Correlation between insulin-like growth factor binding protein 3 and metastasis-associated gene 1 protein in esophageal squamous cell carcinoma

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Abstract. The present study aimed to investigate the correlation between insulin-like growth factor binding protein 3 (IGFBP-3) and metastasis-associated gene 1 (MTA1) protein, and the clinicopathological features and prognosis of esophageal squamous cell carcinoma (ESCC). Patients with ESCC who underwent surgical resection were enrolled in the current study, ESCC tissues and adjacent normal tissues (control) were obtained from 197 patients. The protein expression levels of IGFBP-3 and MTA1 were detected using immunohistochemistry. The results demonstrated that the expression of IGFBP-3 in ESCC tissues was significantly lower than in the adjacent normal tissues (27.4 vs. 40.6%; P<0.05), and was negatively correlated with smoking status, degree of tumor differentiation and lymph node metastasis (P<0.05). The expression of MTA1 protein in ESCC tissues was significantly higher than that of the adjacent tissues (42.1 vs. 11.2%; P<0.05), and was positively correlated with the tumor size, extent of tumor invasion and lymph node metastasis (P<0.05). No association was identified between the protein expression levels of IGFBP-3 and MTA1. The protein expression levels of IGFBP-3 and MTA1 were not independent risk factors for ESCC prognosis; however, the degree of tumor invasion (P=0.02) and rate of lymph node metastasis (P=0.027) were. IGFBP-3 inhibits the proliferation and metastasis of ESCC; however, MTA1 promotes the proliferation and metastasis of ESCC. There is no interaction between IGFBP-3 and MTA1 in ESCC, and they are not independent risk factors for ESCC prognosis.

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Introduction

Esophageal squamous cell carcinoma (ESCC) is one of the ten most common types of malignancy worldwide, and is associated with a poor prognosis (1). In China, ESCC has fourth highest rate of cancer-related mortality (2). The overall 5-year survival rate is <30%, and the high recurrence rate is the predominant reason for poor quality of life and mortality in patients with ESCC (3,4). Therefore, investigation into the mechanism underlying the recurrence and metastasis of ESCC is of clinical significance for improving the prognosis of these patients. Increased expression levels of metastasis-associated 1 gene (MTA1) are positively correlated with the invasion and metastasis of a variety of types of malignant tumor (5). Toh *et al* (6) observed that the expression level of MTA1 in ESCC is associated with deacetylase activity of the H4 histone, and that the invasion and lymph node metastasis of tumor cells with high expression levels of MTA1 mRNA are significantly increased.

The insulin-like growth factor (IGF) signaling pathway is important for the proliferation, differentiation and apoptosis of cells, among which IGF-1 and IGF binding protein 3 (IGFBP-3) are key in cell growth and tumor formation (7).

Rajah *et al* (8) demonstrated that by blocking the binding of IGFs to their receptors, IGFBP-3 inhibits the activity of IGFs and induces apoptosis, indicating a protective effect. A number of epidemiological studies have demonstrated that high levels of circulating IGF-1 and low levels of IGFBP-1 are associated with increased risk of several common cancers, including breast (9), prostate (10), lung (11) and colorectal (12).

The association of MTAl and IGFBP-3 expression levels with the clinical pathology and prognosis of ESCC is rarely evaluated, and whether the expression levels of these two factors are associated with ESCC remains to be elucidated. The present study investigated the correlation of IGFBP-3 and MTA1 protein expression and the clinicopathological features and prognosis of 197 ESCC patients, with the aim of providing an objective basis for the diagnosis and treatment of ESCC.

Subjects and methods

Subjects. ESCC patients (148 males and 49 females; age, 41-77 years; mean age, 59.8 years) who underwent ESCC resection in the Department of Thoracic and Cardiovascular Surgery, Beijing Luhe Hospital Affiliated to Capital Medical University (Beijing, China) or Department of Thoracic Surgery, Cixian People's Hospital (Handan, China) between October 2008 and June 2010 were enrolled in the present study. All patients were diagnosed with ESCC by preoperative biopsy, had surgical indications and no surgical contraindications. They did not receive preoperative adjuvant therapies, such as radiotherapy or chemotherapy, and had no serious perioperative complications. The pathological specimens embedded in paraffin were preserved well and the medical records were complete. The present study was approved by the Ethics Committee of Beijing Luhe Hospital Affiliated to Capital Medical University (Beijing, China) and informed consent was obtained from all patients.

Grouping of paraffin specimens and detection of IGFBP-3 and MTA1 expression. The paraffin specimens were divided into an ESCC group and control group, which included ESCC tissues (197 samples) and adjacent normal tissues (>5 cm away from the tumor margin; 197 samples), respectively. The expression levels of IGFBP-3 and MTA1 protein were detected by immunohistochemistry according to previously described methods (13,14). Primary antibodies used included rabbit anti-human polyclonal antibody against IGFBP-3 (Wuhan Boster Biological Technology, Ltd., Wuhan, China; cat. no. BA2162; dilution, 1:100) and goat anti-human polyclonal antibody against MTA1 (Santa Cruz Biotechnology, Inc., TX, USA; cat. no. sc-9446; dilution, 1:100). Secondary antibodies including goat anti-rabbit immunoglobulin G (IgG) conjugated to horseradish peroxidase (HRP; cat. no. ZB-2301; dilution, 1:2,000) and rabbit anti-goat IgG-HRP (cat. no. ZB-2306; dilution, 1:2,000) were purchased from Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd., Beijing, China).

Pathological grading. According to the 7th edition of the ESCC staging system (15), there were 35, 51 and 111 cases with phase I, II and III ESCC, respectively. In total, 35 cases were well-differentiated, 123 cases were moderately-differentiated, and 39 cases were poorly-differentiated. Tumor size ≤3 cm was observed in 43 cases, while tumor size >3 cm was observed in 154 cases.

Criteria to judge results. The stained slides were evaluated by two independent pathologists. The proportion of cells with positive brown staining for MTA1 and IGFBP-3 was observed. The positive-cell scoring was as follows: <5%, 0 points; 5-25%, 1 point; 26-50%, 2 points; 51-75%, 3 points; and >75%, 4 points. The staining intensity with MTA1 and IGFBP-3 antibodies was scored was as follows: Minimal staining similar to the background, 0 points; lightly stained, more than the background and pale yellow, 1 point; moderately stained, markedly more than the background and a brown-yellow, 2 points; and clearly stained a dark brown-yellow or tan, 3 points. The total scoring was as follows: Total score = number of positive cells x staining intensity. Total score ≥5 indicated a positive result, and <5 indicated a negative result. The nucleus and cytoplasm were observed to perform the scoring and statistical analysis. All the sections were judged by two pathologists blinded to the groupings and the inconsistencies were negotiated to reach a consensus.

Follow up. All the patients were successfully discharged, and follow up was performed once every three months for the first 2 years and subsequently once every 6 months. Follow-up included physical examination, chest X-ray, biochemical analysis (squamous cell carcinoma antigen, carbohydrate antigen (CA)-125, α-fetal protein, cancer embryo antigen, CA-199, CA-153, ferritin), computed tomography, ultrasound and gastroscopy. The postoperative tumor recurrence and metastasis were diagnosed according to the patients' imaging and histological findings, and the locations and times of recurrence and metastasis were recorded. The disease-free survival period referred to the period starting from the date of surgery to that of tumor recurrence or mortality as a result of non-cancer-associated disease. The overall survival period refers to the period starting from the date of surgery to mortality or to the follow-up deadline. The follow-up deadline of the present study was June 30, 2013, with a median follow-up time of 12 months (2-56 months). The follow-up data was obtained from outpatient and telephone reviewing.

Statistical analysis. SPSS 16.0 statistical software (SPSS, Inc., Chicago, IL, USA) was used for data analysis. The association between positive staining for IGFBP-3 and MTA1, and the clinical pathological characteristics were analyzed with a χ^2 test. The Kaplan-Meier life-table method was performed for the survival analysis and log-rank test was used to determine the survival difference. The multivariate analysis used the COX regression analysis to determine the independent risk factors of prognosis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Expression levels of IGFBP-3 and MTA1 protein in ESCC and adjacent tissues. Positive staining for IGFBP-3 was predominantly localized to the cytoplasm. Among the 197 ESCC cases, 54 cancer tissue samples (27.4%) exhibited positive expression of IGFBP-3, while 80 adjacent tissue samples (40.6%) exhibited expression of IGFBP-3. The intergroup comparison

Table I. Expression of IGFBP-3 and MTA1 protein in cancer tissues and adjacent normal tissues.

	IGFBP-3 (no. of cases)			MTA1 (no. of cases)		
Tissue	Negative	Positive	P-value	Negative	Positive	P-value
Cancer	143	54	0.008	114	83	0.001
Adjacent normal	117	80		175	22	

IGFBP-3; insulin-like growth factor binding protein 3; MTA1, metastasis-associated gene 1.

Table II. Correlation between IGFBP-3 expression and clinicopathological characteristics in 197 patients with esophageal squamous cell carcinoma.

		IGFBP-3, no. of cases (%)		
Parameter	No. of cases	Negative	Positive	P-value
Gender				<0.05
Male	148	101 (68.2)	47 (31.8)	
Female	49	42 (85.7)	7 (14.3)	
Age (years)				>0.05
<59	93	67 (72.0)	26 (28.0)	
≥59	104	76 (73.1)	28 (26.9)	
Smoking status				<0.05
<30 pack-years	103	67 (65.0)	36 (35.0)	
≥30 pack-years	94	76 (80.9)	18 (19.1)	
Family history				<0.05
No cancer	153	105 (68.6)	48 (31.4)	
With cancer	44	38 (86.4)	6 (13.6)	
Tumor size (cm)				>0.05
≤3	43	33 (76.7)	10 (23.3)	
>3	154	110 (71.4)	44 (28.6)	
WHO grade				<0.05
G1	35	17 (48.6)	18 (51.4)	
G2	123	93 (75.6)	30 (24.4)	
G3	39	33 (84.6)	6 (15.4)	
T status				>0.05
T1	29	23 (79.3)	6 (20.7)	
T2	57	37 (64.9)	20 (35.1)	
T3	107	80 (74.7)	27 (25.2)	
T4	4	3 (75.0)	1 (25.0)	
N status				<0.05
N0	109	69 (63.3)	40 (36.7)	
N1	88	74 (84.1)	14 (15.9	
Survival status				>0.05
Alive	71	53 (74.6)	18 (25.4)	
Deceased	126	90 (71.4)	36 (28.6)	

IGFBP-3; insulin-like growth factor binding protein 3; WHO, World Health Organisation; T, tumor invasion degree; N; lymph node metastasis rate.

indicated a statistically significant difference (P<0.05; Table I; Fig. 1A and B).

The staining of MTA1 protein was predominantly localized in the nucleus. Among the 197 ESCC cases, 83 cancer

Table III. Correlation between MTA1 protein expression and clinicopathological characteristics in 197 patients with esophageal squamous cell carcinoma.

Parameter	Case	MTA1 protein, no. of cases (%)		P-value
		Negative	Positive	
Gender				>0.05
Male	148	85 (57.4)	63 (42.6)	
Female	49	29 (59.2)	20 (40.8)	
Age (years)				>0.05
<59	93	55 (59.1)	38 (40.9)	
≥59	104	59 (56.7)	45 (43.3)	
Smoking status				>0.05
<30 pack-year	103	61 (59.2)	42 (40.8)	
≥30 pack-year	94	53 (56.4)	41 (43.6)	
Family history				<0.05
No cancer	153	81 (52.9)	72 (47.1)	
With cancer	44	33 (75.0)	11 (25.0)	
Tumor size (cm)				<0.05
≤3	43	32 (74.4)	11 (25.6)	
>3	154	82 (53.2)	72 (46.8)	
WHO grade				>0.05
G1	35	18 (51.4)	17 (48.6)	
G2	123	75 (61.0)	48 (39.0)	
G3	39	21 (53.8)	18 (46.2)	
T status				<0.05
T1	29	21 (72.4)	8 (27.6)	
T2	57	37 (64.9)	20 (35.1)	
T3	107	54 (50.5)	53 (49.5)	
T4	4	2 (50.0)	2 (50.0)	
N status				<0.05
N0	109	71 (65.1)	38 (34.9)	
N1	88	43 (48.9)	45 (51.1)	
Survival status				>0.05
Alive	71	41 (57.7)	30 (42.3)	
Deceased	126	73 (57.9)	53 (42.1)	

MTA1, metastasis-associated gene 1; WHO, World Health Organisation; T, tumor invasion degree; N; lymph node metastasis rate.

tissue samples (42.1%) exhibited positive expression of MTA1, while 22 adjacent tissue samples (11.2%) exhibited positive expression of MTA1 protein. The intergroup comparison indicated a statistically significant difference (P<0.05; Table I; Fig. 1C and D).

Correlation between IGFBP-3 and MTA1 protein expression levels and clinicopathological characteristics. The expression of IGFBP-3 differed significantly difference between male and female patients and between patients with and without tumor family history (P<0.05), and was negatively correlated with the smoking status, degree of tumor differentiation and lymph node metastasis (P<0.05), but was not correlated with age, tumor size, extent of tumor invasion or survival status (P>0.05, χ^2 test; Table II).

The expression of MTA1 protein was positively correlated with the tumor size, degree of tumor invasion and lymph node metastasis (P<0.05), and negatively correlated with a family history of cancer (P<0.05). It was not correlated with gender, age, the smoking status, degree of tumor differentiation or survival status (P>0.05, χ^2 test; Table III).

Correlation between IGFBP-3 and MTA1 protein expression. Positive expression of MTA1 and IGFBP-3 was observed in 23 cases, while 83 cases were negative for both MTA1 and IGFBP-3 protein expression. The χ^2 test indicated that there was no association between IGFBP-3 and MTA1 (P>0.05; Table IV).

Correlation of IGFBP-3 and MTA1 protein expression with prognosis of patients with ESCC. Based on the follow-up

Table IV. Correlation between IGFBP-3 and MTA1 protein expression.

	IGFBP-3				
MTA1	Negative	Positive	Total	χ^2	P-value
Negative	83	31	114		
Positive	60	23	83		
Total	143	54	197	0.936	>0.05

IGFBP-3; insulin-like growth factor binding protein 3; MTA1, metastasis-associated gene 1.

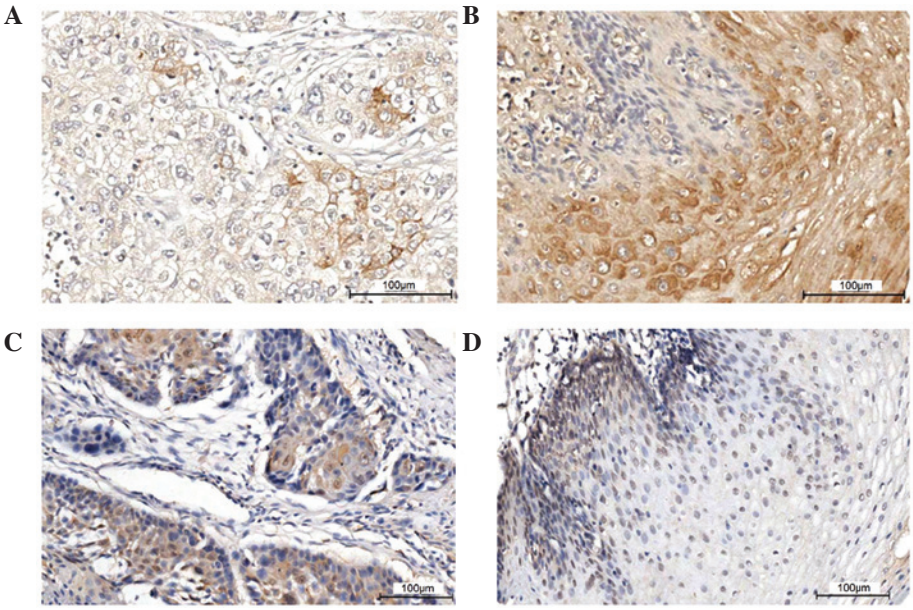

Figure 1. Immunohistochemistry to identify the expression of MTA1 and IGFBP-3. (A) Low expression of IGFBP-3 in ESCC tissue samples and (B) strong expression in adjacent normal tissue samples. Positive staining is located in the cytoplasm. (C) High expression of MTA1 in ESCC tissue and (D) low expression in adjacent normal tissues. Positive staining is located in the nucleus. Magnification, x200.

data of 197 ESCC cases, the Kaplan-Meier survival curve analysis indicated that the 3-year survival rate of all patients was 36.04% (Fig. 2). The 3-year survival rates of the patients with positive and negative expression of IGFBP-3 and MTA1 protein indicated no significant difference by the Log-rank test (P=0.874 and P=0.942, respectively; Fig. 3). The multivariate analysis of COX regression demonstrated that the expression of IGFBP-3 and MTA1 were not independent risk factors of ESCC, while the tumor invasion degree (P=0.020) and lymph node metastasis rate (P=0.027) were (Table V).

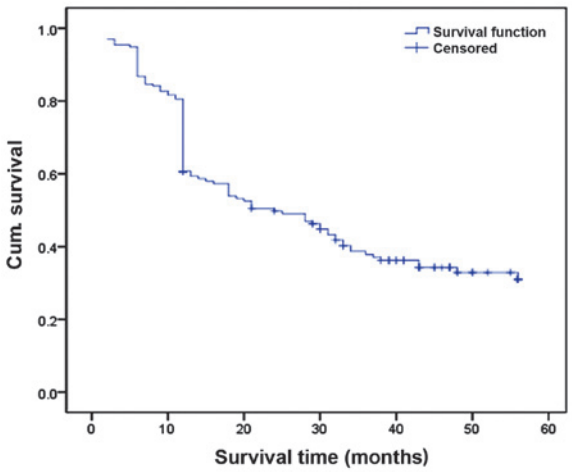

Figure 2. Kaplan-Meier survival curve of 197 patients with ESCC. The 3-year survival rate was 36.04%.

Discussion

The occurrence, development and prognosis of ESCC are the result of multiple factors, including genetics and environment. Various genes that are associated with tumorigenesis, invasion and metastasis have been identified and cloned. The ESCC-associated genes include alcohol dehydrogenase, cytochrome P450, family 1, member A1, IGF-1 and MTA1, which provide a theoretical basis for improvements in the diagnosis, treatment and prognosis of ESCC (16). The IGF system includes IGF-1 and IGF-2, and their receptors IGF-1R and IGF-2R. There are at least seven types of IGFBP (IGFBP1-7). IGF-1R is the most active, and the combination of IGF-1R and IGF-1 promotes mitosis, cell transformation, anti-apoptosis, which

Table V. Results of COX multivariate regression analysis.

Parameter	B	SE	Wald	P-value	95% CI for HR
Gender	0.151	0.314	0.232	0.630	1.163 (0.628-2.154)
Age	0.006	0.013	0.196	0.658	1.006 (0.980-1.033)
Smoking status	0.237	0.262	0.820	0.365	1.267 (0.759-2.117)
Grade	-0.650	0.165	0.154	0.695	0.938 (0.679-1.294)
T	0.349	0.150	5.413	0.020	1.418 (1.057-1.902)
N	0.461	0.208	4.919	0.027	1.586 (1.055-2.383)
Tumor size	0.306	0.290	1.109	0.292	1.358 (0.768-2.399)
IGFBP-3	-0.128	0.221	0.335	0.563	0.88 (0.570-1.358)
MTA1	-0.166	0.195	0.728	0.394	0.847 (0.578-1.241)

B, regression coefficient; SE, standard error; wald, wald value; CI, confidence interval; HR, hazard ratio; IGFBP-3; insulin-like growth factor binding protein 3; MTA1, metastasis-associated gene 1; T, tumor invasion degree; N; lymph node metastasis rate.

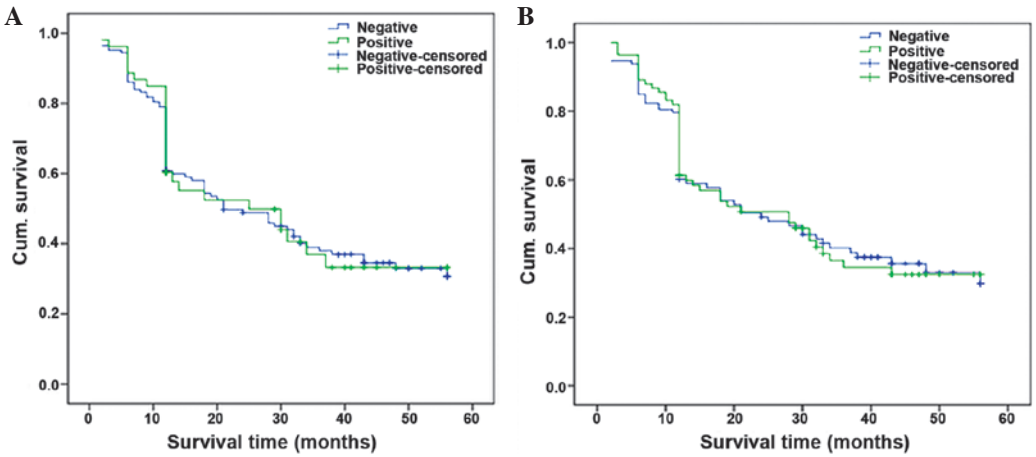

Figure 3. (A) Kaplan-Meier curve indicates that the 3-year survival of patients with IGFBP-3 expression was not improved compared with patients not expressing IGFBP-3 (cytoplasm total score ≥5, positive; plasma total score <5, negative). (B) Kaplan-Meier curve indicates that the 3-year survival of patients with MTA1 expression was not improved compared with patients not expressing MTA1 (nuclear total score total score ≥5, positive; plasma total score <5, negative).

are insulin-like biological functions. The role of IGFBPs is to act as the IGF carrier in the blood circulation, and IGFBP-3 predominates. IGFBP-3 binds with >80% of the IGF-1 in the circulation, which transports IGF-1 to the reaction site, and protects IGF-1 from degradation by proteases. Thus, IGFBP-3 is important in the regulation of the concentration of IGF-1 and inhibits or enhances IGF-1 function. Therefore, IGFBP-3 and IGF-1R are key regulatory aspects in the IGF signaling pathway (17).

IGFBP-3 may also interact with other proteins and, thus, be important in the inhibition of proliferation and promotion of apoptosis in various cells in a non-IGF-1-dependent manner, therefore, IGFBP-3 exhibits a dual regulatory role in the IGF family (18). IGFBP-3 translocates into the nucleus and directly or indirectly interacts with the intranuclear growth inhibition and apoptosis genes, affecting cellular gene expression and inducing apoptosis (19). Overexpression of IGFBP-3 may increase the cellular apoptosis (20,21), suggesting that it may act as a tumor suppressor. Abnormal methylation and gene silencing of the IGFBP-3 promoter has been observed in different types of cancer, and its abnormal expression or dysfunction has been associated with cancer development (22-24).

It has been reported that the expression levels of IGFBP-3 in lung cancer (25), hepatocellular carcinoma (26), ovarian cancer (27) and prostate cancer (28) are reduced. Tas *et al* (29,30) observed that the serum IGFBP-3 concentration did not predict the prognosis of breast and ovarian cancer. Another previous study indicated that high expression of IGFBP-3 is significantly associated with the recurrence of prostate cancer (31). In addition, Kim *et al* (32) investigated 191 cases of lung cancer and observed that IGFBP-3 was not significantly correlated with the patients' clinicopathological changes. Rohrmann *et al* (33) observed that low concentrations of serum IGFBP-3 did not increase the risk of pancreatic cancer. These contradictory studies may be due to the protective effect of increased expression of IGFBP-3, which inhibits cell proliferation and induces apoptosis. However, under different experimental conditions, IGFBP-3 may stimulate cell proliferation in an IGF signaling pathway-dependent or independent manner (34). In certain cases, IGFBP-3 exerts positive effects toward cell growth (35). The expression levels

of IGFBP-3 in ESCC are uncertain. The present study uses the immunohistochemical method to evaluate the IGFBP-3 expression in ESCC and its impact on the prognosis of ESCC patients. The results demonstrate that IGFBP-3 is expressed predominantly in the cytoplasm, and the positive expression of IGFBP-3 in the ESCC tissue samples is significantly lower than that in the adjacent tissue samples (27.4 vs. 40.6%; P<0.05). The low expression levels of IGFBP-3 in the ESCC tissues may be due to IGFBP-3 as a downstream gene of p53, and mutated p53 loses the ability to activate IGFBP-3 via its transcriptional signaling pathway (36), thus the functions of IGFBP-3 that inhibit tumor cell proliferation and apoptosis via the IGF-1-dependent signaling pathway are blocked (37). This may also be associated with the reduction of apoptosis induced by IGFBP-3 via the p53 signaling pathway (8).

The present study also demonstrates that the positive expression of IGFBP-3 in ESCC is associated with gender, smoking status and family history of cancer, which is consistent with esophageal cancer epidemiology. The expression of IGFBP-3 is negatively correlated with the degree of ESCC differentiation and lymph node metastasis, tumors of different grades (G1, G2 and G3). The positive expression rates of IGFBP-3 were 51.4, 24.4 and 15.4%, respectively, and the IGFBP-3 expression in patients with non-lymph node metastasis was significantly higher than those with lymph node metastasis (36.7 vs. 15.9%). This may be associated with the anti-angiogenic and anti-metastatic roles of IGFBP-3 (38,39). In the present study, IGFBP-3 staining was observed inside the nuclei of ESCC cells, although it is markedly weaker compared with in the cytoplasm. This may be due to IGFBP-3 expression inside the nuclei directly or indirectly inducing the apoptosis of cancer cells, thus inhibiting the tumor cell growth (40), however, this requires further elucidation.

MTA1 is upregulated during tumor metastasis, as observed by Toh *et al* in 1994 (41). The human MTA1 gene is located on 14q32.3 (42), with full-length cDNA of 2,756 bp. The encoded protein has 703 amino acid residues, and the product of this gene is a component of the nuclear remodeling and deacetylation complex, which regulates gene transcription by affecting the chromatin state (5). There is a low level of MTA1 in normal body tissues, including the heart, kidney, lung, liver, while in a variety of tumor tissues, such as from liver, lung and ovarian cancer, it is highly expressed. Toh *et al* (6) observed that MTA1 expression in ESCC is associated with the activity of H4 histone deacetylase. As tumor suppressor genes, including p53, p21 and retinoblastoma, are regulated by histone acetylation (43), the invasion and lymph node metastasis of tumor cells that have high MTA1 mRNA expression levels are significantly increased.

Results of the present study demonstrate that the MTA1 protein is predominantly expressed in the nucleus. In ESCC tissue samples, the MTA1 protein expression level was significantly higher than in the control samples (42.1 vs. 11.2%; P<0.05), while its expression was not associated with the gender, age, smoking status or degree of tumor tissue differentiation, while in the patients with no family history of cancer the MTA1 expression is as high as 47.1%. Furthermore, MTA1 expression was positively correlated with tumor size, extent of cancer tissue invasion and lymph node metastasis. In the patients with tumors >3 cm, the percentage of patients that expressed MTA1 was 46.8%, while in the patients with tumors ≤3 cm, the percentage of patients expressing MTA1 was 25.6%. MTA1 expression rates in different stages of invasive cancer (T1, T2 and T3) were 27.6, 35.1 and 49.5%, respectively. The expression of MTA1 in patients with lymph node metastasis was significantly higher than those without lymph node metastasis (51.1 vs. 34.9%; P<0.05). This may be due to the involvement of MTA1 in changing the assembly of the cytokeratin filament system and location of cytoskeletal proteins, thus increasing the cellular invasion and metastasis (44). In the present study, IGFBP-3 and MTA1 exhibited no interaction in the clinicopathological features of ESCC. They were not identified to be correlated with the prognosis of ESCC, and they were not independent risk factors in the prognosis of ESCC; however, the extent of tumor invasion and the rate of lymph node metastasis are the independent risk factors in ESCC prognosis. No significant correlation was identified between the protein expression of IGFBP-3 and tumor size, positive expression of MTA1 and the degree of tumor tissue differentiation, or expression of the two proteins and prognosis. This may be affected by certain cases in the present study coming from the ESCC-high-incidence region (Cixian, China). The patients in this geographical area undergo regular screening and earlier treatment due to the high prevalence of ESCC. Certain cases were also from Beijing, China, which has a low incidence of ESCC and a poorer screening program, thus, these patients usually only seek medical help when clinical symptoms appear and their staging tends to be higher.

The present study has certain limitations. First, the samples are from different regions. A number of the cases were obtained from a region with high-incidence of ESCC, which may have affected the current study. Second, reverse transcription-polymerase chain reaction or western blot analysis were not performed to validate the immunohistochemical results, these should be conducted in the future. Third, the follow-up period was short and should be increased in future research.

In conclusion, low expression levels of IGFBP-3 may be a risk factor of ESCC, and high expression levels of MTA1 are closely associated with the invasion and metastasis of ESCC. The detection of IGFBP-3 and MTA1 may have important clinical implications for the diagnosis, treatment and prognosis of ESCC.

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