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RAPID COMMUNICATION

Overexpression of Ets-like protein 1 in human esophageal squamous cell carcinoma

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Abstract

AIM: To study the expression pattern of Ets-like protein 1 (Elk-1) in human esophageal squamous cell carcinoma (ESCC) and to analyze its relationship with clinicopathologic parameters.

METHODS: The expression of Elk-1 in fresh esophageal cancer tissues and their corresponding normal mucosae was detected immunohistochemically (IHC) by means of tissue microarray (TMA). Its correlation with clinical characteristics was evaluated and analyzed by univariate analysis. All statistical analyses were performed by SPSS version 13.0.

RESULTS: Expression level of transcription factor Elk-1 increased in 78.5% (84/107) ESCC tissues compared with their matched normal esophageal epithelium. However, the expression of Elk-1 did not show any obvious correlation with degree of differentiation of esophageal carcinoma (in well-differentiated, moderately-differentiated and poorly-differentiated tumors, the increased expression was 7/8, 60/74, and 19/25, respectively, $P > 0.05$). Moreover, no obvious correlation was found with lymph node metastasis and depth of invasion.

CONCLUSION: Increased expression of transcription factor Elk-1 may play an important role in esophageal carcinogenesis.

Key words: Ets-like protein 1; Esophageal squamous cell carcinoma; Immunohistochemistry; Tissue microarray

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INTRODUCTION

Esophageal cancer ranks among the 10 most frequent cancers in the world, with a predominant distribution in developing countries. It is one of the most common malignant tumors in China[1,2]. Our previous study showed that genetic susceptibility to esophageal cancer is one of the important causes for the high prevalence and familial aggregation of this disease in some areas of northern China[3]. Ets-like protein 1 (Elk-1) is a member of the ternary complex factor (TCF) subfamily of E twenty-six (ETS)-domain transcription factors[4,5]. The three ternary complex factors (TCFs) Elk-1, Net and Sap-1 form a subfamily of the ETS domain transcription factors. Their characteristic property is the ability to form a ternary nucleoprotein complex with the serum response factor (SRF) over the serum response element (SRE) of the c-*fos* promoter. The molecular mechanisms underlying the function and regulation of these factors have been extensively studied and the TCFs are a paradigm for the study of transcriptional regulation in response to extracellular signalling through the mitogen-activated protein (MAP) kinase pathway. As final effectors of multiple signalling pathways and components of protein complexes on immediate early promoters, they represent key elements in the complex and dynamic regulation of gene expression[6].

Tissue microarray (TMA) was first introduced in 1998[7]. It is a high throughput technique that can significantly accelerate the processing of a large number of tissue specimens with excellent quality, good reliability and the preservation of original tissue. TMA studies can demonstrate their accuracy and reliability compared to those of standard histological techniques and correlate with clinicopathologic information to determine disease progression and prediction of the clinical outcome[8]. It allows simultaneous analysis of many tumors using small diameter cores sampled from larger blocks of tissue, but may be limited by tumor heterogeneity[9]. In this study, we used TMA to investigate the transcription factor Elk-1 in esophageal squamous cell carcinoma (ESCC), including

method for assessing immunohistochemical scoring of microarrays. TMA blocks were constructed from 107 cases of ESCC with corresponding normal tissues, taking two cores from different areas of each tumor and two cores from adjacent esophageal epithelia. Immunohistochemical labelling was performed for Elk-1. The extent and intensity of scoring were determined for each core and the degree of agreement was determined for results from the assessment of two, three or four cores for each case. The results show that TMA is a reliable tool to demonstrate cellular and molecular alterations in ESCC.

In this study, we investigated the protein expression of transcription factor Elk-1 in ESCC. The expression levels of Elk-1 increased in ESCC tissues compared with their normal counterparts. Therefore, Elk-1 might be related to human ESCC and further study on Elk-1 may provide insight into the mechanisms of carcinogenesis of esophagus.

MATERIALS AND METHODS

Materials

Specimens of cancer tissues and matched adjacent normal mucosa were taken from 107 consecutive patients with squamous cell carcinoma of the thoracic esophagus who underwent esophagectomy with regional lymph nodes dissected from July 2005 to April 2006 at the Department of Thoracic Surgery, the First Affiliated Hospital of Anhui Medical University. None of the patients received radiotherapy or chemotherapy before surgery. The patients included 79 men and 28 women with a median age of 60 (range 40-79) years. Fourteen tumors were located in the upper thorax, 60 in the middle thorax and 33 in the lower thorax (Table 1). The removed specimens were stained with hematoxylin and eosin, examined histologically, and then the clinicopathologic stage was determined according to TNM classification.

Table 1 Clinical and histopathological characteristics of patients

Characteristic	*n* (%)
Sex	
Male	79 (73.8)
Female	28 (26.2)
Location of tumor	
Upper thoracic	14 (13.1)
Middle thoracic	60 (56.1)
Lower thoracic	33 (30.8)
Degree of differentiation	
Well-differentiated	8 (7.5)
Moderately-differentiated	74 (69.2)
Poorly-differentiated	25 (23.3)
Depth of invasion	
T1	6 (5.6)
T2	39 (36.4)
T3	62 (58.0)
T4	0 (0)
Lymph node metastasis	
Positive	35 (32.7)
Negative	72 (67.2)

Construction of tissue microarray

The collected samples were fixed with formalin and embedded with paraffin, and then tissue microarray was performed. Two pathologists selected representative areas from each donor tumor block, and then punched cores 1.0 mm in diameter, from the donor blocks, and then transferred these tissue cores to a recipient block using a tissue microarrayer (Beecher Instrument, Silver Spring, Maryland, USA). The resultant tissue microarray was cut into sections and transferred to glass slides for processing of Elk-1 by immunohistochemistry.

Immunohistochemical staining

Immunohistochemical analysis was done retrospectively. Resected esophageal specimens, including both tumor and normal mucosae, were fixed in a 40 g/L formaldehyde solution and embedded in paraffin. Rabbit polyclonal IgG Elk-1 antibody (Santa Cruz Biotech Co, USA) was used in this study (diluted 1:100). Formalin-fixed and paraffin embedded tissue blocks of esophageal tumors were cut into 4-μm thick sections. TMAs were deparaffinized in xylene, rehydrated in ethanol and treated with 30 mL/L H_2O_2 for 30 min to block the endogenous peroxidase activity. Antigen retrieval was achieved by microwaving in 0.01 mol/L citrate buffer (pH 6.0) at 96℃ for 15 min. After incubation with 10% normal goat serum to block non-specific binding, they were then incubated with anti-Elk-1 antibody at 1:100 dilution overnight at 4℃. After antibody was washed in PBS, TMAs were incubated with the secondary antibody and the third antibody (Streptavidin/HRP) according to the manufacturer's instructions. Finally DAB was used as a chromogen and hematoxylin as a counterstain. Negative control was designed by using PBS instead of primary antibody.

Assessment of staining

The percentage of Elk-1-positive tumor cells was determined semiquantitatively by assessing the entire tumor section and scored as: a = 0, < 5% of epithelial cells in the respective lesions; b = 1, 5%-25% of epithelial cells in the respective lesions; c = 2, 26%-50% of epithelial cells in the respective lesions; d = 3, 51%-75% of epithelial cells in the respective lesions; e = 4, > 75% of epithelial cells in the respective lesions. The intensity was graded as: a = 0, negative; b = 1 +, weak; c = 2 +, moderate; d = 3 +, strong. A final score between 0 and 12 was achieved by multiplication of the extent of positivity and intensity[10,11]. Positive staining of more than 5% in cell cytoplasm was defined as positive staining, less than 50% in cell cytoplasm as preserved expression, more than 50% in cell cytoplasm as increased expression[12].

Statistical analysis

Paired-samples T test, chi square test or Fisher's exact probability test was used to assess the association between immunohistochemical features and clinicopathologic characteristics. A P value less than 0.05 was considered statistically significant. All the statistical analyses were performed using the SPSS 13.0 V for Windows.

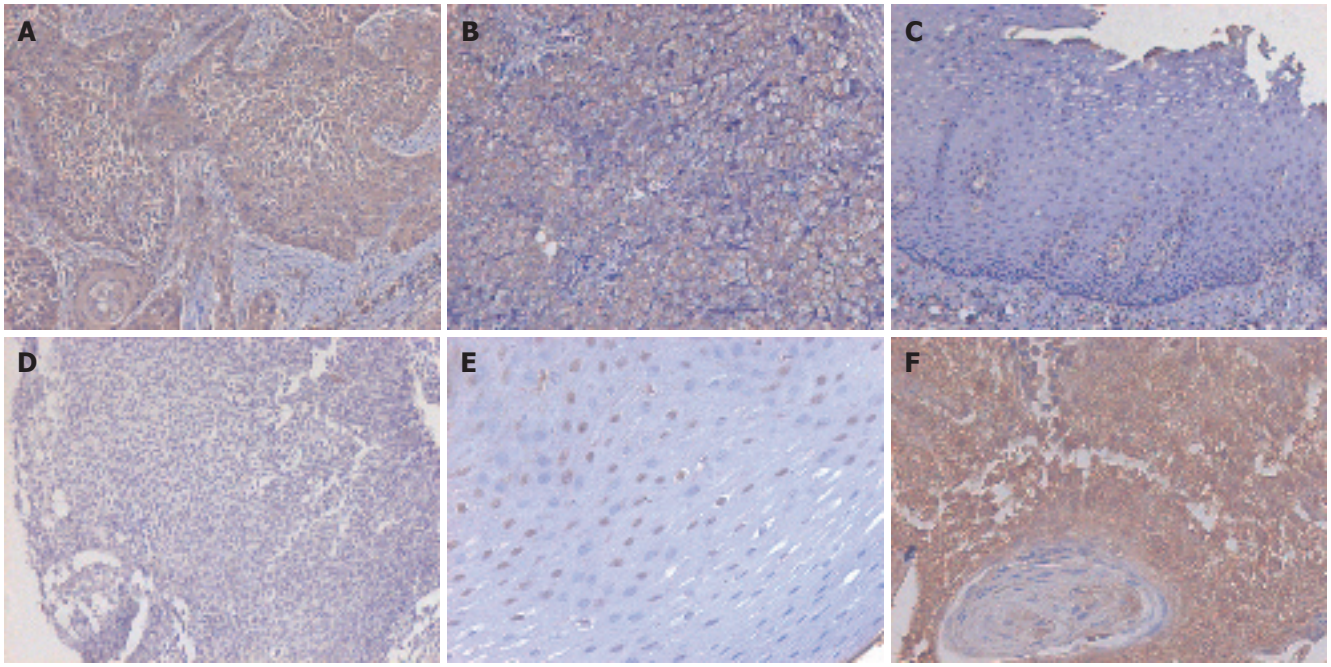

Figure 1 Immunohistochemical analysis of Elk-1 in paired ESCC samples using anti-Elk-1 antibody (1:100) showing diffuse and strong staining in cytoplasm of esophageal cancer epithelial cells well-differentiated tumor (**A**), moderately-differentiated tumor (**B**), sporadic and weak staining in the cytoplasm of normal epithelial cells (**C**), negative control designed using PBS instead of primary antibody (**D**), strong staining in nuclei of normal epithelial cells (**E**) (**A-E** × 100), and in cytoplasm of well-differentiated esophageal cancer epithelial cells (**F**) (× 200).

RESULTS

Expression of Elk-1 in esophageal squamous cell carcinoma

Positive Elk-1 expression showed brown staining signals in ESCC cytoplasm and nuclei, reduced or negative expression of Elk-1 was found in normal squamous epithelium, with only a small number of expressions in cell membranes. The increased expression rate of Elk-1 in 107 esophageal cancer patients was 78.5% (84/107) compared to that in the matched normal tissue. A significant positive correlation was found in Elk-1 expression between esophageal carcinoma tissue and paired normal squamous epithelium ($P < 0.01$). The increased expression rate of Elk-1 was 80.4% (86/107) (Figure 1).

Relationship between Elk-1 expression and clinicopathologic variables in esophageal squamous cell carcinoma

The expression of Elk-1 had no obvious correlation with the degree of differentiation of esophageal squamous cell carcinoma. The increased expression was found in 7/8 well-differentiated, 60/74 moderately-differentiated and 19/25 poorly-differentiated tumors, respectively, ($P > 0.05$). In addition, no significant correlation was found among Elk-1 expression, lymph node metastasis and depth of invasion (Table 2).

Table 2 Relationship between clinicopathologic parameters and expression of Elk-1

Type	Case	Elk-1		*P*
		Preserved	Increased	
Degree of differentiation				
Well-differentiated	8	1	7	> 0.05
Moderately-differentiated	74	14	60	
Poorly-differentiated	25	6	19	
Depth of invasion				
Mucous layer (T1)	6	1	5	> 0.05
Muscular layer (T2)	39	6	33	
Full-thickness (T3)	62	14	48	
Lymph node metastases				
Positive	35	5	30	> 0.05
Negative	72	16	56	

DISCUSSION

Regulations of cell growth are dependent on a number of gene families including proto-oncogene, growth factor, growth factor receptor and immediate early transcription factor gene. The first member of Ets gene family was discovered a decade ago by studying avian erythroblastosis virus, E twenty six (E26). Subsequently, a series of cellular Ets genes were isolated (Ets-1, Ets-2, Erg, Elk-1, Sap-1, PEA-3, PU.1, Fli-1 *etc.*)[13]. The Elk-1 gene is localized on human chromosomes Xp11.2-p11.1 and 14q32[14,15]. Elk-1 was first discovered in a fraction of HeLa cell nuclear extract that forms ternary complexes with SRF on the c-*fos* SRE. This novel component is called p62 due to its 62 kDa molecular mass[16]. Elk-1, Sap-1 and Sap-2/Net comprise the TCF subfamily of Ets-domain transcription factors. The TCF transcription factors play an important role in transducing extracellular signals into a nuclear response by acting as targets for the mitogen-activated protein kinase signaling pathways[4,5,17]. In addition to a N-terminal DNA-binding domain, Elk-1 contains a "B box" mediating its interaction with SRF, a "C domain" acting as a transcriptional activation domain, two repression domains,

and two domains that act as docking sites for multiple mitogen-activated protein kinases, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38[4,18,19]. The ERK cascade responds to growth factors and mitogens, whereas the JNK and p38 cascades are triggered by cytokines and stress.

The understanding of the molecular basis of tumor development has progressed dramatically in the last two decades. Since tumor is essentially a genetic disease, it is important to demonstrate what these oncogenes are and how they work in carcinogenesis. Identifying the genetic differences between normal and tumor cells or tissues will help discover the genes that directly cause tumor or are associated with tumorigenesis and provide novel markers for early detection and appropriate therapy.

Elk-1 is thought to impact neuronal differentiation[20], cell proliferation[4], tumorigenesis[21], and apoptosis[22]. Elk-1 plays a role in the neuronal expression of immediate-early genes like c-*fos* in the brain[23]. Elk-1 functions as a nuclear transcriptional activator via its association with SRF on serum response elements present in the promoters of many immediate-early genes, such as c-*fos*, *egr-1*, *egr-2*, *pip92*, and *nurr77*[17]. In addition to its regulation of growth-responsive genes, Elk-1 has been shown to play a role in regulating differentiation of smooth muscle, skeletal muscle, and neuronal cells[24-26]. Recently the SRF gene has also been identified as a target for Elk-1, thereby providing a positive-feedback loop where Elk-1 activation leads to enhanced expression of its partner protein, SRF[27]. Although the role of Elk-1 has been extensively studied, little information is available concerning its involvement in esophageal epithelia. In our study, we first investigated immunohistochemically the expression of Elk-1 protein in paired ESCC by TMA. The results of IHC revealed that the expression of Elk-1 was increased 78.5% (84/107) in tumor tissue compared to that in corresponding normal tissue. A significant positive correlation was found between esophageal carcinoma tissue and paired normal squamous epithelium ($P < 0.01$). Among the 107 histologically-examined esophageal squamous cell carcinomas, eight tumors were well-differentiated, 74 moderately-differentiated and 25 poorly-differentiated, suggesting that up-regulated Elk-1 expression has no difference in degree of tumor differentiation. No significant correlation was found among expression of Elk-1, degree of differentiation, lymph node metastasis and depth of invasion. Overexpression of two target genes of Elk-1 (c-*fos*, *egr*-1 mRNAs and their proteins) were found in dysplasia and esophageal squamous carcinomas, suggesting that these genes are involved in the development of esophageal carcinoma[28]. In addition to its nuclear location, Elk-1 is found throughout the cytoplasm of tumor and normal epithelial cells (Figure 1). This is in agreement with previous studies on nuclear transcription factor Elk-1 in neuronal cells[29,30].

In conclusion, Elk-1 may have alternative extranuclear functions in esophageal carcinogenesis. The mechanism of the involvement of Elk-1 in the development and progress of esophageal carcinoma remains to be further investigated.

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COMMENTS

Background

Esophageal squamous cell carcinoma (ESCC) has one of the highest malignant potentials of any tumor, and is characterized by poor survival and wide geographical variation in incidence. The molecular pathology underlying the development and progression of ESCC is poorly understood. In this study, the expression of Elk-1 was immunohistochemically examined in 107 ESCCs and its relationship with clinicopathologic parameters was analyzed.

Research frontiers

The molecular mechanisms underlying the function and regulation of the three ternary complex factors (TCFs) Elk-1, Net and Sap-1 have been extensively studied and the TCFs are a paradigm for the study of transcriptional regulation in response to extracellular signalling through the mitogen-activated protein (MAP) kinase pathway. As final effectors of multiple signalling pathways and components of protein complexes play a role in immediate early promoters, they represent key elements in the complex and dynamic regulation of gene expression.

Terminology

Tissue microarrays (TMAs) are means of combining tens to hundreds of specimens of tissues onto a single slide, using all types of *in-situ* analyses including immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH), and RNA *in situ* hybridization (RNA-ISH). Potential applications include the establishment of associations between molecular changes and clinical endpoints, testing of potential therapeutic targets using tissue samples from specific cancer patients, standardization of molecular detection of targets, and rapid translation of results from cell lines and animal models to human cancer.

Peer review

The paper contributes to the mechanisms of carcinogenesis in the squamous epithelium of esophagus. The molecular study is focused on the Elk-1 transcription factor which is overexpressed in esophageal cancer. This fact is well demonstrated, showing that increased expression of transcription factor Elk-1 may play an important role in esophageal carcinogenesis.

S- Editor Wang GP **L- Editor** Wang XL **E- Editor** Bi L