Progression and prognostic value of ECT2 in non-small-cell lung cancer and its correlation with PCNA

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Purpose: Epithelial cell transforming sequence 2 (ECT2) is a guanine nucleotide exchange factor, which is involved in cell division regulation and cell cycle modulation. Recent evidence indicates that ECT2 is overexpressed in many human cancers. However, the exact prognostic value of ECT2 in lung cancer has not been elucidated.

Patients and methods: In the current study, we performed correlation and prognosis analyses using samples from 204 lung cancer patients with survival data.

Results: We found that the expression of ECT2 was markedly increased in lung cancer tissues compared with normal tissues. Moreover, we demonstrated that the expression of ECT2 was related to tumor cell differentiation degree, TNM stage, lymph node metastasis, and prognosis in non-small-cell lung cancer (NSCLC). A correlation analysis indicated that ECT2 levels were significantly correlated with proliferating cell nuclear antigen (PCNA) levels in NSCLC. Furthermore, Kaplan–Meier analyses revealed that high ECT2 expression was associated with unfavorable overall survival (OS) and progression-free survival (PFS) in NSCLC patients.

Conclusion: Taken together, these results indicate that the overexpression of ECT2 contributes to tumor invasion and progression, suggesting that ECT2 is a potential prognostic marker for NSCLC patients.

Keywords: epithelial cell transforming sequence 2, ECT2, non-small cell lung cancer, progression, prognosis, proliferating cell nuclear antigen, PCNA

Introduction

Non-small-cell lung cancer (NSCLC) including lung adenocarcinoma (ADC), lung squamous cell carcinoma (SQC) and large cell carcinoma, is the most common pathological type of lung cancer and is one of the leading causes of cancer-related death worldwide.1 Activation of KRAS is most frequent oncogenic driver for ADC, and a recent study identified that epithelial cell transforming sequence 2 (ECT2)-dependent rRNA synthesis is required for KRAS-driven lung ADC.2 ECT2, a guanine nucleotide exchange factor (GEF), was originally reported to regulate cell division via Rho signaling pathways, and interaction between ECT2 and the plasma membrane during anaphase is required and sufficient for cytokinesis.3 Recent evidence has indicated that ECT2 is overexpressed in various human cancers and is related to tumor cell differentiation, TNM stage, lymph node metastasis, and prognosis. For example, Wang et al4 found that high expression of ECT2 predicted a poor prognosis and may play a critical role in breast cancer. Chen et al5 reported that high ECT2 expression was
an independent prognostic factor for osteosarcoma and can upregulate the metastatic capacity of osteosarcoma cells. Jin et al. found that ECT2 was significantly associated with the degree of histological differentiation, invasion depth, lymph node metastasis, distant metastasis, TNM stage and overall survival rate in gastric cancer patients. Sano et al. reported that the expression of ECT2 was markedly increased in poorly differentiated gliomas compared with well differentiated gliomas, and a high level expression of ECT2 predicted poor survival. A mechanistic study indicated that knockdown of ECT2 can inhibit Rac1 activity and block the growth, invasion and tumorigenicity of lung ADC cells. In summary, ECT2 has been shown to play an important oncogenic role in many human cancers. However, the precise role of ECT2 in lung cancer progression and prognosis is not well defined. To explore the functions of ECT2, we carried out an analysis based on Kaplan–Meier plotted datasets, which indicated that patients with higher mRNA levels of ECT2 had poor overall survival (hazard ratio [HR] =1.71, 95% CI: 1.44–2.02, \(P<0.0001\) (Figure S1 A) and progression-free survival (HR =1.42, 95% CI: 1.08–1.87, \(P=0.011\)) (Figure S1 B). Furthermore, we investigated the effect of ECT2 mRNA levels on the prognosis of ADC and SQC. We found that high ECT2 expression in ADC was an unfavorable prognostic element for overall survival (HR =1.31, 95% CI: 1.03–1.67, \(P=0.029\)) (Figure S1 C) and progression-free survival (HR =1.34, 95% CI: 0.97–1.85, \(P=0.076\)) (Figure S1 D). However high ECT2 expression could not serve as a predictor for overall survival (HR =0.99, 95% CI: 0.72–1.36, \(P=0.94\) and progression-free survival (HR =1.42, 95% CI: 0.85–2.38, \(P=0.18\)) among the SQC population (Figure S1 E, F). In summary, these analyses indicated high ECT2 mRNA expression predicted poor survival in NSCLC. To validate the conclusion from the Kaplan–Meier plotter, we conducted a comprehensive study to investigate the relationship between ECT2 expression and clinical pathological features through a systematic mRNA expression analysis based on open database and immunohistochemical staining.

Materials and methods

Online analysis tool

Kaplan–Meier survival curves with a log-rank test were calculated and plotted using the analysis tool which is available online at: [http://kmplot.com](http://kmplot.com). The background database downloaded from GEO ([https://www.ncbi.nlm.nih.gov/geo/](https://www.ncbi.nlm.nih.gov/geo/)) offers gene expression data, relapse-free and overall survival information. A total of 2,437 lung cancer patients were divided into two groups according to the expression levels of ECT2, and then the Kaplan–Meier survival curves were downloaded from the website and adjusted in Adobe Illustrator CS6.

Human lung cancer tissue array

Three commercial human lung cancer tissue microarrays (TMAs) were purchased, including one BC041115c (Alenabio, Xi’an, China) and two HlugA180Su05 (Outdo biobank, Shanghai, China). Patient personal information was blocked and the study protocol was approved by the Ethics Committee of the Tongji Hospital of Huazhong University of Science and Technology. BC041115c includes 10 cases of normal lung tissues, 4 cases of lung atypical carcinoid tissues, 48 cases of ADC, 40 cases of SQC, 8 cases of small cell carcinoma and 3 cases of large cell carcinoma. HlugA180Su05 includes 94 cases of ADC with 87 matched adjacent lung tissues, with survival follow-up data covering 5–10 years.

Immunohistochemical staining quantification analysis

Immunohistochemical staining was carried out with the three TMAs using a two-step standard protocol by the Bios Biotech. A polyclonal anti-ECT2 antibody (catalog no. 07–1364; Millipore Corporation, Billerica, MA, USA, 1:150) and an anti-PCNA antibody (catalog no. ab18197; Abcam, Cambridge, UK, 1:1500) were utilized for the immunohistochemistry. Immunohistochemical scoring was assessed by two experienced pathologists without clinicopathological information of the patients according to the Fromowitz Standard. The product of intensity and the proportion of positively stained cancer cells in each whole tissue sample was used to represent the protein levels of ECT2. The staining intensity was scored as 0 (no staining), 1 (weak staining, light yellow), 2 (moderate staining, yellow brown) and 3 (strong staining, brown). The proportions of stained tumor cells were identified as 1 (0%–25% positive cells), 2 (26%–50% positive cells), 3 (51%–75% positive cells) and 4 (76%–100% positive cells).

Meta-analysis of the expression of ECT2 using published gene expression omnibus (GEO) databases

We carried out a comprehensive search of relevant GEO databases to assess the mRNA expression of ECT2 through ArrayExpress and Oncomine, as previously described. The dataset met the following criteria: 1) the dataset concerned human NSCLC; 2) the mRNA expression of ECT2
was measured in the dataset; 3) the clinical outcomes of patients were shown in the dataset; 4) the sample capacity was more than 50; 5) only the latest and most complete datasets were included when several databases shared common patients. A total of 21 independent NSCLC microarray databases were enrolled in this systematic analysis (Table 1). Statistical analysis was performed based on the guidelines of meta-analysis of observational studies. The Stata software package (version 12.0) was employed to perform the meta-analysis.

Survival analysis based on immunohistochemical scoring

Based on the immunohistochemical scoring for 94 ADC patients, an overall survival curve was constructed using SPSS and univariate analyses were conducted through Cox regression, which yielded an HR and 95% CI. The cutoff value for ECT2 was the median expression.

The correlation analysis of ECT2 and PCNA

The immunohistochemical (IHC) scores for ECT2 and PCNA for the same tissue arrays (HlugA180Su05) were analyzed to evaluate the correlation between ECT2 and PCNA protein expression. Two public GEO databases, GSE434215 and GSE32474,16 consisting of NSCLC cell lines, and three databases, GSE31210,38 GSE6846546 and GSE30219,37 containing the highest number of NSCLC patients of the 21 databases, were analyzed to evaluate the correlation between the mRNA expression of ECT2 and PCNA.

Statistical analysis

Expression analysis and correlation analyses were calculated using GraphPad Prism 5.0 and SPSS 20 statistical software. The difference between groups was evaluated using Student’s t-test and one-way analysis of variance (ANOVA). A two-tailed P-value <0.05 was considered statistically significant.

Results

ECT2 expression was significantly increased in various subtypes of lung cancer compared with normal lung tissues

We compared ECT2 expression in several subtypes of lung cancer and normal lung tissues through IHC staining and representative images of the IHC staining are shown in Figure 1A. The average score for normal, SQC, adenocarcinoma, ADC, bronchioloalveolar carcinoma, large cell carcinoma, small cell carcinoma and atypical carcinoid was 0.90±0.28, 5.43±0.46, 8.67±1.76, 4.38±0.44,

<table>
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<tr>
<th>Table 1 Microarray databases detailing the mRNA expression of ECT2 (these databases were included in the meta-analysis)</th>
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<td>Der et al45</td>
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<td>Shedden et al46</td>
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<td>Cancer Genome Atlas Research Network (CGARN)47</td>
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Abbreviations: ECT2, epithelial cell transforming sequence 2; NSCLC, non-small-cell lung cancer; ADC, adenocarcinoma; SQC, squamous cell lung cancer; NR, not reported.
Figure 1  ECT2 was enriched in various subtypes of lung cancer.

Notes: (A) Representative images of ihC staining of normal, squamous cell carcinoma, adenosquamous carcinoma, adenocarcinoma, bronchioloalveolar carcinoma, large cell carcinoma, small cell carcinoma, and atypical carcinoid; (B) quantitative ihC scores of eCT2 in various lung cancer subtypes; (C) meta-analysis of eCT2 mRNA expression in tumors vs normal; (D) meta-analysis of eCT2 mRNA expression in SQC vs ADC.

Abbreviations: ECT2, epithelial cell transforming sequence 2; ihC, immunohistochemical; T, tumor; N, normal; OR, odds ratio; ADC, adenocarcinoma; SQC, squamous cell lung cancer.
The expression level of ECT2 was associated with cancer progression and prognosis in NSCLC

Based on the immunohistochemical scoring of the HuguA180SU05 and BC041115c tissue microarrays, we found the immunohistochemical scores of tumor tissues were significantly higher than those of matched adjacent tissues (P<0.0001) (Figure 1A). Moreover, we compared the protein level of ECT2 in lung cancer tissues with clinical-pathological parameters. The protein level of ECT2 in lung cancer was significantly and positively correlated with clinicopathological parameters including TNM stage, tumor cell differentiation, tumor size, and lymph node metastasis (Figure 2B–E). We also used a meta-analysis to examine the relationship between the mRNA level of ECT2 and clinical-pathological characteristics. The patients were divided into ECT2 high and low subgroups based on the median ECT2 mRNA expression values. The level of ECT2 mRNA expression in patients with stage III and IV NSCLC was higher than in patients with stage I and II NSCLC (pooled OR =2.17, 95% CI: 1.69–2.79, P=0.117, and F=36.4%) (Figure 3A). Meanwhile, the level of ECT2 mRNA expression in ADC patients showed a similar trend and the patients with stage III and IV was higher than patients with stage I and II (pooled OR =1.83, 95% CI: 1.32–2.54, P=0.899, and F=0.0%) (Figure 3B). The ECT2 mRNA expression in stage III and IV NSCLC was higher compared with stage I and II NSCLC in SQC, but the difference was not statistically significant (pooled OR =1.32, 95% CI: 0.78–2.25, P=0.429, and F=0.0%) (Figure 3C). The ECT2 mRNA expression of T3 and T4 was higher compared with T1 and T2 in NSCLC (pooled OR =2.27, 95% CI: 1.62–3.20, P=0.023, and F=61.7%) (Figure 3D). The ECT2 mRNA expression of lymph node-positive patients was higher than that of lymph node-negative patients in NSCLC (pooled OR =1.45, 95% CI: 1.12–1.89, P=0.939, and F=0.0%) (Figure 3E). Because the clusters with histological differentiation information were poor, we used GSE68465 to test the ECT2 mRNA expression in patients with different degrees of cell differentiation. The results showed that the ECT2 mRNA expression of the poorly differentiated group was remarkably higher than that in the well differentiated group (P<0.0001) and that of the moderately differentiated group was also higher than that of the well differentiated group (P=0.0001) (Figure 3F). In summary, the protein and mRNA expression of ECT2 were correlated with clinical-pathological characteristics in NSCLC.

Table 2 Correlation between ECT2 expression and the clinicopathological features of 202 lung cancer patients on TMAs (BC041115c and HuguA180SU05)

<table>
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<td></td>
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<td>&gt;6 (high expression)</td>
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<td>Age</td>
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<tr>
<td>≥60</td>
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<tr>
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<tr>
<td>N−</td>
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<td>N+</td>
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<tr>
<td>III−IV</td>
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Notes: aPearson chi-squared test; bContinuity correction chi-squared test; n−, lymph node negative; n+, lymph node positive.

Abbreviations: ECT2, epithelial cell transforming sequence 2; TMAs, tissue microarrays.

High ECT2 expression predicted poor survival in NSCLC

To evaluate the prognostic value of ECT2 in NSCLC, we first investigated the association between ECT2 protein expression and overall survival using a Cox univariate regression analysis. A TMA consisting of 94 ADC patients
was divided into ECT2 high and low subgroups following the immunohistochemical staining score of 3–4 vs 1–2. The median overall survival (OS) time of the ECT2 high group was 29±5.561 months, while that of the low group was 56±3.548 months (P=0.006) (Figure 4A). A Cox univariate regression analysis between the cumulative overall survival rates and clinicopathological factors demonstrated that ECT2 expression (HR =2.010, 95% CI: 1.204–3.355, P=0.008), lymph node metastasis (HR =2.672, 95% CI: 1.541–4.633, P=0.000) and TNM stage (HR =2.658, 95% CI: 1.483–4.765, P=0.008).
node negative; n

**Abbreviations:**

ADC, adenocarcinoma; SQC, squamous cell lung cancer.

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**Figure 3** mRNA level of ECT2 was associated with cancer progression and prognosis.

**Notes:** (A) Meta-analysis of ECT2 mRNA expression at stage III + IV vs I + II; (B) stage III + IV vs I + II in ADC; (C) stage III + IV vs I + II in SQC; (D) tumor size T3 + T4 vs. T1 + T2; (E) lymph node positive vs lymph node negative; (F) the mRNA expression of ECT2 at different degrees of tumor cell differentiation in GSE68465. N+, lymph node positive; N−, lymph node negative.

**Abbreviations:** ECT2, epithelial cell transforming sequence 2; ihC, immunohistochemical staining; CGARN, Cancer Genome Atlas Research Network; OR, odds ratio; ADC, adenocarcinoma; SQC, squamous cell lung cancer.

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P=0.001) were prognostic factors for overall survival in ADC patients. We performed a forward variable-selection procedure and found the ECT2 expression was a statistically significant independent prognostic factor for the OS of ADC patients (HR =0.406, 95% CI: 0.226–0.727, P=0.002) (Table 3).

ECT2 expression was correlated with that of PCNA

Based on the immunohistochemical scoring for PCNA, we found that the protein levels of PCNA in ADC were significantly higher than those in matched adjacent normal lung tissue (P<0.0001), and they were positively correlated...
Table 3 ECT2 expression in ADC is an independent prognostic factor for ADC patients (HlugA180Su05)

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<td>HR (95% CI)</td>
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<tr>
<td>Sex (female/male)</td>
<td>0.733 (0.457–1.176)</td>
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<tr>
<td>Age (&gt;60/≤60)</td>
<td>1.011 (0.632–1.619)</td>
<td>0.962</td>
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<td>Differentiation (poor/moderate + well)</td>
<td>2.360 (0.859–6.486)</td>
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<td>Stage (II + III/I)</td>
<td>2.658 (1.483–4.765)</td>
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<td>Tumor size (T3 + T4/T1 + T2)</td>
<td>1.424 (0.838–2.419)</td>
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<tr>
<td>Lymph node metastasis (N+/N−)</td>
<td>2.672 (1.541–4.633)</td>
<td>0.000</td>
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<tr>
<td>ECT2 expression (high/low)</td>
<td>2.010 (1.204–3.355)</td>
<td>0.008</td>
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Notes: N+: lymph node negative; N−: lymph node positive. Abbreviations: ECT2, epithelial cell transforming sequence 2; ADC, adenocarcinoma; HR, hazard ratio.
eCT2 is a potential novel prognostic factor for NSCLC

Figure 5 eCT2 expression correlated with PCNA expression.

Notes: (A) Representative images of IHC staining of PCNA; (B) representative images of IHC staining of PCNA and eCT2 in the same lung cancer tissues; (C) IHC scores of PCNA in lung cancer; (D) the correlation between eCT2 and PCNA based on protein expression; (E) based on the mRNA level of the GSE4342 cell line; (F) GSE32474 cell line; (G) GSE31210 cell line; (H) GSE68465 cell line; (I) GSE30219 cell line. N−, lymph node negative; N+, lymph node positive.

Abbreviations: IHC, immunohistochemical staining; PCNA, proliferating cell nuclear antigen; eCT2, epithelial cell transforming sequence 2; HR, hazard ratio; ADC, adenocarcinoma; SQC, squamous cell lung cancer.
of lung cancer cells, which contributed to the prognosis of NSCLC. These results are in agreement with those of prior studies of the role of ECT2 in breast cancer, osteosarcoma, gastric cancer and glioma.\(^4\)\(^7\)

We also examined the expression of PCNA in ADC and found that it was positively correlated with clinicopathological parameters including TNM stage, tumor cell differentiation, tumor size, and metastasis, supporting the previous study showing that PCNA is expressed in proliferating cells, and is an important factor for the initiation of cell proliferation.\(^2\)\(^5\)\(^6\) Until now, no studies have reported a correlation between ECT2 and PCNA. In the current study, we demonstrated the ECT2 expression is positively correlated with PCNA expression in ADC at both the protein and mRNA level, suggesting that ECT2 is an important factor in the regulation of NSCLC cell division. The expression level of ECT2 may be a useful biomarker to predict proliferation and aggression in NSCLC. Moreover, high ECT2 expression predicts a shorter survival time, indicating that ECT2 expression may serve as a prognostic marker for NSCLC patients.

As a common GEF for the Rho GTPase family, ECT2 can catalyze guanine nucleotide exchange on RhoA, Rac1, and Cdc42 in vitro.\(^1\)\(^2\)\(^7\) Therefore, gene therapy to abolish ECT2 activity may restrain the Rac1/RhoA/Cdc42 signaling pathways, which may provide an effective approach to block Rho GTPase activity and reverse a malignant phenotype.

One interesting finding is that ECT2 expression in SQC is higher than that in ADC, but ECT2 levels did not significantly affect the OS of SQC cancer patients, suggesting that ECT2 may play a different function in ADC compared with SQC. Therefore, further study of the molecular mechanism of ECT2 in ADC and SQC should provide valuable information. In addition, immunohistochemical staining of lung tissue specimens indicated that ECT2 is expressed both in the cytoplasm and nucleus of lung cancer cells, while ECT2 is only weakly expressed in the nucleus of healthy lung tissue, which supports previous findings that ECT2 is mislocalized to the cytoplasm to activate Rac1 for transformed growth.\(^8\)

Therefore exploring the transport of the ECT2 protein from the nucleus to the cytoplasm and blocking the translocation process of ECT2 may have potential therapeutic value.

**Conclusion**

This study demonstrated that ECT2 expression in various lung cancer subtypes is significantly higher than in normal tissues and its expression was positively related to TNM stage, tumor cell differentiation, tumor size, and metastasis in NSCLC. In the current study, we have reported for the first time that the expression of ECT2 is positively correlated with that of PCNA in lung cancer at the protein and mRNA level. ECT2 overexpression is an unfavorable prognostic factor predicting poor disease-free survival and overall survival for NSCLC patients, especially in ADC, and may serve as a potential prognostic indicator and biomarker for NSCLC patients.

**Acknowledgments**

This study was supported by the National Natural Science Foundation of China (grant No. 81572608, 81172422, and 81874120) and the Wuhan Science and Technology Bureau (grant No. 20170602010170).

**Author contributions**

XB carried out the experiments and drafted the manuscript. MY, SY and XX participated in data collection, analysis and IHC scoring; XZ and KW designed the study, evaluated the results, and revised the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**

Supplementary materials

Figure S1 Overexpression of ECT2 mRNA predicted poor survival.
Notes: Kaplan–Meier curve of patients with low or high ECT2 expression. Median of mRNA expression was used to divide patients into subgroups. (A) Overall survival; (B) progression-free survival; (C) overall survival in ADC; (D) progression-free survival in ADC; (E) overall survival in SQC; (F) progression-free survival in SQC.
Abbreviations: ECT2, epithelial cell transforming sequence; HR, hazard ratio; ADC, adenocarcinoma; SQC, squamous cell lung cancer.