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*Original Article*

# A long noncoding RNA ATB is involved in the progression and prognosis of esophageal cancer

Wei Xiao[1], Xiaoqin Jiang[1], Weiguang Jia[2], Kaijin Lu[2], Jun Zhang[3], Guihong Dai[1], Lin Jiang[4], Hong Yu[1]

*Departments of [1]Pathology, [2]Thoracic Surgery, [3]Nuclear Medicine, [4]Anesthesiology, Taizhou People's Hospital, Jiangsu Province, China*

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**Abstract:** Long non-coding RNAs (lncRNAs) have been demonstrated to be critical mediators in tumor development and progression. This study aimed to elucidate the clinicopathological role and prognostic relevance of lncRNA activated by transforming growth factor beta (ATB) in ESCC. The expression levels of ATB expression in 218 esophageal squamous cell carcinoma (ESCC) and adjacent noncancerous tissues were determined by using quantitative real-time polymerase chain reaction. The potential relationships between ATB expression and clinicopathological characteristics and prognosis were analyzed. ATB in ESCC tissues was significantly upregulated compared with that in adjacent noncancerous tissues ($P$ = 0.001). High ATB expression was significantly associated with poor differentiation ($P$ = 0.036), larger tumor size ($P$ = 0.009), deeper tumor invasion ($P$ = 0.012), LNM ($P$ = 0.009) and advanced TNM stage ($P$ = 0.037). However, there was no association between ATB expression and response to chemotherapy in ESCC patients ($P$ = 0.885). Furthermore, patients with high ATB expression had worse survival time than those with low ATB expression ($P$ = 0.002). Multivariate Cox proportional hazards model analysis revealed that high ATB expression was an independent predictor of poor prognosis in ESCC patients (adjusted HR = 1.379, 95% CI: 1.008-1.979, $P$ = 0.045). This effect remained significant in further stratified analysis. In conclusion, our findings suggest that ATB may play a critical role in ESCC progression and serve as a potential prognostic biomarker for ESCC patients.

**Keywords:** Long non-coding RNA, ATB, esophageal cancer, metastasis

## Introduction

Esophageal cancer is the eighth most common malignancy and the sixth most common cause of death from cancer worldwide with an estimated 455,800 new cases and 400,200 deaths annually [1, 2]. In China, esophageal cancer is the fourth most common cancer and the fourth leading cause of death from cancer in 2015 [3]. Although great progress in cancer treatment has been made in recent years such as target and immune therapies, therapeutic options for esophageal cancer are still limited and its prognosis is far from satisfaction, with the 5-year survival rate of less than 25% [4]. Thus, it is necessary to identify biomarkers that distinguish the patients who may or may not benefit from adjuvant therapy.

Growing evidence has demonstrated that long non-coding RNAs (lncRNAs) play critical roles in the regulation of various biological processes such as embryonic development, differentiation, cell growth, apoptosis, and tumorigenesis by regulating expression of target genes at epigenetic, transcriptional, and post-transcriptional levels [5-7]. Consequently, dysregulation of lncRNA definitely influences cell function, and thus may lead to pathological state and various diseases, including cardiovascular disease and cancer [7-10]. LncRNAs act as an oncogene or a tumor suppressor during tumorigenesis, progression, invasion, and metastasis [7, 10-15]. Numerous studies have showed that lncRNAs are novel type of biomarkers and therapeutic targets for cancer [8, 10, 12-15].

Several lncRNAs have been reported to be regulated by transforming growth factor β (TGF-β) to modulate tumor metastasis by regulating epithelial-to-mesenchymal transition (EMT) [12, 14, 15]. For example, lncRNA activated by

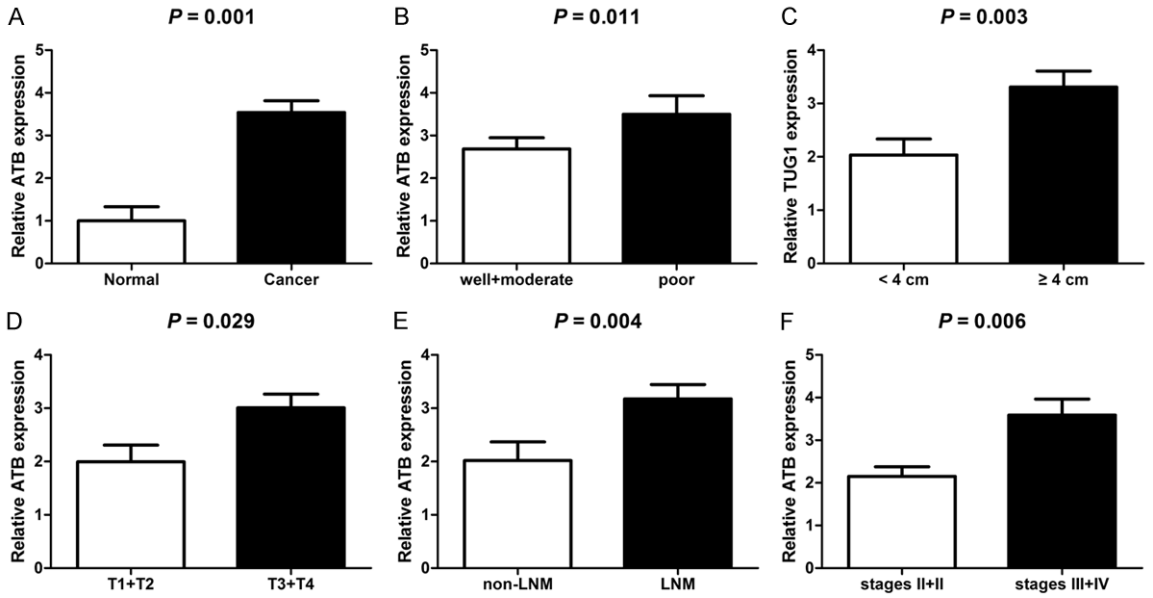


**Figure 1.** ATB was upregulated in ESCC tissues. A. Relative expression of ATB in ESCC and adjacent tissues. B. Relative expression of ATB in ESCC with different grades of differentiation. C. Relative expression of ATB in ESCC with different tumor size. D. Relative expression of ATB in ESCC with different pT category. E. Relative expression of ATB in ESCC with or without LNM. F. Relative expression of ATB in ESCC with different TNM stage.

TGF-β (ATB), originally identified in hepatocellular carcinoma (HCC), is activated by TGF-β and acts as a competing endogenous RNA by sponging miR-200 family which induces EMT, metastasis, and invasion [12]. Aberrant expression of ATB is observed in some types of cancer, including HCC, gastric, colorectal, and prostate cancers, which affect the prognosis of these patients [12-14, 16]. These results indicate that ATB is closely related to the occurrence, development, and progression of tumor. In the current study, we aimed to determine ATB expression in ESCC and evaluate its clinical significance.

## Materials and methods

### *Patients*

Cancerous and adjacent normal tissues were obtained from ESCC patients who underwent radical resections or endoscopic biopsy in Taizhou People's Hospital. These patients were histologically confirmed as ESCC, including 171 male and 47 female. Patients received at least two courses of platinum-combined adjuvant chemotherapy. The details of patient characteristics were described previously [8]. All patients provided written informed consent before enrolling in the study according to the study protocol approved by the Ethical Committee of Taizhou People's Hospital.

### *Quantitative real-time PCR (qRT-PCR)*

Total RNA was isolated using the TRIzol reagent (Life Technologies, Gaithersburg, MD, USA) according to the manufacturer's instructions. Complementary DNA was synthesized using the PrimeScript™ RT reagent Kit with gDNA Eraser (Takara, Dalian, China) according to the manufacture's instructions. The expression level of ATB was examined by qRT-PCR using SYBR Premix Ex TaqII kit (Takara, Dalian, China) on ABI Prism 7900HT Sequence Detection System (Applied Biosystems, CA, USA). The relative expression level of ATB was determined using the $2^{-\Delta\Delta Ct}$ method relative to GAPDH.

### *Statistical analyses*

SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The differences in ATB expression between groups were evaluated using the nonparametric test Mann-Whitney-Wilcoxon. Patients were divided into high and low ATB expression groups that high and expression levels of ATB were defined value above and below median expression level of ATB, respectively. The survival curves were

**Table 1.** Association of ATB expression with clinicopathologic parameters

| Variables | ATB expression | | Chi-Square | *P* value |
|---|---|---|---|---|
| | High | Low | | |
| Age (years) | | | | |
| < 65 | 51 (46.8) | 57 (52.3) | 0.416 | 0.498 |
| ≥ 65 | 58 (53.2) | 52 (47.7) | | |
| Sex | | | | |
| Male | 86 (78.9) | 85 (78.0) | 0.869 | 1.000 |
| Female | 23 (21.1) | 24 (22.0) | | |
| Pathologic type | | | | |
| Ulcerative | 53 (55.8) | 58 (58.6) | 0.694 | 0.772 |
| Others | 42 (44.2) | 41 (41.4) | | |
| Differentiation | | | | |
| Well+moderate | 70 (64.2) | 85 (78.0) | 0.025 | 0.036 |
| Poor | 39 (35.8) | 24 (22.0) | | |
| Tumor size (cm) | | | | |
| < 4 | 20 (19.6) | 39 (36.4) | 0.007 | 0.009 |
| ≥ 4 | 82 (80.4) | 68 (63.6) | | |
| Clinical response | | | | |
| Sensitivity | 39 (37.9) | 37 (38.9) | 0.876 | 0.885 |
| Resistance | 64 (62.1) | 58 (61.1) | | |
| pT categories | | | | |
| T1+T2 | 12 (11.9) | 27 (26.5) | 0.008 | 0.012 |
| T3+T4 | 89 (88.1) | 75 (73.5) | | |
| LNM | | | | |
| Non-LNM | 16 (14.8) | 33 (30.3) | 0.006 | 0.009 |
| LNM | 92 (85.2) | 76 (69.7) | | |
| TNM stage | | | | |
| I+II | 40 (38.1) | 56 (53.3) | 0.027 | 0.037 |
| III+IV | 65 (61.9) | 49 (46.7) | | |

generated using the Kaplan-Meier method, and differences between curves were compared by the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model. All reported *P* values were two-sided, and a *P* value < 0.05 was considered statistically significant.

## Results

### *Upregulation of ATB expression in ESCC tissues*

The ATB expression in ESCC and noncancerous tissues was measured by qRT-PCR. ATB was significantly upregulated in ESCC. The expression levels of ATB in ESCC tissues were prominently higher than those in noncancerous tissues (*P* = 0.001 **Figure 1**). Furthermore, we examined the difference in ATP expression between different clinical feature groups. As shown in **Figure 1**, tumors with poor differentiation (*P* = 0.011), tumor size ≥ 4 cm (*P* = 0.003), pT categories T3 and T4 (*P* = 0.029), lymph node metastasis (LNM) (*P* = 0.004), and TNM stages III and IV (*P* = 0.006) had obviously higher level of ATB than those with well and moderate differentiation, tumor size < 4 cm, pT categories T1 and T2, non-LNM, and TNM stages I and II, respectively.

### *Association between ATB expression and clinical features of ESCC patients*

As shown in **Table 1**, high ATB expression was closely related to clinical features including poor differentiation (*P* = 0.036), larger tumor size (*P* = 0.009), pT categories T3 and T4 (*P* = 0.012), LNM (*P* = 0.009) and advanced TNM stage (*P* = 0.037). However, there was no correlation between ATB expression and other clinical parameters including sex, age, pathologic type and drug response. Taken together, these results implied that upregulated ATB expression may contribute to the progression and metastasis of ESCC.

### *Survival analysis*

We further explored the effect of ATB expression on the prognosis of ESCC patients. There was a significant trend of the increased expression level of ATB with decreased survival time. Patients with high ATB expression had shorter survival time than those with lower ATB expression (16.0 months vs 26.0 months, *P* = 0.002, **Figure 2**). In univariate analyses, ATB expression (HR = 1.546, 95% CI: 1.132-2.114, *P* = 0.006), pT category (HR = 1.977, 95% CI: 1.244-3.142, *P* = 0.004), LNM (HR = 2.349, 95% CI: 1.528-3.611, *P* < 0.001), and TNM stage (HR = 2.050, 95% CI: 1.479-2.840, *P* < 0.001) were associated with overall survival (OS) of ESCC patients, whereas no association was observed between OS and other clinical parameters including sex, age, pathologic type and drug response (*P* > 0.05, **Table 2**). Multivariate analysis showed that ATB expression (adjusted HR = 1.379, 95% CI:

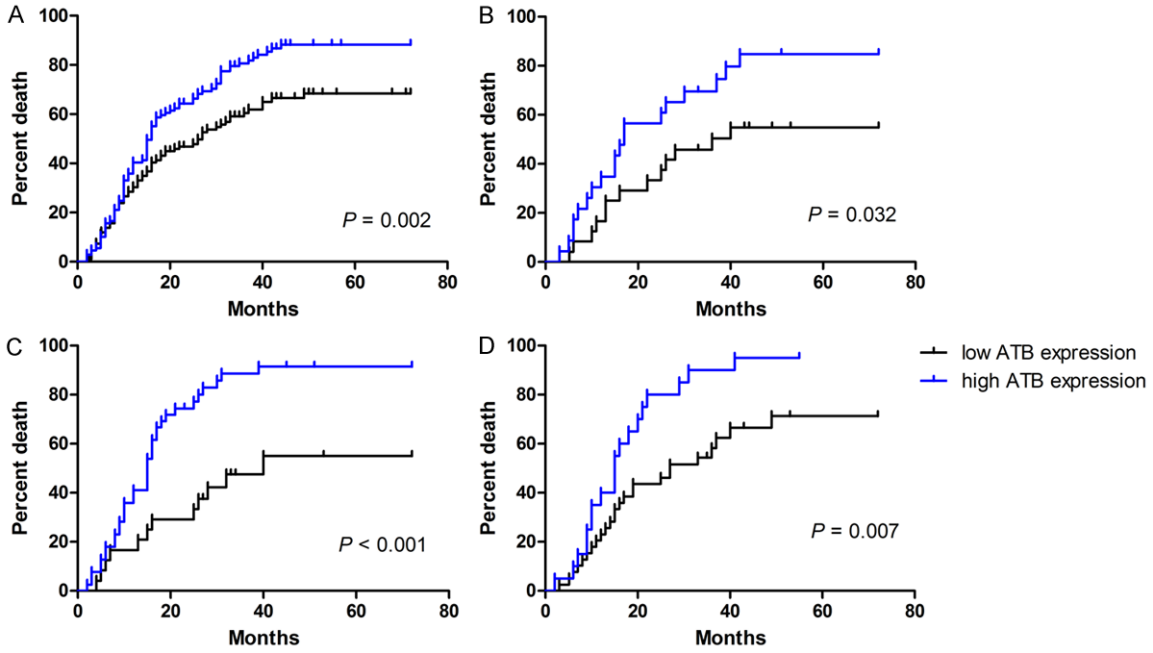


**Figure 2.** Kaplan-Meier estimates of the overall survival of ESCC patients according to ATB expression. A. Patients with high ATB expression had shorter survival time than those with low ATB expression ($P = 0.002$). B-D. Further analysis revealed that this effect only existed for female patients ($P = 0.032$), or those with poor differentiated ($P < 0.001$) or smaller tumors ($P = 0.007$).

**Table 2.** Univariate and multivariate Cox regression analysis of overall survival in 218 ESCC cases

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Beta | HR (95% CI) | *P* value | Beta | HR (95% CI) | *P* value |
| Age (years), < 65 *vs* ≥ 65 | 0.246 | 1.279 (0.939-1.744) | 0.119 | | | |
| Sex, male *vs* female | -0.347 | 0.707 (0.479-1.043) | 0.081 | | | |
| Pathologic type, ulcerative vs others | 0.214 | 1.238 (0.888-1.726) | 0.208 | | | |
| Differentiation, well+moderate vs poor | -0.056 | 0.945 (0.673-1.328) | 0.746 | | | |
| Clinical response, resistance *vs* sensitivity | 0.286 | 1.331 (0.956-1.851) | 0.090 | | | |
| Tumor size (cm), ≥ 4 *vs* < 4 | 0.062 | 1.064 (0.750-1.510) | 0.727 | | | |
| pT categories, T3+T4 *vs* T1+T2 | 0.682 | 1.977 (1.244-3.142) | 0.004 | 0.328 | 1.388 (0.835-2.308) | 0.206 |
| LNM, positive *vs* negative | 0.854 | 2.349 (1.528-3.611) | < 0.001 | 0.555 | 1.743 (1.043-2.912) | 0.034 |
| TNM stage, III+IV *vs* I+II | 0.718 | 2.050 (1.479-2.840) | < 0.001 | 0.280 | 1.323 (0.880-1.990) | 0.179 |
| ATB expression, low *vs* high | 0.490 | 1.546 (1.132-2.114) | 0.006 | 0.343 | 1.379 (1.008-1.979) | 0.045 |

1.008-1.979, $P = 0.045$) and LNM (adjusted HR = 1.743, 95% CI: 1.043-2.912, $P = 0.034$) were independent prognostic factors for the prognosis of ESCC patients.

We further performed stratification analysis to investigate the effect of ATB expression on patients prognosis based on clinical features. The results showed that ATB was an independent prognostic risk factor only in female patients (adjusted HR = 2.276, 95% CI: 1.031-5.028, $P = 0.042$), or those with poor differentiated (adjusted HR = 2.789, 95% CI: 1.352-5.752, $P = 0.006$) or smaller tumor (adjusted HR = 2.385, 95% CI: 1.043-2.912, $P = 0.034$) (**Table 3**).

## Discussion

Many studies have revealed that lncRNAs can served as diagnostic or prognostic biomarkers in human cancers [7, 8, 10, 14, 17]. For example, lncRNA UCA1 is upregulated in many types of human cancer, which promotes cancer

**Table 3.** ATB expression and overall survival after ESCC diagnosis by clinical variables

| Variables | HR (95% CI)* | *P* value |
|---|---|---|
| Age (years) | | |
| < 65 | 0.998 (0.571-1.744) | 0.995 |
| ≥ 65 | 1.347 (0.708-2.564) | 0.364 |
| Sex | | |
| Male | 1.191 (0.816-1.739) | 0.366 |
| Female | 2.276 (1.031-5.028) | 0.042 |
| Pathologic type | | |
| Ulcerative | 1.035 (0.619-1.728) | 0.897 |
| Others | 1.237 (0.654-2.340) | 0.512 |
| Differentiation | | |
| Well+moderate | 0.991 (0.617-1.591) | 0.969 |
| Poor | 2.789 (1.352-5.752) | 0.006 |
| Tumor size (cm) | | |
| < 4 | 2.385 (1.214-4.685) | 0.012 |
| ≥ 4 | 1.043 (0.670-1.623) | 0.852 |
| Clinical response | | |
| Sensitivity | 1.305 (0.728-2.339) | 0.372 |
| Resistance | 1.062 (0.685-1.646) | 0.787 |
| pT categories | | |
| T1+T2 | 4.141 (0.260-66.025) | 0.315 |
| T3+T4 | 1.155 (0.765-1.745) | 0.492 |
| LNM | | |
| Non-LNM | 0.890 (0.279-2.847) | 0.845 |
| LNM | 1.071 (0.696-1.648) | 0.754 |
| TNM stage | | |
| I+II | 1.421 (0.727-2.776) | 0.304 |
| III+IV | 0.860 (0.511-1.447) | 0.570 |

*Adjusted for pT categories, LNM and TNM stage, as appropriate.

development and progression, and confer cancer cells resistance to anticancer drug, including chemotherapy and targeted therapy drugs [10, 18-20]. Several studies reported that lncRNA CCAT2 overexpression is associated with metastasis and advanced TNM stage of some cancers and is suggested to be a negative prognostic factor for these cancers [7, 21-23]. These findings suggest that lncRNAs have potential roles as therapeutic targets or biomarkers of diagnosis, prognosis, or therapeutic response in ESCC.

Recent studies have shown that ATB is overexpressed in some types of human cancer, including HCC [12], glioma [24], prostate cancer [16], gastric cancer [14], which lead to poor prognosis of these cancer patients. However, a recent report by Qu et al. [25] described different results that ATB was downregulated in pancreatic cancer, and patients with low ATB expression presented poor prognosis. ATB displays tissue-specific expression pattern and thus might act as an oncogene or a tumor suppressor in different type of human cancer. In the current study, we found that ATB overexpression was associated with poor differentiation, larger tumor size, deeper tumor invasion, LNM, and advanced TNM stage, was an independent prognostic indicator of poor survival Furthermore, Li et al. [26] found that ATB promoted ESCC proliferation and metastasis. These findings indicate that ATB plays an important role in the direct regulation of ESCC progression, and may be potential biomarker for ESCC.

Metastasis is the cause of 90% of deaths from cancer. EMT is a key process for cancer progression and metastasis. Many studies have unraveled functional associations between lncRNAs and the EMT process in the cancer development and progression [12, 23, 27, 28]. ATB activation mediated by TGF-β promotes the invasion-metastasis cascade by competitively biding miR-200 family, upregulating miR-200s target genes, and then stimulating EMT [12, 16, 26, 29, 30]. In addition, ATB promotes distant colonization of cancer cells by activating IL-11/STAT3 signaling independent of EMT and mesenchymal-epithelial transition (MET) [12]. A study by Shi et al. [28] showed that ATB overexpression conferred drug resistance to breast cancer cells. These results indicate that upregulated ABT promotes proliferation, invasion, and metastasis of cancer cells, and confers resistance to anticancer drug in cancer cells [12, 16, 26, 29, 30]. These may partly explain why cancer patients with high ATB expression have poor prognosis. However, in the present study, ATB expression revealed no association with response to chemotherapy. Therefore, ESCC with ATB overexpression might have high potential for metastasis which lead to shorter survival time in these ESCC patients with high ATB expression.

In conclusion, the findings of the present study provide evidence that ATB overexpression is associated with aggressive progression and poor clinical outcome of ESCC. ATB may serve as a novel biomarker and a potential therapeu-

tic target to improve survival and the long-term outcome of ESCC.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Hong Yu, Department of Pathology, Taizhou People's Hospital, Taizhou, Jiangsu Province, China. Tel: +86-523-86361511; E-mail: yuhongmiaomiao@163.com; Lin Jiang, Department of Anesthesiology, Taizhou People's Hospital, Jiangsu Province, China. Tel: +86-523-86361511; E-mail: 459883821@qq.com

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