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Original Article

Invasion-related signal pathways in Epstein-Barr virus (EBV)-associated gastric carcinoma

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Abstract: Objective: The protein expression levels of NF-κβ, MMP-9, HIF-1α, AP-1, K-Ras, STAT3, CXCL12 and CXCR4 were detected in Epstein-Barr virus (EBV)-associated gastric carcinoma (EBVaGC) and EBV negative gastric carcinoma (EBVnGC) for exploring the potential mechanism of low lymph node metastasis and invasiveness in EBVaGC. Methods: The small nuclear EBER1, encodes EBV, was detected using In situ hybridization in 600 gastric cancer-specimens. Thirty of all were positive for EBV and identified as EBVaGC. Another 30 samples negative for EVB were identified as EBVnGC. Immunohistochemical staining was performed to determine the expression levels of NF-κβ, MMP-9, HIF-1α, AP-1, K-Ras, STAT3, CXCL12 and CXCR4. Results: In all 600 gastric cancer specimens, the positive incidence of EBV was 5%. The clinicopathologic features showed that EBVaGC was associated with gender, pathological pattern, lesion sites and lymphatic metastasis ($P<0.05$), but was not related to age ($P>0.05$). NF-κB, MMP-9 and HIF-1α were lowly expressed in EBVaGC and highly expressed in EBVnGC, with a statistical difference between these two groups ($P<0.05$). All proteins AP-1, K-Ras, STAT3, CXCL12 and CXCR4 were highly expressed both in EBVaGC and EBVnGC, with no statistical difference between two groups ($P>0.05$). Conclusion: The inactivation of NF-κB, MMP-9 and HIF-1α pathways, failed to induce and promote tumor cell angiogenesis and proliferation, probably contributes to the biological characteristics with lower occurrence of lymphatic metastasis and higher survival rate.

Keywords: EBVaGC, lymphatic metastasis, NF-κβ, MMP-9, HIF-1a, AP-1, Ras, STAT3, CXCL12/CXCR4

Introduction

Lymph node metastasis is the major way of gastric cancer metastasis, and it greatly contributes to the survival rate of patients. Mechanism underlying lymph node metastasis is extremely complex. The attenuation of intercellular adhesion and enhancement of surrounding matrix as well as endothelial cells are involved in the degradation of surrounding matrix and cancer cells, which lead to shed from the tumor tissue and wander into the lymphatic system [1, 2]. Various molecules are secreted by cancer cells and surrounding cells and functions as different roles in lymph node metastasis. The activation of NF-κB pathway has been reported to be related to occurrence of gastric cancer [3], which causes a stronger anti-apoptosis effect and results in the rapid development of tumors.

Matrix metallopeptidase 9 (MMP-9) is an enzyme involved in the degradation of the extracellular matrix (ECM). The activation of MMP-9 destroys the ECM of tumor surrounding cells, leading to the infiltration of tumor cells to the position of missing ECM [4]. NF-κB and nuclear transcription factor AP-1 trans-activate MMP-9 expression, which is critical to promoting tumor invasion and metastasis [5, 6]. Hypoxia inducible factor-1alpha (HIF-1), Ras (A small guaninenucleotide bindingprotein) and signal transducer andactivator of transcription (STAT) have been well known to promote tumor

Table 1. Clinical and pathological characteristics

	Cases (n=600)	Positive (n=30)	Negative (n=570)	X^2	*P* value
Gender					
Male	384	25	359	3.879	0.049
Female	216	5	211		
Age					
<45	32	4	32	3.228	0.073
<60	223	13	210		
60~	345	13	334		
Pathological pattern					
Well-differentiated adenocarcinoma	68	8	60	15.691	<0.001
Moderately differentiated adenocarcinoma	124	12	112		
Poorly differentiated adenocarcinoma	408	10	398		
Lesion site					
Gastric cardia	102	12	90	14.997	<0.001
Gastric body	139	10	129		
Gastric antrum	359	8	351		
Lymphatic metastasis					
Metastasis	580	9	559	47.6248	0.000
Non-metastasis	20	21	11		

vessels proliferation and lymphatic metastasis via altering expression of vascular endothelial growth factor (VEGF) [2]. CXCL12/CXCR4, involved in the decrease of cell apoptosis and increased of cell proliferation, plays an important roleinlymphatic metastasis of gastric cancer [7]. The increased CXCL12/CXCR4 expression accelerates angiogenesis and promotes tumor cell proliferation and growth [8].

Burke firstly reports Epstein-Barr virus is associated with gastric cancer. The presence of EBV in the gastric cancer cell is defined as EBV-associated gastric carcinomas (EBVaGC). The findings has indicated that EBVaGC comprise about 10% of all gastric carcinomas worldwide, and more than 90% of EBVaGC patients are lifelong carrier of the virus [9]. EBVaGC in clinical pathology and genetics shows many different features with gastric cancer in absence of EBV, and considered an independent lesion type. Lymphatic metastasis is less occurred in EBVaGC [10]. The 5-year survival rate is up to 66.2%, which is higher than that gastric cancer without EBV. However, the mechanism underlying it remains unclear.

EBV latent membrane protein (LMP1) is a viral oncogene leading to malignant transformation of cancer cell. The studies have showed that LMP1 is deficiency in EBVaGC [11, 12]. LMP1 takes part in the activation of NF-κB pathway through tumor necrosis factor receptor associated factors (TRAFs) and tumor necrosis factor associated death domain protein (TRADD). AP-1 is one important gene on the signal transduction pathway of LMP1, and directly or indirectly involves in the LMP1-mediated cell transformation with or without the alteration of Ras pathway [11]. It has also demonstrated that LMP1 in nasal pharyngeal cancer cells promotes VEGF expression via STAT3 [13]. The further study showed that LMP1, independent of NF-κB pathway, increased HIF-1α expression and promoted VEGF expression [14]. We found the positive rate of EBVaGC was 5%, and LMP1 was lower expressed in EBVaGC. In present study, we investigated the protein expression levels of NF-κB, MMP-9, HIF-1α, AP-1, Ras, STAT3, CXLL12 and CXCR4 in tumor tissues of EBVaGC and EBVnGC, in order to elaborate the possible biological mechanisms of low lymphatic metastasis and high survival rate in EBVaGC.

Materials and methods

Reagents and kits

ISH-5022 EBER *in situ* hybridization kit and anti-HIF-1α antibody were purchased from

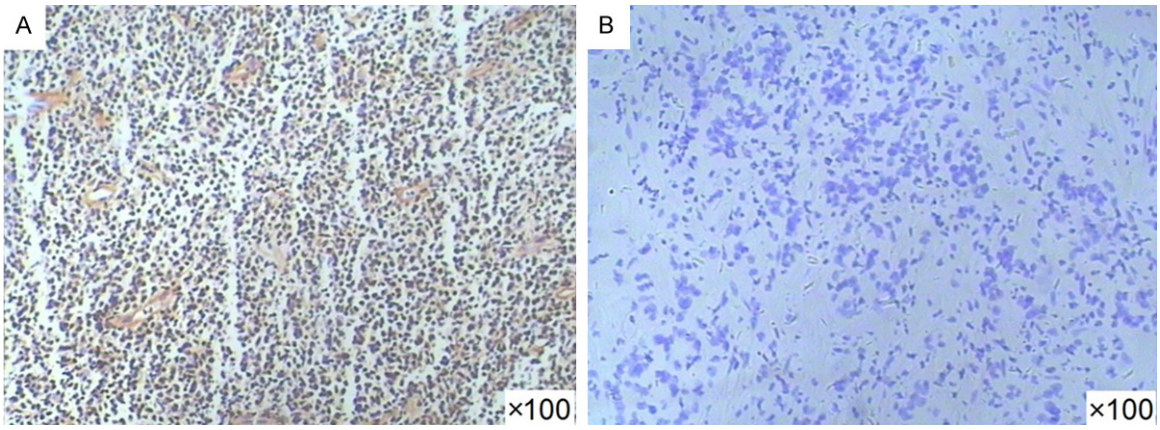

Figure 1. The expression of EBV-encoded small RNA1 in specimens was detected using*In situ* hybridization. A. Positive for EBV-encoded small RNA1; B. Negative control.

Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd (Beijing, China). Anti-CXCL12 and anti-CXCR4 monoclonal antibodies were purchased from RD Systems (USA). Anti-MMP-9, anti-STAT3, anti-AP-1 and anti-k-Rasmonoclonal antibodies were obtained from Beijing Bo Orson Biological Technology Co., Ltd (Beijing, China). Anti-NF-κB monoclonal antibody and Ultra SensitiveTM SP (Mouse/Rabbit) IHC Kit were purchased from Fuzhou Maixin Biotechnology Development Co., Ltd (Fuzhou, China).

Specimen collection

A total of six hundreds specimens of gastric tumor were collected from 2008 to 2012 in Shandong provincial Institute of tumor prevention and treatment Institute and Affiliated Hospital of Jining medical college. Written informed consents were obtained from all participants. *In situ* molecular hybridization technique was conducted to screen the gastric tumors with EBV, and 30 specimens were included. The characteristics of subjects were shown in **Table 1**. Another 30 specimens without EBV were also included and served as control in this study. The specimens positive for EBV were identified as EBVaGC, and the ones negative for EVB were identified as EBVnGC.

Preparation of pathological specimen

All tumor specimens were fixed with 10% neutral buffered formalin and embedded in paraffin. Five μmserial sections were performed to slice. The histopathological classification was conducted with hematoxylin and eosin (H&E) staining via light microscopy.

Protein detection

The small nuclear EBER1, encodes EBV, in tumor tissues was detected by ISH-5022 EBER *in situ* hybridization kit. The gastric tumors positive for EBV were screened and used to the detect the protein expression of NF-κB, MMP-9, HIF-1α, AP-1, Ras, STAT3, CXLL12 and CXCR4 by immunohistochemical staining with Ultra Sensitive TM SP (Mouse/Rabbit) IHC Kit according to the manufacturer's recommendations. The monoclonal antibodies were diluted into 1:200.

Results determination

Take the double-blind read the results of slices. In experiment of *in situ* hybridization,tumor specimens without EBV should be negative for EBER1 and without any staining, otherwise the experiment was invalidity. Tumor specimens with EBV should be positive for EBER1. The positive cells (for NF-κB, MMP-9, HIF-1α, AP-1, Ras, STAT3, CXLL12 or CXCR4) appeared with brown granules in the cytoplasm, cytomembrane or nuclei. All slices were counted at least in 10 fields at 400 magnification. Positive cells/all cells >25% was considered as positive, with the proportion of positive cells rate divided into: <10% (-), 11% to 25% (+), 25% ~ 50% (++) and >50% (+++). Staining intensity determination: non-staining (-), light brown (+), brown (++) and sepia (+++).

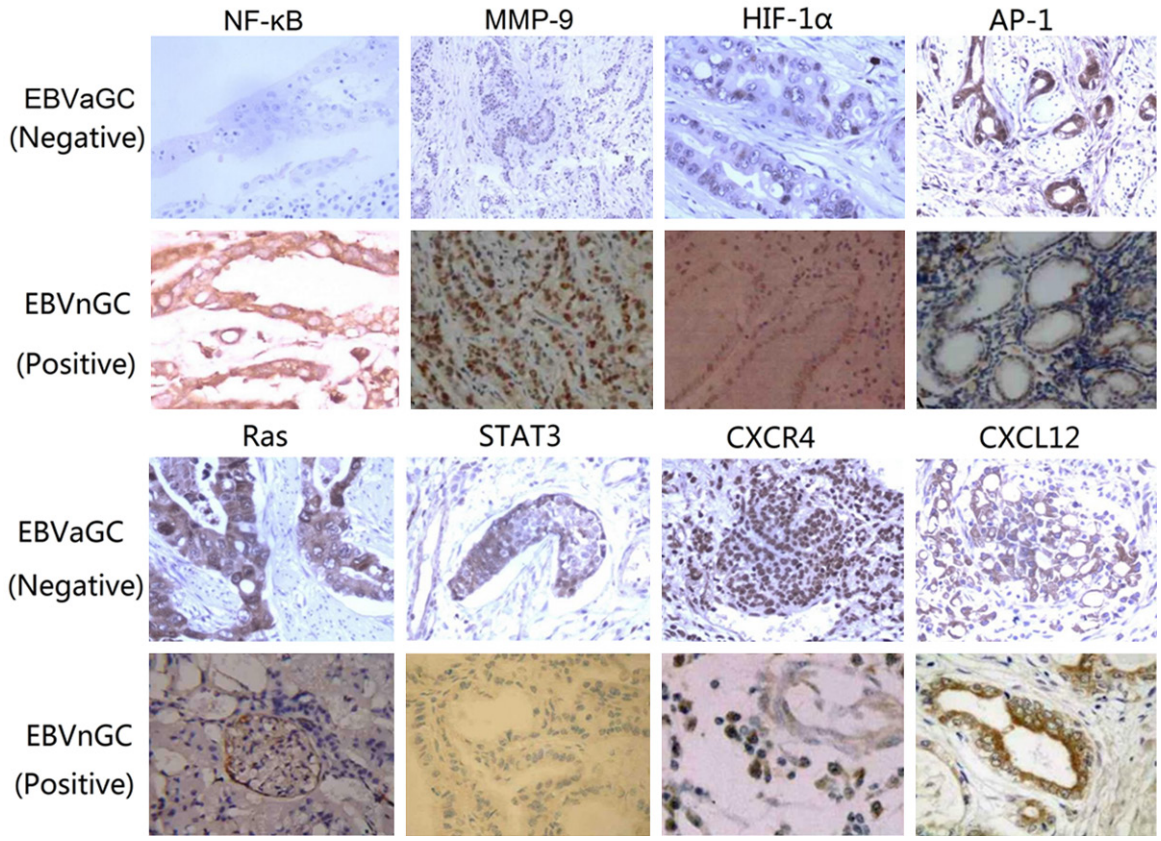

Figure 2. The expression of NF-κB, MMP-9, HIF-1α, AP-1, Ras, STAT3, CXCR4 and CXCL12 of tumors in EBVaGC and EBVnGC was detected by immunohistochemicalstaining (400×).

Statistical analysis

All calculation and statistical analysis were conducted using SPSS 13.0 statistical software. The χ^2 test was used to compare the difference of positive rates between EBVaGC and EBVnGC. $P<0.05$ was considered to be statistically significant.

Results

Clinical and pathological characteristics

Thirty tumor specimens were detected to be positive for EBV in all 600 specimens. *In situ* hybridization showed that positive granules were purple blue and located in the nucleus. Positive signal intensity was general homogeneous and few with varied intensity (**Figure 1**). All EBVnGC specimens were negative for EBV. Clinical and pathological analysis demonstrated that EBVaGC was associated with gender, pathological pattern, lesion sites and lymphatic metastasis ($P<0.05$), but not related to age ($P>0.05$) (**Table 1**).

Immunohistochemical results

NF-κB, MMP-9, HIF-1α, AP-1, Ras, STAT3, CXLL12 or CXCR4 in tumor specimens were determined using immunohistochemical staining (**Figure 2**). The results showed that the positive rates of NF-κB, MMP-9 and HIF-1α in EBVaGC were significantly different from that in EBVnGC ($P<0.05$) (**Table 2**). Only 6.7%, 13.3% and 16.7% EBVaGC specimens were positive for NF-κB, MMP-9 and HIF-1α, respectively. While 86.7%, 93.3% and 80.0% specimens were positive for NF-κB, MMP-9 and HIF-1α in EBVnGC, respectively. The expression intensity of NF-κB, MMP-9 and HIF-1α in EBVaGC were presented in **Table 3**, and data showed that most samples were weakly positive. In addition, the positive rates of AP-1, Ras, STAT3, CXLL12 and CXCR4 in samples had no statistical difference between two groups ($P>0.05$) (**Table 2**). The positive rates of AP-1, Ras, STAT3, CXLL12 and CXCR4 in EBVaGC samples respectively were 90.0%, 90.0%, 93.3%, 86.7% and 100%. It's worth noting that the positive CXCL12 in

Table 2. Immunohistochemical staining results

		EBVaGC	EBVnGC	X^2	P
NF-κB	Negative	28	2	0.000	<0.001
	Positive	2	26		
MMP-9	Negative	26	2	0.267	<0.001
	Positive	4	28		
HIF-1α	Negative	25	6	0. 067	<0.001
	Positive	5	24		
AP-1	Negative	3	2	41.667	0.647
	Positive	27	28		
Ras	Negative	3	2	41.667	1.000
	Positive	27	28		
STAT3	Negative	2	3	41.667	0.647
	Positive	28	27		
CXLL12	Negative	4	10	17.067	0.069
	Positive	26	20		
CXCR4	Negative	0	1	56.067	0.321
	Positive	30	29		

Table 3. Expression intensity of NF-κB, MMP-9 and HIF-1α in EBVaGC

Protein	NF-κB			MMP-9			HIF-1α		
Expression intensity	+	++	+++	+	++	+++	+	++	+++
EBVaGC	2	0	0	4	0	0	0	5	0

EBVaGC and EBVnGC respectively were 86.7% and 66.7%, with a *P* value at 0.069.

Discussion

EBV is a member of the herpesvirus family, and associated with several human tumors [15]. Gastric carcinoma is one of the most common cancers worldwide and the second most common cause of cancer-related death [16]. Almost 10% of the gastric carcinomas throughout the world are monoclonal proliferations of EBV-carrying tumor cells [17]. EBVaGChas a lower occurrence of lymphatic metastasis and higher 5-year survival rate than gastric carcinomawithout EBV [10]. EBV can directly infect epithelial cells of the gastric mucosa. In addition, EBV infects lymphocytes which commonly aggregate in the impaired gastricmucosa and then enters lymphatic system [12], leading to the further infection and spread.

EBV encoded LMP1 has been identified to contribute to the malignant phenotype in cancer [18]. Emerging studies have demonstrated that the activation of NF-κB signaling pathway is an important part of the EBV transformation program [19]. Canonical NF-κB activation is critical for almost all LMP1 TES2 RNA effects [20]. In present study, NF-κB was expressed at lower level in EBVaGC specimens and at higher level in EBVnGC. MMP-9 is an enzyme involved in the degradation of ECM, and reported to promote tumor cell growth, invasion, metastasis and angiogenesis [21]. Human MMP-9 promoter contains cis-acting element and transcription factor binding sites. NF-κB and AP-1 are two transcriptionfactors binding to MMP-9 and regulate its expression. Here we found MMP-9 was low expressed in EBVaGC and high expressed in EBVnGC. In previous study, it indicated LPM1 was down-regulated in EBVaGC [11, 12]. However, the expression levels of AP-1 had no significant difference between two groups. Therefore, we speculated that the inactivation of LMP1-NF-κB-MMP-9 pathway probably contributes to the biological characteristics with lower occurrence of lymphatic metastasis and higher 5-year survival rate.

HIF-1α is a nuclear transcription factor, adapting to thehypoxia environment. Hypoxia is one characteristic of micro-environment in gastric carcinoma and important for promoting tumor growth, thereby HIF-1α is critical in this process. The previous studies demonstrated that LMP1 expression was closely related to the microvascular count in nasopharyngeal carcinoma. The further study showed LMP1 up-regulated VEGF expression to promote angiogenesis and tumor metastasis via increasing HIF-α expression [22, 23]. The overexpressed HIF-1α expression has been observed in several cancers specimens and participants in tumor angiogenesis. In gastric carcinoma, high expression level of HIF-1α can be used as an important indicator of local invasion and metastasis, which provides a theoretical basis for early diagnosis and clinical prognosis of gastric

cancer.In present study, HIF-1α expression was low expressed in EBVaGC and high expressed in EBVnGC. Therefore, we speculated that LMP1-HIF-1α was not activated in EBVaGC, and it also a possible mechanism to explain the biological characteristics with lower occurrence of lymphatic metastasis and higher 5-year survival rate.

STAT3, a latent cytoplasmic transcription factor, is reported to be activated in various tumor tissues [24]. It also plays a pivotal role in tumor growth and metastasis [25]. In nasopharyngeal carcinoma cells, EBV LMP1 up-regulated VEGF expression to promote lymphangiogenesis and angiogenesis and increase tumor invasiveness [26]. Ras is a human proto-oncogene and required for initiating and maintaining the malignant transformation phenotype. Its mutations are very common in many human malignant epithelial tumors [27]. The excitation of Raspersistently activates the PLC to produce second messengers, which results in an uncontrolled cell proliferation and malignant transformation. Chemokines are generally considered to be a class of cytokines to play a role in directional migration of cells. A close relationship has also been found in chemokinesand tumorigenesis. During the tumor growth, a variety of chemokines can be secreted. CXCR4 and its ligand CXCL12, termed as CXCL12/CXCR4 biological axis, are involved in the process of tumor invasion and metastasis. It has been also illustrated that CXCL12/CXCR4 biological axis serves as an important role in lymph node metastasis of gastric cancer [8]. In some tumors, CXCR4 is highly expressed and participants in the tumor-specific transfer.

However, we found there were no statistical differences in expression levels of Ras, STAT3, CXLL12 and CXCR4 between EBVaGC and BVnGC. The results suggested that Ras, STAT3, CXLL12 and CXCR4 might not relate to the low occurrence of lymphatic metastasis and higher 5-year survival rate in EBVaGC.

In summary, we demonstrated that NF-κB, MMP-9 and HIF-1α pathways, but not Ras, STAT3 and CXLL12/CXCR4, probably contributed to the biological characteristics with low occurrence of lymphatic metastasis and higher 5-year survival rate.

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Disclosure of conflict of interest

None.

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