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Original Article

Clinicopathological significance of expression of JAB1 and Smad4 in human esophageal squamous cell carcinoma

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Abstract: c-Jun activation domain-binding protein-1 (JAB1) and mothers against decapentaplegic homolog (Smad) 4 are abnormally expressed in many malignant tumors, and involved in occurring and progressing of malignant tumors. The aim of this study is to investigate the expression of JAB1 and Smad4 in human esophageal squamous cell carcinoma (ESCC) and explore their clinical and pathological significance. The expression of JAB1 and Smad4 protein were detected in 187 cases of human ESCC and 23 cases of tumor-adjacent tissues by immunohistochemical method. Our results demonstrate that the positive rate of JAB1 was 65.2% in human ESCC which was higher than that in tumor-adjacent tissues (17.4%), <0.001. High levels of JAB1 protein were significantly related to differentiation, TNM stage, lymphatic metastasis and depth of invasion (P = 0.011, P = 0.001, P<0.001 and P = 0.002, respectively). The positive rate of Smad4 was 43.3% in ESCC tissues, which was lower than that in tumor-adjacent tissues (78.3%), P = 0.002. Low levels of Smad4 protein were significantly related to tumor differentiation, TNM stage, lymphatic metastasis and depth of invasion (P = 0.039, P = 0.003, P<0.001 and P<0.001, respectively). JAB1 protein was inversely correlated with Smad4 protein (r = -0.518, P<0.001). Patients with higher JAB1 or lower Smad4 expression had shorter overall survival time, while patients with lower JAB1 or higher Smad4 expression had better survival time. Multivariate logistic regression analysis showed that TNM stage, lymphatic metastasis as well as the JAB1 expression were negatively correlated with disease free survival (P = 0.018, P = 0.019 and P = 0.035, respectively) and overall survival of ESCC (P<0.001, P = 0.043 and P = 0.012, respectively), and Smad4 expression were positively correlated with disease free survival (0.033) and overall survival of ESCC (P = 0.023). In conclusion, expression of JAB1 and Smad4 are markedly related with differentiation, TNM stage, lymphatic metastasis and depth of invasion of ESCC. JAB1 is inversely related with the expression of Smad4. To detect JAB1 and Smad4 may be helpful to evaluate prognosis and infiltrative capability of ESCC.

Keywords: Esophageal squamous cell carcinoma, immunohistochemistry, JAB1, Smad4, invasion, survival

Introduction

Esophageal squamous cell carcinoma (ESCC) is one of common malignant tumors of gastrointestinal cancers, and is the eighth leading causes of cancer-related mortality worldwide [1]. There are two main histological types of ESCCs, including squamous cell carcinoma and adenocarcinoma. More than 70% of esophageal cancers worldwide are squamous cell carcinomas [2, 3]. It is one of the most deadly gastrointestinal tumors, with a 5-year survival rate of 20%-30% after curative surgery [4]. Early diagnosis and early treatment are the well known methods for prolonging the survival time of patients with tumor [5]. Therefore, it is very important for the diagnosis of ESCC to find out some tumor markers, which can help diagnose it as early as possible, contributing to improving the operation effect and increasing the survival rate of patients.

JAB1 (also known as CSN5) is as a modulator of intracellular signaling and influences cellular proliferation and apoptosis [6]. JAB1 is overexpressed in many kinds of malignant tumors

Table 1. Expressions of JAB1[a] and Smad4[b] in esophageal squamous cell carcinoma and tumor-adjacent tissues

Related factor	Carcinoma tissue		Tumor-adjacent tissue		χ^2	*P* Value
	Negative (-)	Positive (+)	Negative (-)	Positive (+)		
JAB1	65 (34.8)	122 (65.2)	19 (82.6)	4 (17.4)	19.539	<0.001
Smad4	106 (56.7)	81 (43.3)	5 (21.7)	18 (78.3)	10.037	0.002

[a]c-Jun activation domain-binding protein-1. [b]Mothers against decapentaplegic homolog 4.

Table 2. Analysis of JAB1[a] and Smad4[b] positive expression and related factors

Related Factor	n	JAB1 expression		χ^2	*P* Value	Smad4 expression		χ^2	*P* Value
		Negative (-)	Positive (+)			Negative (-)	Positive (+)		
Age									
>60	79	25 (31.6)	54 (68.4)	0.589	0.444	44 (55.7)	35 (44.3)	0.544	0.816
≤60	108	40 (37.0)	68 (63.0)			62 (57.4)	46 (42.6)		
Gender									
Male	135	46 (67.7)	89 (32.3)	0.101	0.751	78 (57.8)	57 (42.2)	0.236	0.627
Female	52	19 (30.2)	33 (69.8)			28 (53.8)	24 (46.2)		
Differentiation									
Well+Moderate	97	42 (43.3)	55 (56.7)	6.481	0.011	48 (49.5)	49 (50.5)	4.255	0.039
Poor	90	23 (25.6)	67 (74.4)			58 (64.4)	32 (35.6)		
TNM stage									
I+II	104	47 (45.2)	57 (54.8)	11.247	0.001	49 (47.1)	55 (52.9)	8.738	0.003
III	83	18 (21.7)	65 (78.3)			57 (68.7)	26 (31.3)		
Lymphatic metastasis									
Yes	84	15 (17.9)	69 (82.1)	19.212	<0.001	62 (43.6)	22 (56.4)	18.215	<0.001
No	103	50 (48.5)	53 (51.5)			44 (20.7)	59 (79.3)		
Depth of invasion									
T1-2	72	35 (48.6)	37 (51.4)	9.906	0.002	29 (40.3)	43 (59.7)	12.836	<0.001
T3-4	115	30 (26.1)	85 (73.9)			77 (67.0)	38 (33.0)		
Tumer size (cm)									
>5	63	22 (34.9)	41 (65.1)	0.001	0.974	33 (52.4)	30 (47.6)	0.717	0.397
≤5	124	43 (34.7)	81 (65.3)			73 (58.9)	51 (41.1)		
BMI[c] (kg/m^2)									
≥25	82	28 (34.1)	54 (65.9)	0.024	0.876	49 (59.8)	33 (40.2)	0.561	0.454
<25	105	37 (35.2)	68 (64.8)			57 (54.3)	48 (45.7)		

[a]c-Jun activation domain-binding protein-1. [b]Mothers against decapentaplegic homolog 4. [c]body mass index.

(such as lung adenocarcinoma, hepatocellular carcinoma, colon cancer, hepatocellular carcinoma, oral squamous cell carcinoma, glioma) and it implicates in carcinogenesis and may play a role in tumor progression towards a more malignant phenotype [7-12].

P27 is well known as a CDK inhibitor, which influences the function of cyclic protein, inhibiting cell cycle progression from G1 to S phase, acting as a tumor suppressor [13-15]. Low expression of p27 is associated with advanced tumor stage and poor prognosis [16, 17]. JAB1 can promote ubiquitin degradation of p27 by translocating it from nucleus to cytoplasm, resulting in carcinogenesis, invasion and metastasis of malignant tumor [16-18]. Smad4 which is located on chromosome 18q21.1 is a central transducer of the transforming growth factor beta (TGF-β) pathway, and an important multifunctional cytokine that regulates cell proliferation and differentiation [19, 20]. Recent researches have shown that Smad 4 is low expressed in many kinds of malignant tumors

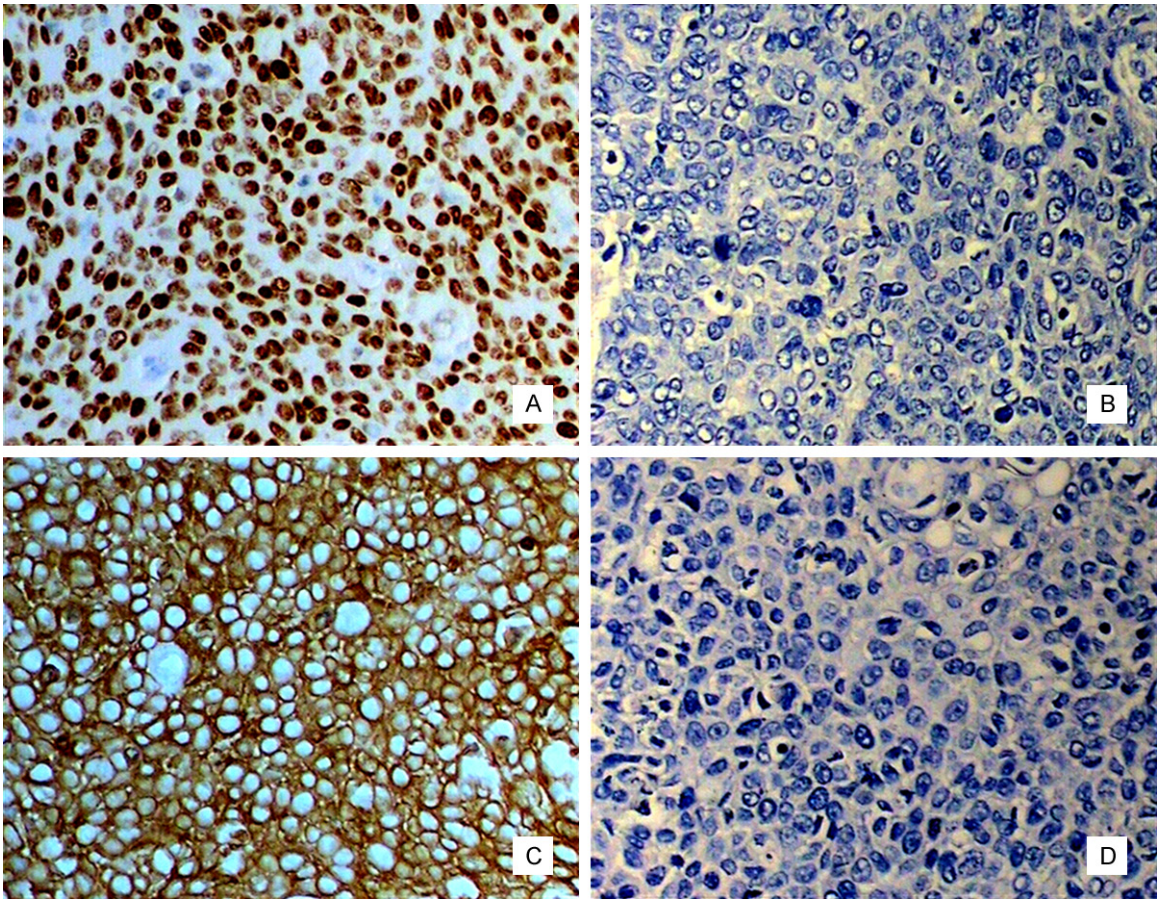

Figure 1. JAB1 were higher expressed in ESCC tissues and its nucleus was stained brown (200×) (A). JAB1 were lower expressed in ESCC tissues and tumor cells were not stained (200×) (B). Smad4 were higher expressed in ESCC tissues and its cytoplasm was stained yellow (200×) (C). Smad4 were lower expressed in ESCC tissues and tumor cells were not stained (200×) (D).

and it implicates in carcinogenesis and may play a role in tumor progression towards a more malignant phenotype [21-23]. Studies focusing on the relationship between JAB1 and Smad4 in ESCC are rarely reported. In the present study, we use immunohistochemical method to evaluate the clinical and prognostic significance of JAB1 and Smad4 in 187 cases of ESCC. They may be useful in diagnosing and monitoring the prognosis for ESCC.

Materials and methods

Patients

The study protocol was approved by the ethics committee of the Nanjing Hospital Affiliated to Nanjing Medical University, and all tissue samples were collected from patients with appropriate informed consent. The average age of the 187 patients is 61.5 ranging from 34 to 83 years old, undergoing surgery between September 2010 and September 2015. 23 cases of tumor-adjacent tissues were taken from the control group (each patient with detailed clinical data and operation record). None of these patients received pre-operative chemotherapy or radiotherapy. ESCC patients in the experimental group were shown in **Tables 1** and **2**. TNM classification system was proposed by American Joint Committee on Cancer (AJCC) in 2010 [24]. All sections were confirmed as human ESCC by two pathologists. Gastroscope or CT scan was performed once at 6-month intervals after surgery. They were followed up for 3 to 60 months after surgery via the telephone.

Immunohistochemical (IHC) analysis

Expression of the JAB1 and Smad4 were detected by streptavidin-biotin-peroxidase co-

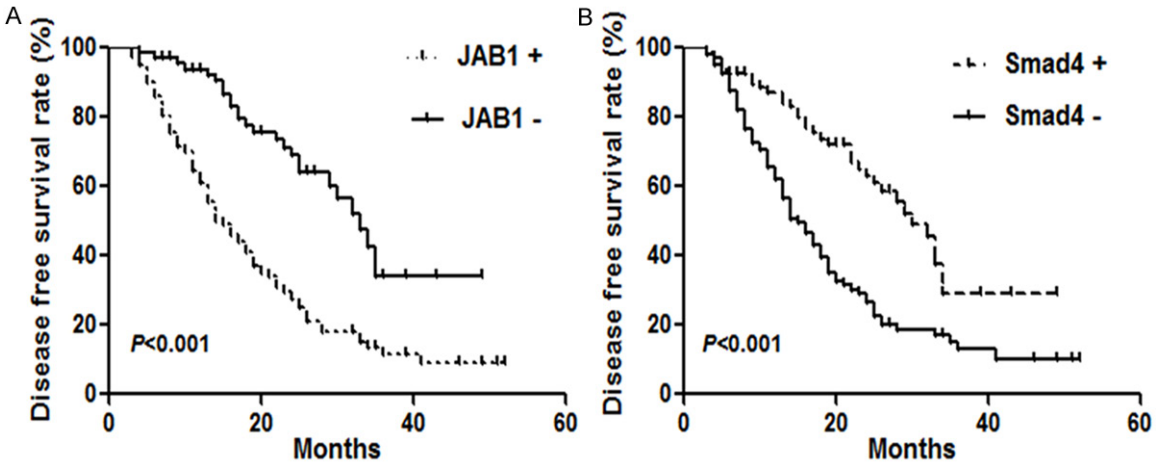

Figure 2. Kaplan-Meier curves for disease free survival in ESCC patients based on JAB1 expression (A) or Smad4 expression (B).

mplex method based on previous publication [21]. JAB1 antibody, mouse monoclonal IgG (1:80) was purchased from BD Pharmingen, San Diego, CA, USA. Smad4 antibody, mouse monoclonal IgG (1:100) was purchased from Santa Cruz Biotechnology (Dallas, TX, USA); Secondary antibody (goat anti-mouse IgG) and DAB solution were purchased from Wuhan Boster Biological Technology, Ltd, P.R.C. Sections immunostained with nonspecific IgG were used as negative control.

Evaluation of ESCC-1 and cyclin D1 staining

Combined with a previous publication, the sections were evaluated mostly according to the immunoreactive score (IRS) by two pathologists (21). An IRS was calculated by multiplying (a) and (b). (a) staining intensity (0 = colorless, 1 = pallide-flavens, 2 = yellow, 3 = brown); (b) Percentage of positive cells: 0 (no positive cells), 1 (<10% positive cells), 2 (11-50% positive cells) and 3 (51 to 75% of positive cells), and 4 (>75% positive cells positive). In the study, the JAB1 and Smad4 expression were defined as positive (+, high expression) when the score was more than 2, and negative (-, low expression) when score was less than or equal to 2.

Statistical analysis

Statistical analyses were performed using SASS software version 9.2 and GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA). The numeration data among different groups were compared by using χ^2 test (**Tables 1** and **2**). The relationship between JAB1 and Smad4 expression was evaluated using Pearson χ^2 test. Kaplan-Meier method and log-rank tests were used to analyze disease free survival and overall survival rates. The risk factors for disease free survival and overall survival were estimated by odds ratio (OR) and 95% confidence Limits of them computed by multivariate logistic regression analysis.

Results

Relationship of JAB1 and Smad expression and clinicopathological parameters

Nucleus appearing yellow or brown granules were defined as positive expression of JAB1, and positive (**Figure 1A**), and negative (**Figure 1B**). The cytoplasm or nucleus appearing yellow or brown granules were defined as positive expression of Smad4, and positive (**Figure 1C**), and negative (**Figure 1D**). As was shown in **Tables 1** and **2**, the positive rate of JAB1 was 65.2% in ESCC tissues which was higher than that in tumor-adjacent tissues (17.4%), P< 0.001. High levels of JAB1 protein were significantly related to tumor differentiation, TNM stage, lymphatic metastasis and the depth of invasion (P = 0.011, P = 0.001, P<0.001 and P = 0.002, respectively). However, JAB1 protein expression was not associated with BMI (body mass index), age, gender and tumor size (P = 0.876, P = 0.444 P = 0.751 and P = 0.974, respectively). The positive rate of Smad was 43.3% in ESCC tissues, which was lower than that in tumor-adjacent tissues (78.3%), P =

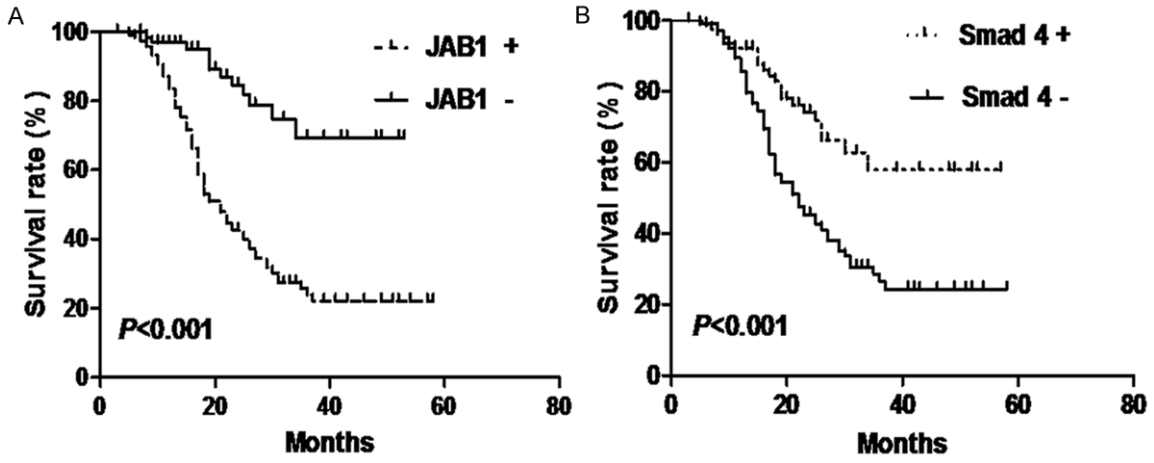

Figure 3. Kaplan-Meier curves for overall survival in ESCC patients based on JAB1 expression (A) or Smad4 expression (B).

Table 3. Correlations between JAB1[a] and Smad4[b] expression in esophageal squamous cell carcinoma tissues

Smad4	JAB1		Contingency coefficient (r)	χ^2	*P* value
	+	-			
+	30	51	-0.518	50.123	<0.001
-	92	14			

[a]c-Jun activation domain-binding protein-1. [b]Mothers against decapentaplegic homolog 4.

0.002. Low levels of Smad4 protein were significantly related to tumor differentiation, TNM stage, lymphatic metastasis and the depth of invasion (P = 0.039, P = 0.003, P<0.001 and P<0.001, respectively). However, Smad4 protein expression was not associated with BMI, age, gender, tumor size (P = 0.454, P = 0.816, P = 0.627, P = 0.397, respectively).

Correlation between the expression of JAB1 and Smad4 and their survival

The correlation was shown in **Figures 2**, **3**. Kaplan-Meier survival curves of ESCC patients were based on JAB1 or Smad4 expression. Patients with high JAB1 expression had significantly shorter disease free survival compared to those patients with low expression (P<0.001, log-rank test) (**Figure 2A**). Patients with high Smad4 expression had significantly longer disease free survival compared to those patients with low Smad4 expression (P<0.001, log-rank test) (**Figure 2B**). Patients with high JAB1 expression had significantly worse survival compared to those patients with low expression (P<0.001, log-rank test) (**Figure 3A**). Patients with high Smad4 expression had significantly better survival compared to those patients with low Smad4 expression (P<0.001, log-rank test) (**Figure 3B**). Multivariate logistic regression analysis showed that TNM stage, lymphatic metastasis as well as the JAB1 expression were negatively correlated with disease free survival (P = 0.018, P = 0.019 and P = 0.035, respectively) and overall survival of ESCC (P<0.001, P = 0.043 and P = 0.012, respectively), and Smad4 expression were positively correlated with disease free survival (0.033) and overall survival of ESCC (P = 0.023). These suggested that high stage of TNM, lymphatic metastasis, high levels of JAB1 and low levels of Smad4 are independent risk factors for prognosis (**Tables 4**, **5**).

Correlation between JAB1 and Smad4 expression in ESCC tissues and clinicopathological parameters

There was a negative correlation between JAB1 and Smad4 expression in ESCC tissues (r = -0.518, P<0.001), as was shown in **Table 3**.

Discussion

In this study, JAB1 expression was observed in the nucleus and the positive rate of JAB1 in ESCC was significantly higher than that of the tumor-adjacent tissues. JAB1 expression in poorly was much higher than that in well-moderately differentiation, and the higher the dif-

Table 4. Multivariate logistic regression analyses of different clinicopathological variables and JAB1[a] and Smad4[b] expression status as predictors for disease free survival in esophageal squamous cell carcinoma tissues

Variable	Odds ratio	95% Odds Ratio Confidence Limits		χ^2	*P* value
Age	1.023	0.985	1.063	1.435	0.231
Gender	1.031	0.424	2.507	0.005	0.946
Differentiation	0.567	0.240	1.339	1.675	0.196
TNM stage	4.016	1.271	12.694	5.607	0.018
Lymphatic metastasis	4.137	1.260	13.582	5.483	0.019
Depth of Invasion	1.692	0.620	4.618	1.052	0.305
Tumer size	2.400	0.874	6.587	2.889	0.089
BMI (body mass index)	1.125	0.511	2.474	0.086	0.770
JAB1 (positive vs. negative)	2.574	1.071	6.186	4.469	0.035
Smad4 (positive vs. negative)	0.395	0.168	0.928	4.538	0.033

[a]c-Jun activation domain-binding protein-1. [b]Mothers against decapentaplegic homolog 4.

Table 5. Multivariate logistic regression analyses of different clinicopathological variables and JAB1[a] and Smad4[b] expression status as predictors for overall survival in esophageal squamous cell carcinoma tissues

Variable	Odds Ratio	95% Odds Ratio Confidence Limits		χ^2	*p* value
Age	0.983	0.943	1.026	0.610	0.435
Gender	1.131	0.419	3.048	0.059	0.808
Differentiation	0.629	0.238	1.665	0.871	0.351
TNM stage	9.596	2.939	31.336	14.028	<0.001
Lymphatic metastasis	3.495	1.041	11.738	4.098	0.043
Depth of Invasion	0.940	0.174	1.736	1.041	0.308
Tumer size	1.077	0.345	3.363	0.016	0.899
BMI (body mass index)	1.032	0.422	2.523	0.005	0.945
JAB1	4.242	1.369	13.151	6.267	0.012
Smad4	0.295	0.103	0.842	5.204	0.023

[a]c-Jun activation domain-binding protein-1. [b]Mothers against decapentaplegic homolog 4.

ferentiation was, the lower the positive rate was. It suggested that JAB1 might participate in tumorigenesis of ESCC. The positive rate of JAB1 was closely related to the TNM stage, lymphatic metastasis and the depth of invasion, which indicated that the JAB1 protein could lead to the invasion and metastasis of tumor. The study found that the patients with JAB1 overexpression was correlated with poorer overall survival than the lower expressed patients [11, 12]. Therefore, JAB1 was expected to be an independent tumor prognostic factor.

Our follow-up results also showed that the patients with JAB1 overexpression had unfavorable effect and the survival time was shorter than those with low JAB1 expression. Multivariate logistic regression analysis also suggested that high JAB1 expression was negatively correlated with disease free survival and overall survival of ESCC. It was an independent risk factor for prognosis. The number of our samples was still relatively small. In future, expanded samples of ESCC were needed to further investigate its application in predicting prognosis.

In recent years, JAB1 as the target drug of gene therapy also has got more and more attention. The proliferation and the invasion ability of tumor cells have been inhibited by using RNA interference [25, 26]. JAB1 may become the new target for tumor gene therapy.

In the current study, Smad4 expression was observed in the cytoplasm and/or nucleus in esophageal ESCC cells. This study found that the positive rate of Smad4 in ESCC tissue cells were significantly lower than that in the tumor-adjacent tissues. Smad4 expression was inversely associated with the tumor differentiation. The loss or reduction in the expression of Smad4 was also significantly correlated with the grade of differentiation exhibited by the carcinoma. Expression of Smad4 was also inversely related to the tumor TNM stage, lymphatic metastasis and the depth of invasion. Above all, these suggested that Smad4 may be a

tumor inhibition factor participating in tumorigenesis, invasion and metastasis of ESCC.

Studies showed that patients with low Smad4 expression had poor prognosis [22, 23]. Our study also showed that patients with low Smad4 expression had significantly worse survival compared with those with high Smad4 expression. The multivariate logistic regression analysis also suggested that low Smad4 expression was an independent risk factor for prognosis. It may be helpful to consider the auxiliary diagnosis of ESCC, and judge the prognosis of patients.

Our study also found that the expression of JAB1 was up-regulated, while the expression of Smad4 protein in ESCC was down-regulated, and they were inversely correlated. It suggested that JAB1 had inversely regulation on Smad4 protein and it might be related to TGF-β signal pathway. Li J found out that JAB1 could cause degradation of Smad4 via TGF-β signal pathway in PANC-1 cells [27].

In conclusion, JAB1 overexpression or Smad4 low expression were closely related to tumor progression and metastasis in ESCC. JAB1 overexpression or Smad4 low expression correlates to poor prognosis. JAB1 was inversely correlated with Smad4 levels. In future, the detailed mechanism of JAB1 in regulating the Smad4 of ESCC may help us to further reveal the aggressive nature of this malignancy and combined detection of them can be used as an important index to evaluate the prognosis of ESCC.

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Disclosure of conflict of interest

None.

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References

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917.

[2] Cook MB. Non-acid reflux: the missing link between gastric atrophy and esophageal squamous cell carcinoma? Am J Gastroenterol 2011; 106: 1930-1932.

[3] Dawsey SM, Lewin KJ, Liu FS, Wang GQ and Shen Q. Esophageal morphology from Linxian, China. Squamous histologic findings in 754 patients. Cancer 1994; 73: 2027-2037.

[4] Holmes RS and Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. Semin Radiat Oncol 2007; 17: 2-9.

[5] Huang L, Xu A, Li T, Han W, Wu S and Wang Y. Detection of perioperative cancer antigen 72-4 in gastric juice pre- and post-distal gastrectomy and its significances. Med Oncol 2013; 30: 651.

[6] Shackleford TJ and Claret FX. JAB1/CSN5: a new player in cell cycle control and cancer. Cell Div 2010; 5: 26.

[7] Goto A, Niki T, Moriyama S, Funata N, Moriyama H, Nishimura Y, Tsuchida R, Kato JY and Fukayama M. Immunohistochemical study of Skp2 and Jab1, two key molecules in the degradation of P27, in lung adenocarcinoma. Pathol Int 2004; 54: 675-681.

[8] Wang Y, Yu YN, Song S, Li TJ, Xiang JY, Zhang H, Lu MD, Ji F and Hu LQ. JAB1 and phospho-Ser10 p27 expression profile determine human hepatocellular carcinoma prognosis. J Cancer Res Clin Oncol 2014; 140: 969-978.

[9] Nishimoto A, Kugimiya N, Hosoyama T, Enoki T, Li TS and Hamano K. JAB1 regulates unphosphorylated STAT3 DNA-binding activity through protein-protein interaction in human colon cancer cells. Biochem Biophys Res Commun 2013; 438: 513-518.

[10] Qin J, Wang Z, Wang Y, Ma L, Ni Q and Ke J. JAB1 expression is associated with inverse expression of p27(kip1) in hepatocellular carcinoma. Hepatogastroenterology 2010; 57: 547-553.

[11] Gao L, Huang S, Ren W, Zhao L, Li J, Zhi K, Zhang Y, Qi H and Huang C. Jun activation domain-binding protein 1 expression in oral squamous cell carcinomas inversely correlates with the cell cycle inhibitor p27. Med Oncol 2012; 29: 2499-2504.

[12] He SM, Zhao ZW, Wang Y, Zhao JP, Wang L, Hou F and Gao GD. Potential role of Jun activation domain-binding protein 1 and phosphory-

lated p27 expression in prognosis of glioma. Brain Tumor Pathol 2012; 29: 3-9.
[13] Toyoshima H and Hunter T. p27, a novel inhibitor of G1 cyclin-Cdk protein kinase activity, is related to p21. Cell 1994; 78: 67-74.
[14] Polyak K, Kato JY, Solomon MJ, Sherr CJ, Massague J, Roberts JM and Koff A. p27Kip1, a cyclin-Cdk inhibitor, links transforming growth factor-beta and contact inhibition to cell cycle arrest. Genes Dev 1994; 8: 9-22
[15] Che X, Liu J, Huang H, Mi X, Xia Q, Li J, Zhang D, Ke Q, Gao J and Huang C. p27 suppresses cyclooxygenase-2 expression by inhibiting p38 beta and p38delta-mediated CREB phosphorylation upon arsenite exposure. Biochim Biophys Acta 2013; 1833: 2083-2091.
[16] Ahn J, Hong SA, Lee SE, Kim J, Oh YS, Park SJ and Chung YJ. Cytoplasmic localization of Jab1 and p27 Kip1 might be associated with invasiveness of papillary thyroid carcinoma. Endocr J 2009; 56: 707-713.
[17] Esteva FJ, Sahin AA, Rassidakis GZ, Yuan LX, Smith TL, Yang Y, Gilcrease MZ, Cristofanilli M, Nahta R, Pusztai L and Claret FX. Jun activation domain binding protein 1 expression is associated with low p27(Kip1) levels in node-negative breast cancer. Clin Cancer Res 2003; 9: 5652-5659.
[18] Sui L, Dong Y, Watanabe Y, Yamaguchi F, Sugimoto K and Tokuda M. Clinical significance of Skp2 expression, alone and combined with Jab1 and p27 in epithelial ovarian tumors. Oncol Rep 2006; 15: 765-771.
[19] Massague J. TGFbeta in Cancer. Cell 2008; 134: 215-230.
[20] Massague J. TGFbeta signalling in context. Nat Rev Mol Cell Biol 2012; 13: 616-630.
[21] Liu NN, Xi Y, Callaghan MU, Fribley A, Moore-Smith L, Zimmerman JW, Pasche B, Zeng Q and Li YL. SMAD4 is a potential prognostic marker in human breast carcinomas. Tumour Biol 2014; 35: 641-6.
[22] Wang C, Zhou Y, Ruan R, Zheng M, Han W and Liao L. High expression of COUP-TF II cooperated with negative Smad4 expression predicts poor prognosis in patients with colorectal cancer. Int J Clin Exp Pathol 2015; 8: 7112-7121.
[23] Wang LH, Kim SH, Lee JH, Choi YL, Kim YC, Park TS, Hong YC, Wu CF and Shin YK. Inactivation of SMAD4 tumor suppressor gene during gastric carcinoma progression. Clin Cancer Res 2007; 13: 102-110.
[24] In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A, editors. AJCC Cancer Staging Manual. 7th edition. New York, NY: Springer; 2010.
[25] Schutz AK, Hennes T, Jumpertz S, Fuchs S and Bernhagen J. Role of CSN5/JAB1 in Wnt/beta-catenin activation in colorectal cancer cells. FEBS Lett 2012; 586: 1645-1651.
[26] Fukumoto A, Tomoda K, Yoneda-Kato N, Nakajima Y and Kato JY. Depletion of Jab1 inhibits proliferation of pancreatic cancer cell lines. FEBS Lett 2006; 580: 5836.
[27] Li J, Gu Z, Li S, Xiao Z and Sun K. Reverse correlation of Jab1 and Smad4 in PANC-1 cells involved in the pathogenesis of pancreatic cancer. Int J Clin Exp Pathol 2015; 8: 9279-9285.