Low	15.00(10.00–21.00)	78(67.83%)	11(9.6%)		
Stage III–IV and High	30.00(2.50–39.50)	7(77.78%)	4(44.4%)	5.818	0.016

lines and in 69% of the gastric cancer tissues. Besides, they also found that combined treatment with a DNA methylation inhibitor and a histone deacetylase inhibitor strongly induced BVES expression. Therefore, it concluded that epigenetic inactivation of BVES occurred frequently in gastric tumors and might promote gastric cancer cell migration and invasion. The study is similar to our result. However, they could not clarify the clinical impact of Bves expression or the prognostic value for gastric cancer because the number of gastric cancer patients was too small. Thus, our study is the first report to determine the correlation between Bves expression and clinical and prognostic factors in gastric cancer.

The current study clearly demonstrated that Bves were apparently down regulated in gastric cancer tissues in comparison with those in normal gastric tissues. Low levels of Bves protein were found to closely correlate with the prognosis of gastric cancer. The data revealed that decreased level of Bves protein expression in gastric cancer lesions is mainly associated with histologic differentiation, depth of invasion, regional lymph nodes and distant metastasis, and TNM stages. Further multivariate analysis revealed that lymph node metastasis, distant metastasis, surgical treatment(R classification), and the expression of Bves were independent prognostic factors for the disease. Additionally, the Kaplan-Meier plot showed that for patients with low Bves protein expression, 1 and 3 year survival were 78.6% and 12.2% respectively, that was significantly lower than in patients with high Bves expression 81.65%, 73.4%, respectively. Further compared the survival times between the patients who differed in Bves expression respectively in early TNM stage (stages I and II) or late stages (stages III and IV) showed that low Bves expression had a much more significant effect on the survival of those patients with early stage tumors, highlighted by a >51.3% reduction in 3-year survival compared with that of patients with high Bves expression. In late stages, the difference was also significant, with a 34.8% reduction in 3-year survival. All these data suggested Bves expression as an independent prognostic variable for gastric cancer in early stage and late stage.

By and large, our study suggests that degradation of Bves is a common feature in gastric cancer that might play an important role in the progression and metastases of gastric cancer. These data are consistent with the idea that critical changes in metastatic potential may be determined early during the development of cancer . Additionally, our study also identified down regulation of Bves in gastric cancer, including an assessment of Bves expressions in gastric cancer tissues and noncancerous gastric tissues. The importance of Bves reduction in gastric cancer are further highlighted by our results that correlate the pathologic parameters of tumors with a poorer patient prognosis.

Nevertheless, Jayagopal al. [20] recently observed that Bves over expression in uveal melanoma increased expression of the tight junction(TJ) proteins occludin and ZO-1, reduced cell proliferation, and increased sequestration of ZONAB at TJs and reduced ZONAB transcriptional activity. A further insight into the interaction of Bves with other signaling pathways may reveal other distinct roles for this protein in tumor cell migration, extravasation, and survival[23, 24]. Thus, it is of great importance to investigate a potential diagnostic and therapeutic value for Bves.

In summary, the potentially important consequence of our work is that Bves may be an attractive therapeutic candidate for gastric cancer, because reduced Bves expression is predictive of outcome in early stage disease, it may also be a feasible target for earlier intervention and treatment. In this light, routine detection of methylation of this gene in blood might have utility in monitoring and detecting tumor recurrence in early-stage gastric cancer after curative surgical resection. Thus, we believe that the studied protein has further provided a basis for the development of potential biomarker for the diagnosis and candidate for molecular-targeted therapeutics of gastric cancer.

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Conflict of Interest None.

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