

Clinicopathological and prognostic significance of galectin-1 and vascular endothelial growth factor expression in gastric cancer

Jie Chen, Su-Jun Zhou, Yun Zhang, Guo-Qiang Zhang, Tian-Zhou Zha, Yi-Zhong Feng, Kai Zhang

Jie Chen, Su-Jun Zhou, Yun Zhang, Guo-Qiang Zhang, Tian-Zhou Zha, Kai Zhang, Department of General Surgery, Yixing People's Hospital, the Affiliated Hospital of Jiangsu University, Yixing 214200, Jiangsu Province, China
Yi-Zhong Feng, Department of Pathology, the Second Affiliated Hospital of Soochow University, Suzhou 215004, Jiangsu Province, China

Author contributions: Chen J carried out data analysis and wrote the manuscript; Zhou SJ designed this study and performed the statistical analyses; Zhang Y, Zhang GQ, Feng YZ and Zha TZ participated in clinicopathological data collection; Chen J and Zhang K scored the immunostained slides, prepared the images and reviewed the manuscript.

Correspondence to: Kai Zhang, MD, Department of General Surgery, Yixing People's Hospital, the Affiliated Hospital of Jiangsu University, No. 75, Tongzhen Guan Road, Yixing 214200, Jiangsu Province, China. yxphpwk@163.com

Telephone: +86-510-87071163 Fax: +86-510-87918767

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Abstract

AIM: To evaluate the expression of galectin-1 and vascular endothelial growth factor (VEGF) in gastric cancer and investigate their relationships with clinicopathologic factors and prognostic significance.

METHODS: Galectin-1 and VEGF were immunohistochemically investigated in tumor samples obtained from 214 gastric cancer patients with all tumor stages. Immunohistochemical analyses for galectin-1 and VEGF expression were performed on formalin-fixed, paraffin-embedded sections of surgical specimens. The relationship between the expression and staining intensity of galectin-1 and VEGF, clinicopathologic variables, and patient survival were analyzed. All patients underwent follow-up until cancer-related death or more than five years after tumor resection. *P* values < 0.05 were considered statistically significant.

RESULTS: Immunohistochemical staining demonstrated that 138 of 214 gastric cancer samples (64.5%) were positive for galectin-1, and 116 out of 214 gastric cancer samples (54.2%) were positive for VEGF. There was a significant association between galectin-1 and VEGF expression; VEGF was detected in 60.1% of galectin-1-positive samples and 43.4% of galectin-1-negative samples ($P < 0.05$). Galectin-1 expression was associated with tumor size, tumor location, stage, lymph node metastases, and VEGF expression (all $P < 0.05$). VEGF expression was related to tumor size, stage, and lymph node metastases (all $P < 0.05$). The 5-year survival rate was 56.6% for galectin-1-positive patients and 69.2% for galectin-1-negative patients, and the prognosis for galectin-1-positive patients was significantly poorer compared with galectin-1-negative patients ($\chi^2 = 13.880$, $P = 0.000$). The 5-year survival rates for VEGF-positive and VEGF-negative patients were 53.4% and 70.5%, respectively ($\chi^2 = 4.619$, $P = 0.032$). The overall survival rate of patients with both galectin-1 and VEGF overexpression in gastric cancer tissue samples was significantly poorer than other groups (both $P < 0.05$).

CONCLUSION: Galectin-1 expression was positively associated with VEGF expression. Both galectin-1 and VEGF can serve as independent prognostic indicators of poor survival for gastric cancer after gastrectomy.

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Key words: Galectin-1; Vascular endothelial growth factor; Gastric cancer; Prognosis

Core tip: Galectin-1 and vascular endothelial growth factor (VEGF) played important roles in angiogenesis and progression of malignant tumor, while their expression in Chinese gastric cancer and relationship between the two parameters and clinicopathological features, as well as prognostic value remained largely unknown. In this present study, we examined 214 gastric cancer samples

for the presence of galectin-1 oncoprotein and VEGF by immunohistochemistry and found that overexpressions of galectin-1 and VEGF were related with tumor progression and poor survival, and our findings supported an association between galectin-1 and VEGF expression. These two molecules may serve as independent predictive markers for patient prognosis in gastric cancer.

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INTRODUCTION

Gastric cancer is one of the most common cancers in the world. It is the second leading cause of cancer death after lung cancer^[1,2]. The incidence of gastric cancer is highest in Eastern Asia, including China, Japan and South Korea^[3]. Despite advances in diagnostic techniques, neoadjuvant chemoradiotherapy, and surgery, the 5-year survival rate for gastric cancer remains poor, particularly in more advanced stages^[4]. Recently, therapeutic strategies have been improved by the availability of monoclonal antibodies. Additionally, studies have evaluated new biologic and molecular targets for their potential roles as prognostic markers and targets for therapy in patients with gastric cancer.

Galectin-1, a β -galactoside-binding protein, is a 14 kDa homodimer and the first protein discovered in the galectin family^[5-7]. Accumulating evidence clearly shows that galectin-1 is involved in numerous essential cancer-related processes, including immunosuppression, angiogenesis, and metastasis^[8-15]. Galectin-1 overexpression in tumor stromal cells has been detected in several malignant tumors, such as colon cancer^[16], breast cancer^[17], hepatocellular cancer^[18], prostate cancer^[19], and pancreatic ductal adenocarcinoma^[20]. Furthermore, high galectin-1 expression was shown to correlate with poor survival in several types of cancer^[21-25].

Vascular endothelial growth factor (VEGF) is an angiogenic factor produced by tumor cells that stimulates intratumoral microvessel proliferation. Angiogenesis is a fundamental process in tumor growth and metastasis, and it contributes to the metastatic process by providing large numbers of leaking blood vessels for vascular invasion^[26,27]. VEGF is the most potent and specific promoter of tumor angiogenesis^[28]. It is able to stimulate the growth of epithelial cells of various origins, promote vasculature construction, and enhance blood vessel permeability, especially microvessels^[29]. A few published studies have shown that VEGF overexpression in gastric cancer is associated with poor prognosis^[30-32]. However, no previous studies have clarified the correlation between

galectin-1 and VEGF overexpression in gastric cancer. In this study, we performed immunohistochemical staining and extensively examined galectin-1 and VEGF expression in gastric cancer tissues. The aims of this study were to determine whether the expression levels of galectin-1 and VEGF were correlated with each other and with clinicopathological features and prognosis, including patient survival.

MATERIALS AND METHODS

Patient information

From January 2004 to October 2006, a total of 214 patients with gastric cancer who underwent gastrectomy at the Department of General Surgery of the Affiliated Hospital of Jiangsu University were enrolled in this retrospective study. There were 129 men and 85 women between the ages of 31 and 84 years (mean, 64.5 years). None had received chemotherapy or radiotherapy before surgery. Follow-up was completed on 30 October 2012. Patient clinicopathologic parameters were collected, including age, gender, differentiation, and pathological tumor-node-metastasis classification (according to the International Union Against Cancer).

Immunohistochemistry

Immunohistochemical analyses of galectin-1 and VEGF expression were performed on formalin-fixed, paraffin-embedded sections of surgical specimens. Tissue microarray blocks were serially cut into 4 μ m-thick sections and stained. Paraffin sections were deparaffinized in xylene and rehydrated in a gradient of ethanol solutions. Endogenous peroxidases were blocked with 3% hydrogen peroxide in methanol for 10 min. The slides were immersed in 10 mmol/L citrate buffer (pH 6.0) and heated for 30 min for antigen retrieval. The slides were then cooled at room temperature for 20 min and washed with phosphate-buffered saline (PBS). Non-specific binding was blocked by pre-incubation with 10% fetal calf serum in PBS with 0.01% sodium azide. The slides were then incubated in a humidified chamber for 1 h with antibodies against galectin-1 (titer 1:100, New Castle, United Kingdom) and VEGF (titer 1:50, DakoCytomation, Denmark). After washing three times in PBS, the slides were incubated with the envision-HrP complex (undiluted; Dako) for 60 min and visualized with diaminobenzidine and counterstained with hematoxylin. For substitute negative controls, the primary antibodies were replaced with PBS. Positive controls were provided by the kit supplier. The results were assessed by two independent pathologists who had no knowledge of the patient clinical status.

Evaluation of immunohistochemical staining

A scoring system was used to evaluate the immunoreactivity of gastric cancer. Galectin-1 staining was scored semiquantitatively using the following criteria: 0, no staining and less than 10% of tumor cells or stromal cells with membrane staining; 1+, more than 10% of tumor cells or stromal cells with faint partial membrane staining; 2+,

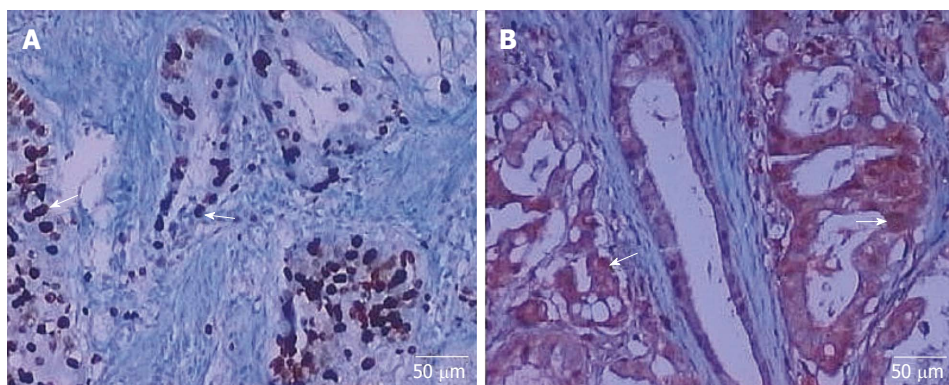


Figure 1 Immunohistochemical staining for galectin-1 and vascular endothelial growth factor (original magnification, $\times 200$). A: Positive galectin-1 expression in gastric cancer tissue; B: Positive vascular endothelial growth factor expression in gastric cancer tissue. The over-expressed markers are shown with arrows.

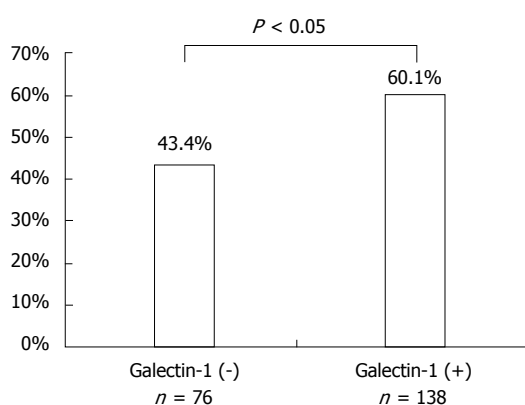


Figure 2 Vascular endothelial growth factor was expressed more frequently in galectin-1-positive gastric cancers than galectin-1-negative.

more than 10% of tumor cells or stromal cells with weak to moderate partial membrane staining; 3+, more than 10% of tumor cells or stromal cells with strong partial membrane staining. Specimens with scores of 0 or 1+ were considered negative, and scores of 2+ or 3+ were considered positive for galectin-1 expression. VEGF staining was considered positive when at least 10% of the tumor cells were stained, as previously described^[33,34].

Follow-up

Patients underwent continuous follow-up up to September 2012. No patients were lost to follow-up. The median follow-up duration was 48.5 mo (range, 0-60 mo) after surgery.

Ethics

This work was performed in accordance with the Declaration of Helsinki of the World Medical Association. This study was ethically approved by the Affiliated Hospital of Jiangsu University (JSUH-EC-189923). All patients provided written informed consent.

Statistical analysis

Statistical analyses were performed with SPSS 16.0 for Windows (SPSS, Chicago, IL, United States). The correlations between galectin-1 and VEGF expression and

clinicopathological features were analyzed using the 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. *P* values < 0.05 were considered statistically significant.

RESULTS

Galectin-1 and VEGF expression in gastric cancer tissues

Galectin-1 expression in tumor stromal cells was detected in 197 (92.1%) of 214 tumor tissues. Galectin-1 expression was positive in 138 out of 214 gastric cancer samples (64.5%) and negative in the remaining 76 samples (35.5%); 86 samples were 2+ (40.2%), and 52 were 3+ (24.3%). VEGF expression was positive in 116 of 214 gastric cancer samples (54.2%) and negative in the remaining 98 samples (45.8%); 30 samples were 1+ (14.0%), 53 were 2+ (24.8%), and 33 were 3+ (15.4%). Figure 1 shows galectin-1 and VEGF staining in gastric cancer tissues.

Correlation between galectin-1 and VEGF expression and clinicopathological features

There was a significant association between galectin-1 and VEGF expression; VEGF was detected in 60.1% of galectin-1-positive tumors and 43.4% of galectin-1-negative tumors (*P* < 0.05, Table 1, Figure 2). The correlations between galectin-1 and VEGF expression and clinicopathological features are shown in Table 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).

Correlation between galectin-1 and VEGF expression and patient survival

All patients underwent follow-up until cancer-related death or more than five years after tumor resection. The median follow-up interval was 48.5 mo. The 5-year sur-

Table 1 Relationship of galectin-1 and vascular endothelial growth factor expression in gastric cancer tissues

VEGF	Galectin-1		P value
	Positive (n = 138)	Negative (n = 76)	
Positive (n = 116)	83	33	0.022
Negative (n = 98)	55	43	

VEGF: Vascular endothelial growth factor.

vival rate was 56.6% for galectin-1-positive patients and 69.2% for galectin-1-negative patients, and the prognosis for galectin-1-positive patients was significantly poorer than that of galectin-1-negative patients ($\chi^2 = 13.880$, $P = 0.000$). The 5-year survival rates for VEGF-positive and VEGF-negative patients were 53.4% and 70.5%, respectively ($\chi^2 = 4.619$, $P = 0.032$). Additionally, VEGF-positive patients had a shorter survival time than VEGF-negative patients. The cumulative overall survival rates for these two populations were determined (Figure 3A and B).

To evaluate the combined effect of galectin-1 and VEGF expression on the prognosis of gastric cancer, we classified patients into four subgroups according to galectin-1 and VEGF expression: group I, low expression of both markers; group II, high galectin-1 expression and low VEGF expression; group III, low galectin-1 expression and high VEGF expression; and group IV, high expression of both markers. We found that the 5-year survival rate in group IV was 40.9%, which was significantly lower compared with groups I (53.5%), II (49.1%), and III (48.5%) (Figure 3C, $P < 0.05$).

DISCUSSION

Despite the development of surgical techniques and new cytotoxic agents, which have improved the prognosis of gastric cancer, once patients develop resistance to chemotherapeutic regimens, no other treatment options are available. Given the frequent failure of conventional treatment strategies, many cancer-related molecules have been characterized with the goal of developing novel anticancer therapies^[35]. To guide clinical decision making in therapy and prognosis prediction, efforts have been made to identify prognostic biomarkers for patients with gastric cancer.

Galectin-1 is a β -galactoside-binding protein that is abundantly secreted by almost all types of malignant tumor cells. Galectin-1 expression is regulated by hypoxia-inducible factor-1, and it plays vital protumorigenic roles within the tumor microenvironment. Furthermore, galectin-1 suppresses T cell-mediated cytotoxic immune responses and promotes tumor angiogenesis. Recent evidence has demonstrated that galectin-1 plays an important role in tumor progression and metastasis^[36]. The amplification and overexpression of galectin-1 have been demonstrated in several tumors, including colon cancer, breast cancer, and hepatocellular cancer. The frequency

Table 2 Relationship of galectin-1 and vascular endothelial growth factor expression to clinicopathological variables in gastric cancer tissues

Variable	Galectin-1		P value	VEGF		P value
	(+)	(-)		(+)	(-)	
Age (yr)			0.200			0.784
≤ 60	58	39		54	48	
> 60	80	37		62	50	
Gender			0.308			0.583
Male	87	42		62	48	
Female	51	34		54	50	
Tumor size			0.026			< 0.001
< 3 cm	43	36		48	73	
≥ 3 cm	95	40		68	25	
Tumor location			0.004			0.287
Upper third	18	3		35	21	
Middle third	60	50		44	38	
Lower third	60	23		37	39	
Differentiation			0.112			0.998
Well	12	14		30	25	
Moderate	53	27		26	22	
Poor	73	35		60	51	
TNM stage			< 0.001			< 0.001
T1	3	37		25	65	
T2-T4	135	39		91	33	
Lymph node status			< 0.001			0.002
Positive	30	46		66	35	
Negative	108	30		50	63	

TNM: Tumor-node-metastasis; VEGF: Vascular endothelial growth factor.

of positivity appears to increase with the clinical stage of the disease and is associated with a worse prognosis^[16-18]. However, the prevalence of galectin-1 overexpression in gastric cancer and its relationship with prognosis is not clear. There are only two studies in the literature evaluating the correlation between galectin-1 expression and survival. In these studies, galectin-1 expression in tumor cells was significantly correlated with short survival in astrocytic neoplasms and colon cancer^[16,37]. In the present study, we examined 214 gastric cancer samples for the presence of the galectin-1 oncoprotein by immunohistochemistry. In all, 138 samples (64.5%) 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 distant metastasis. We also confirmed a significant prognostic value of galectin-1 in gastric cancer using a Kaplan-Meier survival analysis. The outcome of galectin-1-positive patients was significantly poorer than galectin-1-negative patients. Thus, detecting galectin-1 expression in gastric cancer tissues might be helpful for predicting patient prognosis.

Angiogenesis is essential for tumor growth and metastasis^[38]. VEGF is the most potent angiogenic factor identified to date. Tumor angiogenesis and neovascularization require VEGF expression^[39]. VEGF is primarily secreted by tumor cells, and its functions are largely restricted to endothelial cells^[40]. VEGF strongly stimulates the growth of endothelial cells, leading to the formation of new blood vessels and providing essential nutrients

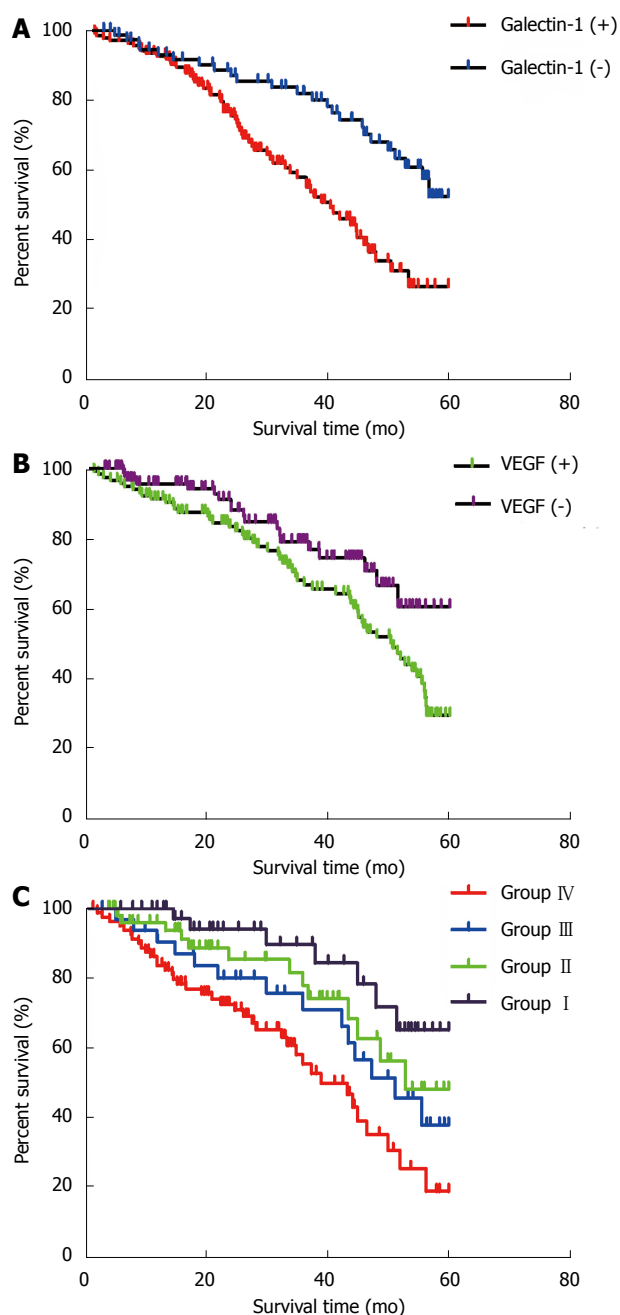


Figure 3 Overall survival rate of patients. A: The overall survival rate of patients relative to galectin-1-positive expression and galectin-1-negative expression in gastric cancer tissue samples. Galectin-1 overexpression was significantly associated with poor patient survival ($P < 0.05$); B: The overall survival rate of patients relative to vascular endothelial growth factor-positive expression and vascular endothelial growth factor-negative expression in gastric cancer tissue samples. Vascular endothelial growth factor overexpression was significantly associated with poor patient survival ($P < 0.05$); C: The overall survival rates of patients relative to groups I, II, III and IV. Both galectin-1 and vascular endothelial growth factor overexpression was significantly associated with poor patient survival ($P < 0.05$).

for tumor growth. Therefore, VEGF-based antiangiogenesis therapy may be of therapeutic benefit against solid tumors and has been tested in several tumor types, including gastric cancers. In our study, VEGF expression was detected in more than half of gastric cancers (54.2%). Both the incidence and proportion of VEGF expres-

sion increased with the progression of gastric cancer, and it was correlated with tumor size, stage, and lymph node metastases. VEGF expression has been identified as a significant marker for tumor recurrence and reduced survival independent of conventional clinicopathological variables in gastric cancer^[41,42]. In this study, using Kaplan-Meier analysis, we also demonstrated a significant association between VEGF expression and poor survival.

VEGF is one of the most potent inducers of angiogenesis, whereas galectin-1 has been implicated in the regulation of VEGF. Koopmans *et al.*^[43] demonstrated that galectin-1 activation led to the translational up-regulation of VEGF and increased angiogenesis through the JAK/STAT pathway in myeloproliferative neoplasia. Fischer *et al.*^[44] demonstrated that galectin-1 inhibited rearranged during transfection and Janus kinase 2 signals and up-regulated vascular endothelial growth factor receptor 3 signaling in trophoblast tumor cells. Hsieh *et al.*^[45] 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^[16]. However, few studies have evaluated the correlation between VEGF and galectin-1 in gastric cancer.

The present study showed that VEGF expression was increased in galectin-1-positive tumors compared to galectin-1-negative tumors. Meanwhile, galectin-1 expression was also increased in VEGF-positive tumors compared to VEGF-negative tumors. Galectin-1 expression was positively associated with VEGF expression. Galectin-1 and VEGF played concordant roles in tumor angiogenesis, progression, metastasis, and prognosis, which suggests a connection between them. Our results also indicated that galectin-1 and VEGF overexpression was significantly correlated with poor survival in Chinese gastric cancer patients, especially patients with both galectin-1 and VEGF expression. Therefore, detecting galectin-1 and VEGF expression might help to identify gastric cancer patients with a poor prognosis and could therefore be a novel prognostic marker. To date, the galectin-1 regulatory mechanism of VEGF in gastric cancer has not been well explored and requires further study.

COMMENTS

Background

Galectin-1 and vascular endothelial growth factor (VEGF) played important roles in angiogenesis and progression of malignant tumor. The high expression of galectin-1 and VEGF are correlated with disease behavior in some cancers, while their expression in Chinese gastric cancer and relationship between the two parameters and clinicopathological features, as well as prognostic value remained largely unknown.

Research frontiers

Even with the advancement of diagnosis, neoadjuvant chemoradiotherapy and surgery, the 5-year survival for gastric cancer remains poor, especially in more

advanced stages. Recently therapeutic strategies have been improved by the availability of monoclonal antibodies. Researches have been evaluating new biologic and molecular targets for their potential role as prognostic markers and as targets for therapy in patients with gastric cancer.

Innovations and breakthroughs

Given the frequent failure of conventional treatment strategies, many cancer-related molecules have been characterized with the goal of developing novel anticancer therapies. In order to guide clinical decision-making in therapy and prognosis prediction, efforts have been invested in identifying prognostic biomarkers for patients with gastric cancer. Galectin-1 is a β -galactoside binding protein that is abundantly secreted by almost all types of malignant tumor cells. The expression of galectin-1 is regulated by hypoxia-inducible factor-1 (HIF-1) and it plays vital protumorigenic roles within the tumor microenvironment. However, the prevalence of galectin-1 overexpression in gastric cancer as well as its relationship with prognosis is not clear. There are only two studies in the literature evaluating the correlation between galectin-1 expression and survival. In these studies, galectin-1 expression in tumor cells significantly correlated with short survival in astrocytic neoplasms and in colon cancer. In this present study, the authors examined 214 gastric cancer samples for the presence of galectin-1 oncoprotein by immunohistochemistry.

Applications

The study aimed at evaluating the expression of galectin-1 and VEGF in gastric cancer by immunohistochemical methods. The authors found that overexpressions of galectin-1 in tumor stroma cells and VEGF in tumor cells were related with tumor progression and poor survival in gastric cancer, and our findings supported an association between galectin-1 and VEGF expression. These two molecules may serve as independent predicative markers for patient prognosis in gastric cancer.

Terminology

Galectin-1 is a β -galactoside binding protein that is abundantly secreted by almost all types of malignant tumor cells. The expression of galectin-1 is regulated by HIF-1 and it plays vital protumorigenic roles within the tumor microenvironment. Galectin-1 suppresses T cell-mediated cytotoxic immune responses and promotes tumor angiogenesis. VEGF is the most potent angiogenic factor identified so far. Tumor angiogenesis and neovascularization require VEGF expression. VEGF is mainly secreted by tumor cells with its functions largely restricted to endothelial cells, and it strongly stimulate the growth of endothelial cells leading to the formation of new blood vessels, thus providing essential nutrients for tumor growth.

Peer review

This manuscript describes convincingly the expression of galectin-1 and VEGF in gastric cancer patients. The paper is well prepared and its publication in the journal is recommended with minor corrections.

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