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Expression and clinical significance of FOS-like antigen 1 in gastric adenocarcinoma

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ABSTRACT

Background: The overexpression of FOS-like antigen 1 (FOSL1) in several types of cancers was reported before. However, the expression and clinical significance of FOSL1 in gastric cancer (GC) have not been elucidated.
Materials and methods: The expression of FOSL1 in 105 cases of GCs was detected with immunohistochemistry, and the mRNA of FOSL1 was investigated with quantitative real-time polymerase chain reaction(qRT-PCR) in 15 pairs of GCs and tumor adjacent tissues. With Chi-square test or Fisher test, we analyzed the correlation between FOSL1 expression and clinicopathological factors. With univariate analysis, we evaluated the correlations between clinicopathological factors including FOSL1 and overall survival (OS) rates. With multivariate analysis, we identified the independent prognostic risk factors of GC.
Results: The percentages of patients with low and high FOSL1 expression in our study accounted for 43.81% and 56.19%, respectively. The mRNA levels of FOSL1 in GCs were significantly higher than those in tumor adjacent tissues. FOSL1 expression was demonstrated to be significantly correlated with lymphatic invasion ($P = 0.036$) and TNM stage ($P = 0.016$). High expression of FOSL1 was significantly correlated with lower 5-year OS ($P = 0.002$), and FOSL1 expression was identified as an independent prognostic biomarker of GC ($P = 0.001$).
Conclusions: FOSL1 is an independent prognostic biomarker of GC. Detecting FOSL1 expression could help stratify GC patients with high-risk and guide the precious treatment.

1. Introduction

Gastric cancer (GC) is the fourth most common cancer and the third leading cause of cancer-related death in the world [1]. In China, GC is the second leading cause of cancer death [2]. The standard treatment to advanced GC is based on surgery combined with adjuvant therapy like chemotherapy and radiotherapy [3]. The morbidity of GC declined because of the modification of chemotherapy, application of targeted drugs or development of surgical instruments, but the overall survival (OS) rate of GC is still dismal, remaining under 30% in most countries [4]. There are many reasons contributing to this unfavorable prognosis of GC. For example, many patients are present with locally advanced or metastatic disease. Another reason is that the treatment options like targeted drugs of GC are very limited compared to other tumors, such as melanoma. The identification of new biomarkers and drug targets is important because it may help develop new strategies for the treatment to GC.

Oncogenic transcription factor FOS-like antigen 1 (FOSL1) is a member of FOS family, which play important roles in physical processes like cell proliferation or differentiation, and pathological processes especially oncogenic progression by inducing the expression of several tumor progression relevant proteins [5]. As a main effector of Ras and ERK, FOSL1 was demonstrated to be associated with a more aggressive phenotype and cancer progression [6]. The overexpression of FOSL1 is detected in multiple human carcinomas, including colon cancer, ovarian cancer, breast cancer, lung and esophageal squamous cell carcinoma, and so on [6]. In gastric cancer, FOSL1 expression was elevated and it was suggested to influence the PI3K/Akt and p53 signaling pathway [7]. Moreover, the functional SNP rs1892901 of *FOSL1* gene was reported to affect the expression of FOSL1 protein, and ultimately increase the risk of gastric cancer in Chinese population [8]. However, the expression and prognostic value of FOSL1 in gastric cancer has not

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systemically elucidated yet.

Here in our study, we detected the expression of FOSL1 in GCs and their adjacent tissues with immunohistochemistry and qRT-PCR. With Chi-square test or Fisher test, we analyzed the correlation between FOSL1 expression and the clinicopathological factors. With univariate analysis, we evaluated the correlation between clinicopathological factors including FOSL1 and OS. With multivariate analysis, we identified the independent prognostic risks of GC in our study.

2. Materials and methods

2.1. Patients and samples

From 2009–2016, a total of 324 patients were diagnosed as gastric cancer and underwent surgery in Yidu Central Hospital, and the Sixth People's Hospital of Qingdao. 105 patients were selected into the test cohort following: (1) radical surgery and standard adjuvant therapy if needed, no preoperational adjuvant therapy, (2) follow-ups were more than 3 months, (3) no other malignancies. The study was approved by the Ethics Broad of Yidu Central Hospital and the Ethics Broad of Sixth People's Hospital of Qingdao. All specimens were obtained with prior consent of patients. The test cohort consisted of 40 female patients and 65 male patients, with average follow-up time as 49.2 months after operation.

2.2. RNA extraction and qRT-PCR

The mRNA level of FOSL1 in GC tissues and their tumor adjacent tissues were analyzed with qRT-PCR. Trizol reagent (Thermo Fisher Scientific, Waltham, MA, USA) was used for mRNAs extraction, and the StepOnePlus real-time PCR system (Applied Biosystems, Waltham, MA, USA) with SYBR Green method was applied for the cDNA synthesis and quantitative PCR. GAPDH was as an internal control for the $2^{-\Delta\Delta}$ CT equation. The average mRNA level of tumor adjacent tissues was set as 1.0 and other mRNA levels were standardized to this baseline. The sequences of primers of GAPDH and FOSL1 were as follows:

FOSL1 forward: 5'-CAGTGGATGGTACAGCCTCA-3';
FOSL1 reverse: 5'-CAGTTTGTCAGTCTCCTGTTCAC-3';
GAPDH forward: 5'-TGGAGAATGAGAGGTGGGATG-3';
GAPDH reverse: 5'-GAGCTTCACGTTCTTGTATCTGT-3'

2.3. Immunohistochemistry

Immunohistochemistry (IHC) with streptavidin peroxidase complex method was applied to detect the expression of FOSL1 in GC tissues. In brief, the specimens were deparaffinized and rehydrated with xylene and graded alcohol, and then incubated in boiled 0.01 M pH = 6.0 citrate buffer for optimal antigen retrieval. The endogenous peroxidase was inactivated by 3% H_2O_2 and the unspecific binding was blocked by incubation in 5% bovine serum albumin. The primary antibody of FOSL1 (R&D Systems, Minneapolis, MN, USA) at 1:100 concentration was used to incubate the specimens overnight at 4 ℃ and the corresponding secondary antibody (Beyotime, Shanghai, China) was applied at room temperature for 1 h. The streptavidin peroxidase complex reagent (Sangon, Shanhai, China) and 3,3′-diaminobenzidine solution (Sangon, Shanhai, China) was finally added to visualize the antigen.

2.4. IHC score system

The results of IHC were evaluated with IHC score by two pathologists who were unaware of clinical data. The IHC score was analyzed by calculating the score of staining intensity multiplied by the score of IHC positive cell percentage. According to previous study [9], the scores of staining intensity were defined as: 0 for negative staining; 1 for weak staining; 2 for median staining; and 3 for strong staining. The scores of positive cell percentage were set as: 1 for 0–25% positive cells; 2 for 25%–50% positive cells; 3 for above 50% positive cells. The test cohort was divided into two groups according to the cut-off, which was defined by receiver operating characteristic(ROC) curve according to previous study [10]. In the ROC curve, the point 3.5 had highest sum of sensitivity and specificity, meaning that score ≥ 4 was high FOSL1 expression.

2.5. Statistical analysis

All the data was analyzed with SPSS 22.0 software (IBM cooperation, Chicago, USA). The correlation between the expression of FOSL1 and the clinicopathological factors was evaluated with Chi-square or Fisher test. The correlations between clinicopathological factors and the OS were evaluated with Kaplan-Meier test and statistical differences of subgroups were analyzed with log-rank test. The independent prognostic factors were identified with the Cox-regression model. $P < 0.05$ was defined as statistically significant.

3. Results

3.1. Expression of FOSL1 in GC and GC adjacent tissues

The expression and cellular localization of GC was investigated with IHC in 105 patients with radical surgery. In almost all the specimens, FOSL1 was expressed in nucleus, which is corresponding to its function as a transcription factor (Fig. 1A and 1B). The percentages of patients with low and high FOSL1 expression in our study accounted for 43.81% and 56.19%, respectively (Table 1). In addition, we performed qRT-PCR to detect the mRNA level of FOSL1 in GCs and adjacent normal tissues. A total of 15 pairs of GCs and tumor adjacent tissues were used for mRNA detection. In our study, the mRNA levels of FOSL1 in GCs were significantly higher than those in tumor adjacent tissues, indicating that FOSL1 may be involved in tumorigenesis of GC.

3.2. Correlation between FOSL1 expression and clinicopathological factors

The clinicopathological factors were collected, including the patients' sex, age, tumor size, histological grade, tumor infiltration (T stage), lymphatic invasion (N stage), distant metastasis (M stage) and TNM stage. With Chi-square test or Fisher test (if the sample number < 5), FOSL1 expression was demonstrated to be significantly correlated with lymphatic invasion ($P = 0.036$) and TNM stage ($P = 0.016$) (Table 2). Patients with high expression of FOSL1 were more likely to be predisposed to positive lymphatic invasion or advanced TNM stage. These results indicated that FOSL1 may play an essential role in tumor invasion or lymphatic metastasis.

3.3. FOSL1 expression is correlated with OS of GC

The prognostic value of FOSL1 was first evaluated with univariate analysis by log-rank test (Table 3). The survival curves of different parameters were displayed with Kaplan-Meier method in Fig. 2. In our study, the high expression of FOSL1 was demonstrated to be significantly associated with lower 5-year OS rate ($P = 0.002$). The median survival times of patients with low and high FOSL1 expression were 62.3 and 36.5 months, while the 5-year OS rate of patients with low and high FOSL1 expression were 50.0% and 22.0%, respectively. Besides FOSL1 expression, larger tumor size ($P = 0.002$), high histological grade ($P = 0.006$), advanced tumor infiltration ($P = 0.006$), positive lymphatic invasion ($P = 0.036$) and distant metastasis ($P < 0.001$), advanced TNM stage ($P < 0.001$) all could indicate the unfavorable prognosis of GC.

3.4. FOSL1 was an independent prognostic biomarker of GC

The prognostic factors in univariate analysis were enrolled into

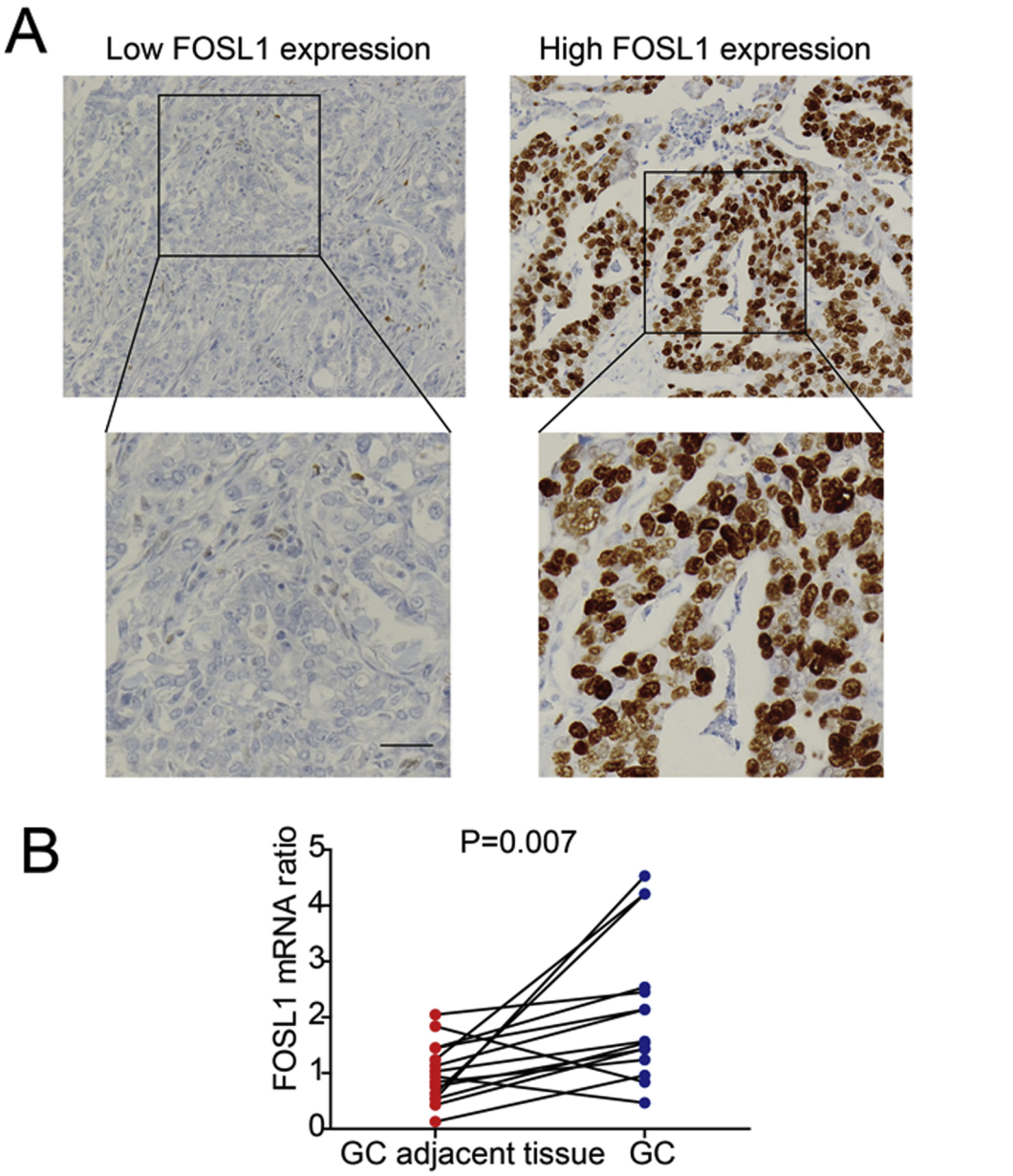

Fig. 1. Expression of FOSL1 in GC and adjacent tissues.
A. The expression of FOSL1 in GC was detected with IHC. Images of low and high FOSL1 expression were displayed. Scare bar: 50 μm.
B. The mRNA levels of FOSL1 in 15 pairs of GCs and adjacent tissues were investigated with qRT-PCR. FOSL1 mRNA in GC was significantly higher compared with in adjacent tissues.

multivariate analysis to identify the independent risk factors of GC with Cox-regression model (Table 4). The TNM stage was excluded because it was naturally the outcome of tumor size, lymphatic invasion and metastasis. In our study, FOSL1 was an independent prognostic risk factor of GC, and the percentage of GC-related death of patients with high FOSL1 expression was 2.38 folds higher than those with low FOSL1 expression (P = 0.001). Moreover, advanced histological grade (grade II: HR = 1.83, 95%CI = 1.02–3.31, P = 0.045; grade III: HR = 4.62, 95%CI = 2.02–10.82, P = 0.001), and positive metastasis (HR = 2.38, 95%CI = 1.43–6.74, P = 0.004) were all identified as independent prognostic factors of GC.

4. Discussion

There are several classifications of GCs. For example, the Lauren classification system divides GC into two main subtypes, the intestinal type and the diffuse type [11]. The intestinal type accounts for the majority of GC and is usually associated with better prognosis, while the diffuse type is poorly cohesive and usually indicates unfavorable prognosis [12]. However, almost all classifications are not able to guide the treatment of GC patients. In the trend of precious and individual treatment, the molecular profiling of GCs was mapped by different lines of evidence [13,14]. GC patients with different genetic mutations or biomarker overexpression may have different outcomes and targeted therapies. GC is a highly heterogeneous cancer, so the discovery of GC molecular features and prognostic biomarkers is very important because that would guide the precise treatment and improve the development of targeted drugs, just like that the discovery of Her2 initiate a new targeted drug-Herceptin to GC. In our study, we for the first time demonstrated that FOSL1 was an independent biomarker of GC in 105 patients with radical surgery of GC. The sample size in our study may be not large enough, but the statistical significance of FOSL1 to predict

Table 1
Basic information of the validation cohort.

Characters	Number	Percentage
Sex		
Female	40	38.10%
Male	65	61.90%
Age		
≤60	34	32.38%
> 60	71	67.62%
Tumor diameter (cm)		
≤5	43	40.95%
> 5	62	59.05%
Histograde		
I	31	29.52%
II + III	74	70.48%
Tumor invasion		
T1 + T2	18	17.14%
T3 + T4	87	82.86%
Lymph node metastasis		
No(N0)	26	24.76%
Yes(N1/2/3)	79	75.24%
Distant metastasis		
M0	97	92.38%
M1	8	7.62%
TNM stage		
I-II	39	37.14%
III–IV	66	62.86%
FOSL1		
low	46	43.81%
high	59	56.19%

Abbreviation: FOSL1 = FOS-like antigen 1.

Table 2
Correlation between FOSL1 and clinicopathological factors.

Characters	FOSL1		P*
	Low	High	
Sex			
Female	18	22	0.847
Male	28	37	
Age			
< 60	15	19	0.965
≥60	31	40	
Tumor diameter (cm)			
≤5	22	21	0.206
> 5	24	38	
Histograde			
I	16	15	0.297
II + III	30	44	
Tumor invasion			
T1 + T2	8	10	0.952
T3 + T4	38	49	
Lymph node metastasis			
No(N0)	16	10	0.036
Yes(N1/2/3)	30	49	
Distant metastasis			
M0	42	55	0.717
M1	4	4	
TNM stage			
I-II	23	16	0.016
III–IV	23	43	

Abbreviation: FOSL1 = FOS-like antigen 1.
* Calculated by Chi-square test.

Table 3
FOSL1 was significantly associated with low survival rates.

Parameters	survival time (months)	5-year survival rate	P*
Sex			
Female	45.5	32.5	0.5
Male	49.6	35.4	
Age			
< 60	50	29.4	0.509
≥60	47	36.6	
Tumor diameter(cm)			
≤5	63.8	53.5	0.002
> 5	37.1	21	
Histograde			
I	63.7	48.4	0.001
II	44.8	38.3	
III	22.9	8.3	
Tumor invasion			
T1	95.8	83.3	0.006
T2	56.5	58.3	
T3	47.1	30.9	
T4	29.9	15.8	
Lymphatic invasion			
No(N0)	64.8	46.2	0.036
Yes(N1/2/3)	42.5	30.4	
Distant metastasis			
M0	50.9	38.1	< 0.001
M1	14.3	0	
TNM stage			
I	77.2	66.7	< 0.001
II	62.9	50	
III	40.2	27.6	
IV	14.3	0	
FOSL1			
Low	62.3	50	0.002
High	36.5	22	

Abbreviation: FOSL1 = FOS-like antigen 1.
* Calculated by log-rank test.

prognosis of GC was very notable. More experiments should be performed to reveal the underlying mechanism of how FOSL1 lead to poor prognosis. We hope our study could trigger more interest on FOSL1 in GC progression and help improve the insight into the oncogenic role of FOSL1.

KRAS is a proto-oncogene, most frequently mutated in human cancer, especially in epithelial tumors, such as lung cancer, pancreas cancer, colon cancer, or cholangiocarcinoma [15]. However, although the oncogenic function of KRAS has been elucidated by numerous studies, there is no available drug applied to directly inhibit KRAS. New therapeutic approaches are being explored to inhibit downstream molecular of KRAS to eliminate the oncogenic role of KRAS. 8 genes including *FOSL1* were identified to be overexpressed in mutant KRAS tumors of different tissue origins [16]. In Kras-driven lung cancer, FOSL1 was highly expressed in tumor tissues compared to normal lung epithelia. Moreover, the high expression of FOSL1 was a marker of poor survival in mutant *KRAS* patients with lung and pancreatic cancer [17]. JUN and FOS family comprised of oncogenic transcription factors family AP-1, which could transduce oncogenic signals by inducing the transient expression of several transient 'immediate early' genes under continuous MAPK pathway over-activation like *KRAS* mutation. FOSL1 is one important member of FOS family, which also includes FOS, FOSB and FOSL2 [18]. So FOSL1 is an important effector of KRAS mutation and continuous MAPK activation.

Mutant *KRAS* and ectopic MAPK activation usually promote mitotic machinery functions and cell proliferation [19], but the oncogenic role of FOSL1 is not limited to tumor cell proliferation in previous studies [20,21]. FOSL1 was also demonstrated to promote tumor cell epithelial-mesenchymal transition and cellular detachment [20,21]. In our study, we observed that FOSL1 high expression was significantly associated with positive

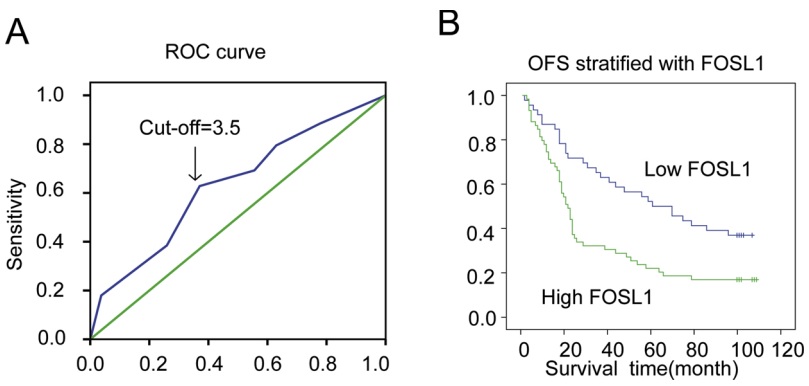

Fig. 2. The survival curves of GC were stratified with FOSL1 expression.
A. The cut-off was defined as the point with the highest sum of sensitivity and specificity in the ROC curve.
B. High expression of FOSL1 ($P = 0.002$) could indicate the unfavorable prognosis of GC. The survival curves were displayed with Kaplan-Meier method and statistical significance was generated with log-rank test.

Table 4
FOSL1 expression was an independent prognostic factor of GC.

Parameters	HR	95%CI	P*
Tumor diameter (cm)			
≤5	1		
> 5	2.03	0.98–4.21	0.058
Histograde			
I	1		
II	1.83	1.02–3.31	0.045
III	4.62	2.02–10.82	0.001
Tumor invasion			
T1 + T2	1		
T3 + T4	2.03	0.98–4.21	0.058
Lymphatic invasion			
No(N0)	1		
Yes(N1/2/3)	1.28	0.72–2.30	0.414
Distant metastasis			
M0	1		
M1	3.11	1.43–6.74	0.004
FOSL1			
Low	1		
High	2.38	1.45–3.90	0.001

Abbreviation: FOSL1 = FOS-like antigen 1.
* Means calculated by Cox-regression model.

lymphatic invasion. This result indicated that FOSL1 may have an essential role in GC cells migration and invasion, which of certain need further studies to prove. Our demonstration that FOSL1 was an independent prognostic biomarker suggested that patients with high FOSL1 expression is more risky and need stronger attention after operation. FOSL1 may be a potential drug target to GC or other tumors with KRAS mutation since drugs directly inhibiting KRAS are not available.

In conclusion, we identified FOSL1 as an independent prognostic biomarker of GC. Detecting FOSL1 expression could help stratify GC patients with high-risk and guide the precious treatment. FOSL1 may be a promising target for the development of targeted drug of GC.

Conflict of interest

There are no conflicts of interest.

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