Clinicalopathological 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
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Table 1. Expressions of JAB1 and Smad4 in esophageal squamous cell carcinoma and tumor-adjacent tissues

<table>
<thead>
<tr>
<th>Related factor</th>
<th>Carcinoma tissue</th>
<th>Tumor-adjacent tissue</th>
<th>( \chi^2 )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative (-)</td>
<td>Positive (+)</td>
<td>Negative (-)</td>
<td>Positive (+)</td>
</tr>
<tr>
<td>JAB1</td>
<td>65 (34.8)</td>
<td>122 (65.2)</td>
<td>19 (82.6)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Smad4</td>
<td>106 (56.7)</td>
<td>81 (43.3)</td>
<td>5 (21.7)</td>
<td>18 (78.3)</td>
</tr>
</tbody>
</table>

\*c-Jun activation domain-binding protein-1. \*Mothers against decapentaplegic homolog 4.

Table 2. Analysis of JAB1 and Smad4 positive expression and related factors

<table>
<thead>
<tr>
<th>Related Factor</th>
<th>n</th>
<th>JAB1 expression</th>
<th>Smad4 expression</th>
<th>( \chi^2 )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Negative (-)</td>
<td>Positive (+)</td>
<td>Negative (-)</td>
<td>Positive (+)</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td>79</td>
<td>25 (31.6)</td>
<td>54 (68.4)</td>
<td>0.589</td>
<td>0.444</td>
</tr>
<tr>
<td>Age ≤60</td>
<td>108</td>
<td>40 (37.0)</td>
<td>68 (63.0)</td>
<td>1.101</td>
<td>0.751</td>
</tr>
<tr>
<td>Gender Male</td>
<td>135</td>
<td>46 (67.7)</td>
<td>89 (32.3)</td>
<td>0.101</td>
<td>0.751</td>
</tr>
<tr>
<td>Gender Female</td>
<td>52</td>
<td>19 (30.2)</td>
<td>33 (69.8)</td>
<td>0.011</td>
<td>0.976</td>
</tr>
<tr>
<td>Differentiation Well+Moderate</td>
<td>97</td>
<td>42 (43.3)</td>
<td>55 (56.7)</td>
<td>6.481</td>
<td>0.011</td>
</tr>
<tr>
<td>Differentiation Poor</td>
<td>90</td>
<td>23 (36.2)</td>
<td>67 (63.8)</td>
<td>5.841</td>
<td>0.016</td>
</tr>
<tr>
<td>TNM stage I+II</td>
<td>104</td>
<td>47 (45.2)</td>
<td>57 (54.8)</td>
<td>11.247</td>
<td>0.001</td>
</tr>
<tr>
<td>TNM stage III</td>
<td>83</td>
<td>18 (21.7)</td>
<td>65 (78.3)</td>
<td>5.841</td>
<td>0.016</td>
</tr>
<tr>
<td>Lymphatic metastasis Yes</td>
<td>84</td>
<td>15 (17.9)</td>
<td>69 (82.1)</td>
<td>19.212</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphatic metastasis No</td>
<td>103</td>
<td>50 (48.5)</td>
<td>53 (51.5)</td>
<td>0.001</td>
<td>0.971</td>
</tr>
<tr>
<td>Depth of invasion T1-2</td>
<td>72</td>
<td>35 (48.6)</td>
<td>37 (51.4)</td>
<td>9.906</td>
<td>0.002</td>
</tr>
<tr>
<td>Depth of invasion T3-4</td>
<td>115</td>
<td>30 (26.1)</td>
<td>85 (73.9)</td>
<td>7.707</td>
<td>0.006</td>
</tr>
<tr>
<td>Tumor size (cm) &gt;5</td>
<td>63</td>
<td>22 (34.9)</td>
<td>41 (65.1)</td>
<td>0.001</td>
<td>0.974</td>
</tr>
<tr>
<td>Tumor size (cm) ≤5</td>
<td>124</td>
<td>43 (34.7)</td>
<td>81 (65.3)</td>
<td>3.962</td>
<td>0.047</td>
</tr>
<tr>
<td>BMI (&lt;25 ) (kg/m(^2))</td>
<td>82</td>
<td>28 (34.1)</td>
<td>54 (65.9)</td>
<td>0.024</td>
<td>0.876</td>
</tr>
<tr>
<td>BMI (≥25 ) (kg/m(^2))</td>
<td>105</td>
<td>37 (35.2)</td>
<td>68 (64.8)</td>
<td>0.024</td>
<td>0.876</td>
</tr>
</tbody>
</table>

\*c-Jun activation domain-binding protein-1. \*Mothers against decapentaplegic homolog 4. \*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.
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. Gastroscopie 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 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).
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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 Bo- ster 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 sec-
tions 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) Pe-
centage 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 posi-
tive (+, 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 χ² test (Tables
1 and 2). The relationship between JAB1 and
Smad4 expression was evaluated using Pear-
son χ² test. Kaplan-Meier method and log-rank
tests were used to analyze disease free surviv-
and overall survival rates. The risk factors for
disease free survival and overall survival were
estimated by odds ratio (OR) and 95% confi-
dence 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 signifi-
cantly 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 2. Kaplan-Meier curves for disease free survival in ESCC patients based on JAB1 expression (A) or Smad4 expression (B).](image-url)
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-

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**Table 3. Correlations between JAB1\(^a\) and Smad4\(^b\) expression in esophageal squamous cell carcinoma tissues**

<table>
<thead>
<tr>
<th>Smad4</th>
<th>JAB1</th>
<th>Contingency coefficient (r)</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>30</td>
<td>-0.518</td>
<td>50.123</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>-</td>
<td>92</td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)c-Jun activation domain-binding protein-1. \(^b\)Mothers against decapentaplegic homolog 4.
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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].

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

Table 4. Multivariate logistic regression analyses of different clinico-pathological variables and JAB1 and Smad4 expression status as predictors for disease free survival in esophageal squamous cell carcinoma tissues

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

\*c-Jun activation domain-binding protein-1. \*Mothers against decapentaplegic homolog 4.

Table 5. Multivariate logistic regression analyses of different clinico-pathological variables and JAB1 and Smad4 expression status as predictors for overall survival in esophageal squamous cell carcinoma tissues

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Odds Ratio Confidence Limits</th>
<th>( \chi^2 )</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.983</td>
<td>0.943 - 1.026</td>
<td>0.610</td>
<td>0.435</td>
</tr>
<tr>
<td>Gender</td>
<td>1.131</td>
<td>0.419 - 3.048</td>
<td>0.059</td>
<td>0.808</td>
</tr>
<tr>
<td>Differentiation</td>
<td>0.629</td>
<td>0.238 - 1.665</td>
<td>0.871</td>
<td>0.351</td>
</tr>
<tr>
<td>TNM stage</td>
<td>9.596</td>
<td>2.939 - 31.336</td>
<td>14.028</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphatic metastasis</td>
<td>3.495</td>
<td>1.041 - 11.738</td>
<td>4.098</td>
<td>0.043</td>
</tr>
<tr>
<td>Depth of Invasion</td>
<td>0.940</td>
<td>0.174 - 1.736</td>
<td>1.041</td>
<td>0.308</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.077</td>
<td>0.345 - 3.363</td>
<td>0.016</td>
<td>0.899</td>
</tr>
<tr>
<td>BMI (body mass index)</td>
<td>1.032</td>
<td>0.422 - 2.523</td>
<td>0.005</td>
<td>0.945</td>
</tr>
<tr>
<td>JAB1</td>
<td>4.242</td>
<td>1.369 - 13.151</td>
<td>6.267</td>
<td>0.012</td>
</tr>
<tr>
<td>Smad4</td>
<td>0.295</td>
<td>0.103 - 0.842</td>
<td>5.204</td>
<td>0.023</td>
</tr>
</tbody>
</table>

\*c-Jun activation domain-binding protein-1. \*Mothers against decapentaplegic homolog 4.

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.
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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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