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RESEARCH ARTICLE

High expressions of galectin-1 and VEGF are associated with poor prognosis in gastric cancer patients

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Abstract High expressions of galectin-1 and vascular endothelial growth factor (VEGF) are correlated with biological behavior in some cancers. The aim of this study is to evaluate the expressions of galectin-1 and VEGF in gastric cancer and investigate their relationships with clinicopathological factors and prognostic significance. Immunohistochemical analyses for galectin-1 and VEGF expression were performed on 108 cases of gastric cancer. The relationship between the expression and staining intensity of galectin-1 and VEGF, clinicopathological variables, and survival rates was analyzed. Immunohistochemical staining demonstrated that 68 of 108 gastric cancer samples (63.0 %) were positive for galectin-1 and 62 out of 108 gastric cancer samples (57.4 %) were positive for VEGF. Galectin-1 expression was associated with tumor size, differentiation grade, TNM stage, lymph node metastases, and VEGF expression. VEGF expression was related to tumor size, TNM stage, and lymph node metastases. Kaplan–Meier survival analysis showed that high galectin-1 and VEGF expressions exhibited significant correlations with poor prognosis for gastric cancer patients. Multivariate analysis revealed that galectin-1 and VEGF expressions were independent prognostic parameters for the overall survival rate of gastric cancer patients. The results of the present study suggest that galectin-1 expression is positively associated with VEGF expression. Both galectin-1 and VEGF can serve as independent prognostic indicators of poor survival for gastric cancer.

Keywords Galectin-1 · VEGF · Gastric cancer · Prognosis · Survival

Introduction

Gastric cancer is one of the most common cancers worldwide and is one of the leading causes of cancer-related death in China [1]. Despite many advances in diagnosis and treatment of this disease, the prognosis for gastric cancer remains poor, especially in advanced stages [2]. Therefore, identifying new biological markers to determine the risk of poor prognosis is important for designing treatment strategies in patients with gastric cancer.

Galectin-1, a member of the galectin family of β-galactoside binding protein, is a homodimer of 14-kDa subunits possessing two β-galactoside binding sites. It participates in a variety of biological functions including cell–cell and cell–matrix interactions and cell growth [3, 4]. There are increasing evidences showing that galectin-1 expression is dysregulated in various types of cancer, which suggests that galectin-1 may support the invasion and metastasis of cancer cells, promote tumor angiogenesis, and protect tumors from host immune responses [5, 6]. Recent studies have indicated that high expression of galectin-1 correlates with poor survival in several types of cancer, such as colon cancer, breast cancer, and pancreatic cancer [7].

Jie Chen, Dong Tang, and Sen Wang contributed equally to this paper.

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Tumor angiogenesis is a fundamental process in tumor growth and metastasis. Any increase in a tumor mass must be preceded by an increase in the microvasculature to deliver nutrients and oxygen to the tumor and remove products of tumor metabolism. Vascular endothelial growth factor (VEGF) is the most potent and specific promoter of tumor angiogenesis [8, 9], which is able to stimulate the growth of epithelial cells of various origins, promote vasculature construction, and enhance blood vessel permeability, especially microvessels [10]. Some previously published studies showed that a high expression of VEGF in gastric cancer has been also associated with poor prognosis [11, 12].

Although the high-level expressions of galectin-1 and VEGF in gastric cancer have been reported, the importance of galectin-1 and VEGF expression as clinicopathological parameters and prognostic markers in gastric cancer remains unclear. The purposes of the present study are to examine the expression status of galectin-1 and VEGF in gastric cancer tissues and to evaluate whether the expression levels of galectin-1 and VEGF are correlated with each other and whether they have clinicopathological and prognostic importance.

Materials and methods

Patient information

From January 2006 to August 2007, a total of 108 patients with gastric cancer who underwent a gastrectomy procedure at the Department of Gastrointestinal Surgery of First Clinic Medical School of Yangzhou University were enrolled in this retrospective study. There were 60 men and 48 women between the ages of 33 and 82 years (mean, 63.8 years). None had received chemotherapy or radiotherapy before surgery. Follow-up was completed on 31th August 2013. Patient clinicopathological parameters were collected, including age, gender, differentiation, and TNM pathological classification according to the International Union against cancer (UICC). This study was performed in accordance with the Declaration of Helsinki of the World Medical Association and ethically approved by the First Clinic Medical School of Yangzhou University (YZU-EC-JS2352). All patients provided written informed consent.

Immunohistochemistry analysis

Gastric cancer tissue samples were fixed by immersion in 4 % paraformaldehyde overnight at 4 °C and then embedded in regular paraffin wax and cut into 4-μm sections. Immunohistochemical analyses of galectin-1 and VEGF expression were performed on formalin-fixed paraffin-embedded sections of surgical specimens. For immunohistochemistry, tissue sections were deparaffinized and rehydrated in PBS. After antigen retrieval with target retrieval solution, endogenous peroxidase activity was blocked by incubation in 0.3 % hydrogen peroxide, and sections were then blocked in 10 % fetal calf serum. Nonspecific binding was blocked by pre-incubation with 10 % fetal calf serum in PBS with 0.01 % sodium azide, and then the slides were incubated in a humidified chamber for 1 h with antibodies against galectin-1 (titer 1:100, New Castle, UK) and VEGF (titer 1:50, Dako Cytomation, Denmark). Finally, samples were incubated with peroxidase-conjugated

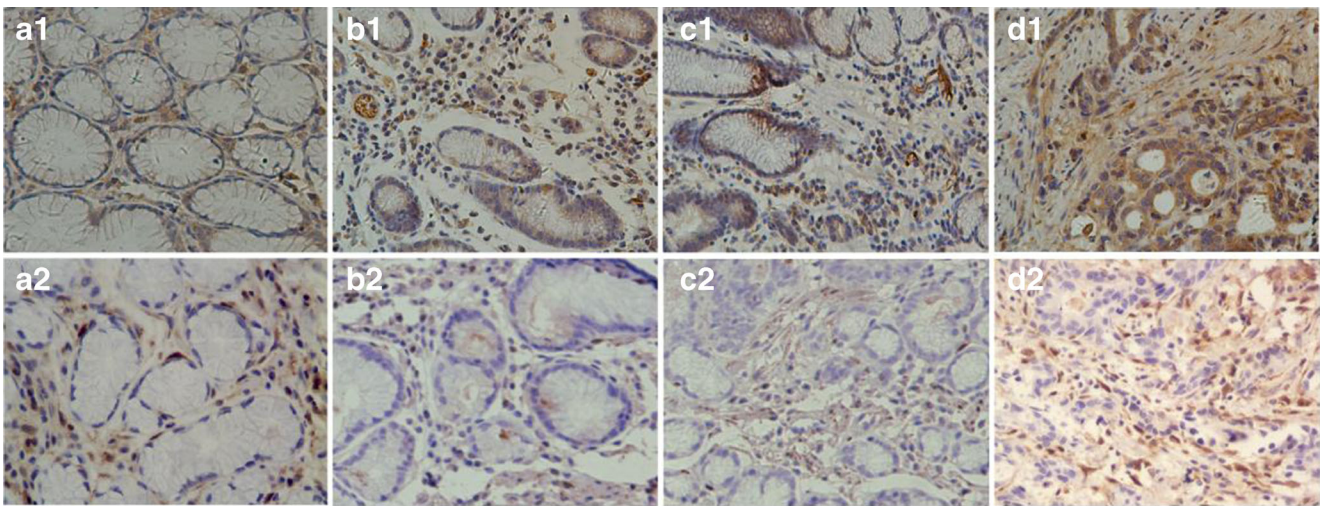

Fig. 1 Immunohistochemical staining for vascular endothelial growth factor (*A1–A4*) and galectin-1 (*B1–B4*) expression in gastric cancer tissues. *A1*: Negative expression of VEGF. *A2*: Weak positive expression of VEGF. *A3*: Moderate positive expression of VEGF. *A4*: Strong positive expression of VEGF. *B1*: Negative expression of galectin-1. *B2*: Weak positive expression of galectin-1. *B3*: Moderate positive expression of galectin-1. *B4*: Strong positive expression of galectin-1. (Original magnification, ×200)

streptavidin (Boster, Wuhan, China). Color was developed by incubating the slides for several minutes with diaminobenzidine, and nuclei were counterstained with hematoxylin. For substitute negative controls, the primary antibodies were replaced with PBS. Positive controls were provided by the kit supplier. The results of immunohistochemical staining were interpreted by two experienced pathologists, and the mean density of staining was calculated using the ImagePro Plus 6.0 software (ImagePro, Bethesda, MD).

Evaluation of immunohistochemical staining

The percentage scoring of the immunoreactive gastric cancer tissues was as follows: 0, no staining and less than 10 % of tumor cells or stroma cells with membrane staining; 1+, more than 10 % of tumor cells or stroma cells with faint partial membrane staining in partial membrane; 2+, more than 10 % of tumor cells or stroma cells with weak to moderate partial membrane staining in partial membrane; 3+, more than 10 % of tumor cells or stroma cells with strong partial membrane staining in partial membrane. Specimens with scores of 0 or 1+ were considered negative, and those with scores of 2+ or 3+ were considered positive for galectin-1 expression. The VEGF staining was considered positive when at least 10 % of the tumor cells were stained, as previously described [13, 14].

Statistical analysis

All statistical analyses were performed using SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA). The corrections between galectin-1 and VEGF expression and clinicopathological features were analyzed by χ^2 test. The Kaplan–Meier test was employed to evaluate the survival rate, and the survival rate curves were compared using the log-rank test. Cox's proportional hazards model was used to identify factors that had a significant influence on survival. Statistical significance was set at $P<0.05$.

Results

Galectin-1 and VEGF expression in gastric cancer tissues

Galectin-1 expression was positive in 68 out of 108 gastric cancer samples (63.0 %) and negative in the remaining 40 samples (37 %), 42 samples were 2+ (61.8 %), and 26 were 3+ (38.2 %). VEGF expression was positive in 62 out of 108 gastric cancer samples (57.4 %) and negative in the remaining 46 samples (42.6 %), 16 samples were 1+ (14.8 %), 29 were 2+ (26.9 %), and 17 were 3+ (15.7 %). Figure 1 shows galectin-1 and VEGF staining in gastric cancer tissues.

Correction between galectin-1 and VEGF expression and clinicopathological features

There was a significant association between galectin-1 and VEGF expression; VEGF was detected in 66.2 % of galectin-1-positive tumor tissues and in 42.5 % of galectin-1-negative tumor tissues ($P=0.016$). The correlations between galectin-1 and VEGF expression and clinicopathological features are shown in Tables 1 and 2. Galectin-1 expression was positively associated with tumor size, tumor location, stage, and lymph node metastases (all $P<0.05$), but it was not correlated with gender, age, or differentiation grade (all $P>0.05$). VEGF expression was positively correlated with tumor size, stage, and lymph node metastases (all $P<0.05$), but it was not correlated with the other clinicopathological features assessed (all $P>0.05$).

Table 1 Relationship between galectin-1 expression and clinicopathological variables in gastric cancer tissues

Clinicopathological variable	Number of patients	Galectin-1 positive ($n=68$)	Galectin-1 negative ($n=40$)	P value
Age				0.171
≤60	47	33	14	
>60	61	35	26	
Gender				0.870
Male	61	38	23	
Female	47	30	17	
Tumor size				0.017
<3 cm	36	17	19	
≥3 cm	72	51	21	
Tumor location				0.002
Upper third	19	7	12	
Middle third	37	20	17	
Lower third	52	41	11	
Differentiation				0.269
Well	15	7	8	
Moderate	44	27	17	
Poor	49	34	15	
TNM stage				0.002
T1	14	3	11	
T2	42	25	17	
T3	41	32	9	
T4	11	8	3	
Lymph node status				0.010
Positive	73	52	21	
Negative	35	16	19	
VEGF				0.016
Positive	62	45	17	
Negative	46	23	23	

TNM tumor–node–metastasis, *VEGF* vascular endothelial growth factor

Table 2 Relationship between VEGF expression and clinicopathological variables in gastric cancer tissues

Clinicopathological variable	Number of patients	VEGF positive (n=62)	VEGF negative (n=46)	P value
Age				0.700
≤60	47	26	21	
>60	61	36	25	
Gender				0.836
Male	61	34	27	
Female	47	28	19	
Tumor size				0.040
<3 cm	36	15	21	
≥3 cm	72	45	27	
Tumor location				0.941
Upper third	19	11	8	
Middle third	37	22	15	
Lower third	52	29	23	
Differentiation				0.310
Well	15	8	7	
Moderate	44	22	22	
Poor	49	32	17	
TNM stage				0.016
T1	14	4	10	
T2	42	21	21	
T3	41	28	13	
T4	11	9	2	
Lymph node status				0.003
Positive	73	49	24	
Negative	35	13	22	
Galectin-1				0.016
Positive	68	45	23	
Negative	40	17	23	

TNM tumor–node–metastasis, *VEGF* vascular endothelial growth factor

Correction between galectin-1 and VEGF expression and patient survival

All patients underwent follow-up until cancer-related death or more than 5 years after tumor resection. Follow-up was completed on 31th August 2013. The median follow-up interval was 50.6 months (range, 0–60 months). The 5-year survival rate was 41.2 % for galectin-1-positive patients and 55.0 % for galectin-1-negative patients, and the prognosis for galectin-1-positive patients was significantly poorer than that for galectin-1-negative patients (P=0.024, Fig. 2). The 5-year survival rates for positive and negative VEGF expressions were 40.3 and 56.5 %, respectively (P=0.033, Fig. 3). Meanwhile, VEGF-positive patients had a shorter survival time than VEGF-negative patients. Survival rates also were evaluated according to the combinations of galectin-1 expression and VEGF expression. Patients who were positive for both galectin-1 and VEGF expression had unfavorable prognosis, and patients who were negative for both galectin-1 and VEGF expression had more favorable prognosis (P=0.025, Fig. 4).

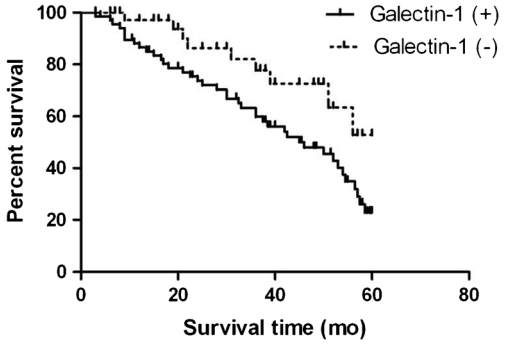

Fig. 2 The overall survival rate of patients relative to galectin-1-positive expression and galectin-1-negative expression in gastric cancer tissue samples. Galectin-1 overexpression was significantly associated with poor patient survival (P=0.024)

Univariate and multivariate analyses

Univariate Cox regression analysis also showed that clinical variables, including tumor size, tumor stage, lymph node metastasis, and galectin-1 and VEGF expression, were significantly associated with the overall survival (Table 3). Furthermore, multivariate Cox's proportional hazard analyses of clinicopathological factors that appeared significant in the univariate analyses revealed galectin-1 expression (hazard ratio (HR) 1.421; 95%*CI* 0.976–2.883; P=0.004) and VEGF expression (HR 1.132; 95%*CI* 0.894–2.768; P=0.012) as independent prognostic indicators of poor survival for gastric cancer after surgery.

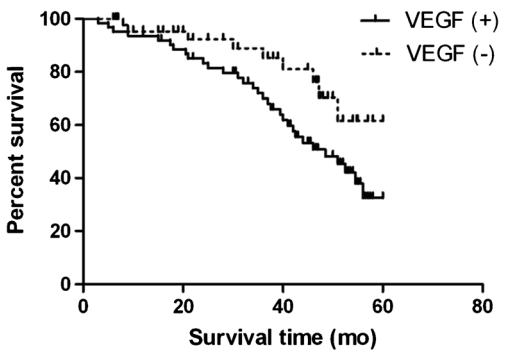

Fig. 3 The overall survival rate of patients relative to VEGF-positive expression and VEGF-negative expression in gastric cancer tissue samples. VEGF overexpression was significantly associated with poor patient survival (P=0.033)

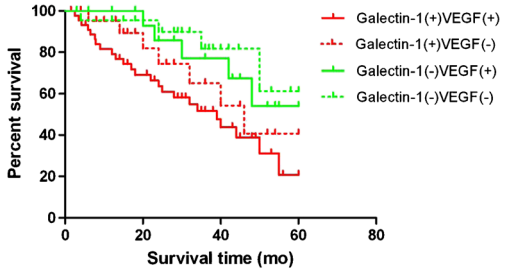

Fig. 4 Survival rates according to the combination of galectin-1 and VEGF expressions. There was a significant difference among groups stratified according to galectin-1/VEGF expression (P=0.025). Patients with galectin-1(+)/VEGF(+) had the worst prognosis

Discussion

Despite the advances in diagnosis and treatment of gastric cancer, the progress on the long-term prognosis is limited. Given the frequent failure of conventional treatment strategies, many cancer-related molecules have been characterized with the goal of developing novel anticancer therapies [15]. Therefore, finding a new prognostic marker and exploring new therapeutic opportunities have become particularly important. Recent studies have indicated that galectin-1 expression may be a prognostic factor in colorectal and breast cancers [16, 17]. However, there are few studies evaluating the correlations between galectin-1 and VEGF expression in gastric cancer, and whether the expressions of galectin-1 and VEGF correlate with the prognosis of gastric cancer patients. In this study, we focused on the possible prognostic values of galectin-1 and VEGF in patients with gastric cancer.

Galectin-1 is encoded by the *LGALS1* gene located on chromosome 22q12 [18]. The methylation status of the promoter is a key mechanism regulating galectin-1 expression [19]. Several transcription factors are implicated in galectin-1 expression, such as hypoxia inducible factor-1 (HIF-1) in colorectal cancer cells [20]. Furthermore, galectin-1 suppresses T-cell-mediated cytotoxic immune responses and promotes tumor angiogenesis. A variety of biological functions of galectin-1, including support in the invasion and metastasis of cancer cells [21], promote tumor angiogenesis [22]. The frequency of positivity appears to increase with the clinical stages of the disease and is associated with a worse prognosis [18]. High galectin-1 expression has been reported in colon [23], breast [24], and prostate cancers [25]. Moreover, galectin-1 is overexpressed in both the stroma surrounding tumor cells and in cancer-associated endothelial cells [26]. Puchades et al. demonstrated a significant relationship between high galectin-1 expression in cancer cells and poor prognosis in patients with high-grade glioblastoma compared with better-prognosis patients [27]. Similar findings in colon [23], breast [24], and prostate cancers [25] strengthen the correlation between galectin-1 expression and survival.

VEGF is the most important regulator of the angiogenesis; it promotes the recruitment and proliferation of endothelial cells and their precursors within the tumor and thus plays a critical role in angiogenesis during tumor development [28]. High VEGF expression is reported in several malignancies [29], and VEGF expression has been correlated with poor prognosis of breast and gastric cancers [30, 31]. Expression of VEGF has been shown to correlate positively with microvessel count and metastasis; it stimulates the growth of endothelial cells, leading to the formation of new blood vessels, and provides essential nutrients for tumor growth [32]. Therefore, VEGF-based antiangiogenesis therapy may be of therapeutic benefit against gastric cancer.

In the present study, we examined 108 gastric cancer cases for the presence of the galectin-1 oncoprotein by immunohistochemistry. Of all cases, 68 (63.0 %) showed positive galectin-1 expression, and galectin-1 expression was related to tumor size, differentiation grade, stage, and lymph node metastases, suggesting that this protein may participate in tumor growth and metastasis. VEGF expression was detected in more than half of gastric cancers (57.4 %). Both the

Table 3 Univariate analysis and multivariate analysis identify factors influencing the overall survival rate of gastric cancer patients

Variable	Univariate analysis			Multivariate analysis		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Age	1.298	0.636–2.527	0.539			
Gender	1.362	0.429–2.236	0.764			
Tumor size	1.575	1.162–4.523	0.004	1.287	0.728–2.329	0.012
Tumor location	1.456	0.884–2.135	0.042	1.253	1.087–2.653	0.108
Differentiation	1.292	0.738–2.274	0.334			
TNM stage	1.832	1.116–3.271	0.013	1.235	1.223–3.187	0.008
Lymph node status	1.426	0.998–2.867	0.006	1.243	1.312–2.887	0.005
Galectin-1	1.525	1.224–3.265	0.018	1.421	0.976–2.883	0.004
VEGF	1.534	1.108–2.896	0.005	1.132	0.894–2.768	0.012

HR hazard ratio; *CI* confidence interval, *TNM* tumor–node–metastasis, *VEGF* vascular endothelial growth factor

incidence and proportion of VEGF expression increased with the progression of gastric cancer, and it was correlated with tumor size, stage, and lymph node metastases. In the Kaplan–Meier survival analysis, the overall survival rate of patients with high galectin-1 and VEGF expressions was significantly shorter than that of patients with low galectin-1 and VEGF expressions. Univariate analyses showed that increased galectin-1 and VEGF expressions in gastric cancer tissues are significantly associated with poor overall survival rate. Moreover, multivariate analysis demonstrated that galectin-1 and VEGF expressions, together with some traditional prognostic factors such as tumor size, lymph node status, and TNM stage, are independent risk factors in the prognosis of gastric cancer patients.

Meanwhile, the present study showed that VEGF expression was increased in galectin-1-positive tumors compared with galectin-1-negative tumors and galectin-1 expression was also increased in VEGF-positive tumors compared with VEGF-negative tumors. Galectin-1 expression was positively associated with VEGF expression. Koopmans et al. [33] demonstrated that galectin-1 activation led to the translational upregulation of VEGF and increased angiogenesis through the JAK/STAT pathway in myeloproliferative neoplasia. Fischer et al. [34] demonstrated that galectin-1 inhibited rearranged during transfection (RET) and Janus kinase 2 (JAK2) signals and upregulated vascular endothelial growth factor receptor 3 (VEGFR3) signaling in trophoblast tumor cells. Hsieh et al. [35] found that galectin-1 was overexpressed in the connective tissue surrounding cancer cells in tumor-associated vascular endothelial cells. Galectin-1 can increase angiogenesis by interacting with neuropilin-1 on the endothelial cell surface. Galectin-1 binding to neuropilin-1, which acts as a co-receptor of VEGF in endothelial cells, enhances VEGF receptor phosphorylation and the subsequent activation of mitogen-activated protein kinases [36]. These study results also indicate that galectin-1 and VEGF overexpression was significantly correlated with poor survival in gastric cancer patients, especially patients with both galectin-1-positive and VEGF-positive expressions. Therefore, galectin-1 and VEGF played concordant roles in tumor angiogenesis, progression, metastasis, and prognosis. The detection of high galectin-1 and VEGF expressions might help predict poor prognosis and could be used as novel prognostic markers for gastric cancer patients.

In conclusion, by evaluating the expression of galectin-1 and VEGF using immunohistochemistry, this study reveals the prognostic significance of galectin-1 and VEGF in patients with gastric cancer. In univariate and multivariate analyses, the high expressions of galectin-1 and VEGF are identified as independent prognostic factors of worse overall survival. Therefore, galectin-1 and VEGF might be used as potential molecular therapeutic targets in gastric cancer.

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Conflicts of interest None

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