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Expression of Eukaryotic Initiation Factor 4E in Atypical Adenomatous Hyperplasia and Adenocarcinoma of the Human Peripheral Lung

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Abstract

The overexpression of eukaryotic initiation factor 4E (eIF4E), a key regulator of protein synthesis, is involved in the malignant progression of various human cancers. We investigated eIF4E expression in atypical adenomatous hyperplasia (AAH) and adenocarcinomas of the human peripheral lung. On the basis of the WHO criteria with minor modifications, adenocarcinomas were classified as bronchioloalveolar carcinoma (BAC), mixed subtypes with a bronchioloalveolar pattern and minor invasion (early MX), and mixed subtypes with a papillary pattern and marked invasion (overt MX). eIF4E immunohistochemistry was performed in 143 tissue samples (31 AAH, 38 BAC, 43 early MX, and 31 overt MX). Both tumoral and stromal eIF4E levels were elevated from AAH, BAC, and early MX to overt MX and significantly associated with histological grade (P < 0.001 and P < 0.001, respectively). Tumoral and stromal eIF4E staining intensities were significantly correlated (P < 0.01). Immunoblot analysis of 51 tissue samples (2 AAH, 11 BAC, 18 early MX, and 20 overt MX) demonstrated that eIF4E expression in adenocarcinomas was 3.4–7.4-fold higher than in normal lung and that its expression progressively increased in the following order: AAH (lowest expression), BAC, early MX, and overt MX (highest expression). Multiple regression analysis revealed that both tumoral and stromal eIF4E expressions were significant independent factors for the histological subtype (P < 0.01 and P < 0.01, respectively). These results suggest that translational control is dysregulated during the development of peripheral lung adenocarcinoma and that progressive increases of tumoral and stromal eIF4E may be part of a positive feedback loop for malignant progression.

Introduction

Lung cancer is a leading cause of cancer death in most industrial countries. Among various histological types of lung cancer, adenocarcinomas are the most common and account for >30% of all lung cancers (1). According to the recently established WHO histological classification system for lung tumors (2), there are five major subtypes of adenocarcinomas: acinar; papillary; BAC3; solid with mucin formation; and a mixture of these four subtypes (MX). In addition to the invasive (non-BAC) adenocarcinomas and noninvasive (BAC) adenocarcinomas, this revised classification system also includes a preinvasive lesion, AAH (2). AAH is histologically characterized by a localized proliferation of atypical cuboidal to low-columnar epithelial cells along the alveolar septa (3–11). On the basis of morphological, immunohistochemical, molecular, and genetic observations (3–12), it has been widely accepted that adenocarcinomas of the human peripheral lung, especially those with bronchioloalveolar features, develop by multiple steps from AAH through BAC to invasive adenocarcinomas.

Translational control is an integral part of the regulation of gene expression (13–15). Changes in the efficiencies of mRNA translation influence gene expression at the protein level, resulting in alterations of cell function and phenotype (15–20). In eukaryotes, almost all mRNAs are modified at their 5'-termini with a m7GpppN cap structure (where N is any nucleotide; Ref. 21). Translation of such mRNAs typically requires cap-dependent unwinding of secondary structure in the 5'-untranslated regions by the initiation complex elf4F. This complex consists of a cap-binding protein elf4F, an adaptor protein elf4G, and an ATP-dependent RNA helicase elf4A (14–16). Because elf4E is the least abundant among these initiation factors (22) and is considered to be the rate-limiting factor for cap-dependent translation initiation (23), changes in the levels of elf4E profoundly affect translation rates. Several investigators have proposed an attractive model of translational control mediated by the quantity and activity of elf4E (24–26). In this model, while increasing global protein synthesis rates, higher levels of

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3 The abbreviations used are: BAC, bronchioloalveolar carcinoma; MX, mixed subtype; AAH, atypical adenomatous hyperplasia; elf, eukaryotic initiation factor; VEGF, vascular endothelial growth factor; FGF-2, fibroblast growth factor 2; LDH, lactate dehydrogenase.
eIF4E preferentially enhance the selective synthesis of potent growth promoting proteins and oncogenic proteins in which the translation is presumably repressed (e.g., VEGF, FGF-2, c-myc, cyclin D1, and ornithine decarboxylase). By this mechanism, malignancy-related events such as transformation, tumorigenesis, angiogenesis, invasion, and metastasis could be induced (24–26). Indeed, stable overexpression of eIF4E induces accelerated growth and malignant transformation in NIH3T3 cells (17) and aberrant growth in HeLa cells (18). Enforced expression of eIF4E inhibits apoptosis in serum-restricted NIH3T3 cells (19). In addition, cells overexpressing eIF4E produce and secrete an increased amount of VEGF, which stimulates the proliferation of vascular endothelial cells (20). Conversely, depletion of eIF4E with antisense RNA suppresses the tumorigenic and angiogenic properties of MDA-435 cells by decreasing a powerful angiogenic factor, FGF-2 (27). eIF4E depletion also reduces the capacity to invade and form metastasis in ras-transformed CREF cells, which is accompanied by the decrease of metastasis-related proteins (i.e., matrix metalloprotease 9 and exom 6 containing variants of CD44; 28). It is well known that many transformed cell lines express higher levels of eIF4E (29). It is also reported that a variety of human solid cancers such as breast, bladder, colon, and head and neck cancers, ubiquitously express eIF4E and that the levels of eIF4E expression are well correlated with clinical outcome and histological malignancy (30–37). Recently, Rosenwald et al. (38) examined eIF4E expression in human lung cancers and suggested that eIF4E is increased frequently in BAC. However, the clinical implication of these findings for lung adenocarcinogenesis remains to be elucidated. In this study, we investigated eIF4E expression in AAH and adenocarcinoma of the human peripheral lung and discussed its possible roles in the development of human lung adenocarcinoma.

Materials and Methods

Patients and Tissue Samples. Approval for this study was obtained from the Institutional Review Board. One hundred-eleven patients with small peripheral pulmonary nodule(s) underwent curative surgical resection without prior chemotherapy or radiotherapy at National Shikoku Cancer Center Hospital from January 1999 to July 2001 and were pathologically diagnosed as having AAH or stage IA adenocarcinoma of the lung. On the basis of the recently established WHO lung tumor classification system with minor modifications (3), tissue samples were subclassified into the following histological groups: AAH, BAC, early MX (MX with a predominantly bronchioloalveolar pattern and a minor invasive component), and overt MX (MX with a predominantly papillary pattern and a marked invasive component). Discrimination between these two subtypes of MX depended upon agreement between two of the investigators (N. S. and K. M.). Patients with multiple synchronous lung tumors were classified into the most advanced histological groups as described previously (39, 40). Medical charts for all patients were reviewed, and the clinicopathological characteristics are summarized in Table 1. Including multiple synchronous lung tumors, a total of 143 lesions were obtained from 111 patients and subjected to immunohistochemistry. Among these subjects, 51 lesions from 43 patients were available for protein extraction and subjected to Western blot analysis.

Immunohistochemistry. Representative blocks of formalin-fixed and paraffin-embedded tissues were cut into 4-μm thick sections. After deparaffinization, sections were boiled for 40 min at 95°C in Dako ChemMate Buffer for Antigen Retrieval (Dako, Kyoto, Japan) and then processed for immunohistochemistry on the TeckMate Horizon automated staining system (Dako). Endogenous peroxidase activity was blocked with methanol containing 3% hydrogen peroxide for 10 min. A mouse monoclonal antihuman eIF4E primary antibody (Transduction Laboratories, Lexington, KY) and Dako ChemMate Envision+ secondary antibody conjugated to peroxidase (Dako) were applied to the sections sequentially. Antibody binding was visualized by 3,3’-diaminobenzidine tetrahydrochloride (Dako). Counterstaining of the nuclei was performed with hematoxylin.

Sections from breast cancer specimens were used as a positive control because breast cancer tissue is known to overexpress eIF4E (30–32). As a negative control, sections were immunostained without exposure to the primary antibody.

Evaluation of eIF4E Immunostaining. Because eIF4E expression in tumor cells and stroma cells was generally homogeneous in each section and the levels of eIF4E staining in stroma cells were relatively weak compared with those in tumor cells, the following internal controls were used to evaluate the intensity of eIF4E staining. For the tumor cells, the intensity of staining was scored on a scale from +1 to +3, where the intensity in normal bronchial epithelium was defined as an internal control and designated as +2. If the intensity in the tumor cells was lower or higher than this internal control, it was designated as +1 or +3, respectively. For the stroma cells, the intensity in normal interstitial lymphocytes was defined as an internal control. The intensity in the stroma cells was scored as follows: 0, negative staining; 1, positive staining but lower than the internal control; 2, equivalent to the internal control; and 3,
higher than the internal control. All sections were evaluated by two investigators (N. S. and K. M.) in a blinded manner without any information regarding clinicopathological characteristics. When the two investigators scored a sample differently, they conferred to achieve consensus.

**Western Blot Analysis.** Frozen tissue samples (~10 mg each) were chopped into tiny pieces and suspended in 0.5 ml of protein lysis buffer [150 mM NaCl, 1.0% NP40, 20 mM Tris (pH 7.5), 5 mM EDTA, and 0.1 volume of protease inhibitor mixture (Sigma Chemical, St. Louis, MO)] and then mechanically homogenized with a Polytron for 1 min at 15,000 rpm. After centrifugation, the protein extracts were recovered and stored at −80°C until they were used. Protein concentrations were determined using the Pierce BCA Protein Assay Kit (Pierce, Rockford, IL). Western blotting was performed as described previously (41). Briefly, protein extracts (50 μg/lane) were separated on 12.5% SDS-polyacrylamide gel and transferred to a polyvinylidene difluoride membrane (Bio-Rad Laboratories, Hercules, CA). The membranes were blocked with PBS containing 0.05% Tween 20 and 5% dry milk and probed either with anti-eIF4E antibody or a mouse monoclonal anti-LDH antibody (Sigma Chemical) and then treated with appropriate horseradish peroxidase-conjugated secondary antibodies. Immunoreactive proteins were visualized using the Enhanced Chemiluminescence Western blotting detection system (Amersham Pharmacia Biotech, Piscataway, NJ). Densitometric analysis was performed by scanning immunoblots and quantitating protein bands using an image analyzer EPIPRO7000 (Aisin Cosmos R&D Co., Ltd., Tokyo, Japan) with the software “EpiPro Imager” (Aisin Cosmos R&D Co., Ltd.). Relative eIF4E expression was obtained by normalizing the densitometric readings in the tumor tissues with those in the adjacent normal lung tissue from the same individual. Anti-LDH antibody was used to check protein loading as described previously (30–32).

**Statistical Analysis.** The χ² test or the one-way ANOVA was used to compare the clinicopathological characteristics (listed in Table 1) of the four histological categories. The Kruskal-Wallis test followed by Scheffe’s post hoc test was used to evaluate the statistical significance of different eIF4E expression levels in the histological subtypes. Spearman’s rank correlation coefficient was used to analyze the relationship between two groups. Multiple regression analysis was performed to identify significant independent factors for histological subtypes. All calculations were carried out using Stat View 5.0 J software (SAS Institute Inc., Cary, NC). Ps < 0.05 were considered statistically significant.

**Results**

**Analysis of eIF4E Immunohistochemistry.** The typical eIF4E immunostaining patterns in normal bronchial and alveolar epithelium, AAH, and three types of lung adenocarcinomas were evaluated (Fig. 1). eIF4E expression was homogeneously positive in the cytoplasm of tumor cells, stroma cells (mainly consisting of fibroblasts), bronchial epithelial cells, and normal interstitial lymphocytes, whereas it was negative in alveolar epithelial cells and fibroblasts in the normal interstitium.

An analysis of eIF4E expression in tumor cells by histological groups was carried out (Fig. 2A). As tissue samples were evaluated from AAH, BAC, early MX, and overt MX, the incidence of intensity +1 decreased in a stepwise manner from 81 to 3%, whereas the incidence of intensity +3 progressively increased from 0 to 74%. The incidence of intensity +2 in BAC and early MX was 53 and 44% (respectively), and relatively higher than that in AAH (19%) and overt MX (23%). The intensity of tumoral eIF4E staining was significantly correlated with the histological subtype (Spearman’s rank correlation coefficient, ρ = 0.629; P < 0.001). In addition, statistically significant differences were found among all histological groups (Scheffe’s post hoc test; P < 0.01), with the exception of BAC versus early MX (Scheffe’s post hoc test; P = 0.271).

The results of eIF4E expression in stroma cells by histological groups showed a similar trend (Fig. 2B). As tissue samples were evaluated from AAH, BAC, early MX, and overt MX, the proportion of intensity 0 decreased in a stepwise manner from 81 to 7%, whereas the proportion of intensity +2 progressively increased from 0 to 38%. The incidence of intensity +1 conspicuously increased from AAH (19%) to BAC (58%) and early MX (65%) and then slightly decreased in overt MX (48%). Intensity +3 was observed only in overt MX (7%). A statistically significant relationship existed between the intensity of stromal eIF4E staining and the histological subtype (Spearman’s rank correlation coefficient, ρ = 0.617; P < 0.001). Statistically significant differences were also found among all histological groups (Scheffe’s post hoc test; P < 0.01), with the exception of early MX versus overt MX (Scheffe’s post hoc test; P = 0.118).

A statistically significant correlation was found between the eIF4E staining intensities of tumor cells and stroma cells (Spearman’s rank correlation coefficient, ρ = 0.701; P < 0.001; Fig. 3). As intensities in tumor cells were evaluated from +1, +2, and +3, the proportion of intensity 0 in stroma cells decreased from 70 to 0%, whereas intensity +2 in stroma cells increased from 0 to 46%. The incidence of intensity +1 in stroma cells was highest in tumoral intensity +2. Stromal intensity +3 was observed only in tumoral intensity +3 (6%).

**Analysis of eIF4E Western Blotting.** Western blot analysis was performed to quantitatively evaluate eIF4E expression (Fig. 4A). eIF4E expression in AAH tumor tissue was equivalent to the expression in the adjacent normal lung tissue. In contrast, eIF4E expression in BAC, early MX, and overt MX tumor tissues was much higher than in the normal lung tissues. Relative eIF4E expression in AAH and the three types of lung adenocarcinomas was compared (Fig. 4B). The level of eIF4E expression in AAH was equivalent to the normal lung (median densitometric value = 1.2), whereas the expression levels in BAC, early MX, and overt MX were substantially higher than those in the normal lung (median densitometric values = 3.4, 4.5, and 7.4, respectively). A progressive increase in eIF4E protein expression was detected as tissue samples were evaluated from AAH, BAC, early MX, and overt MX. Because of the limited numbers of samples, AAH was excluded from the following statistical analysis. Relative eIF4E expression was significantly correlated with the histological subtype (Spearman’s rank correlation coefficient, ρ = 0.476; P = 0.001). Statistically significant differences were also found among the three types of lung adenocarcinomas (Scheffe’s post hoc test; P < 0.05), with the exception of BAC versus early MX (Scheffe’s post hoc test; P = 0.718).
Multiple Regression Analysis for Histological Subtype.

Multiple regression analysis was performed to determine which factors significantly contributed to histological subtype in the 111 patients (Table 2). All six variables consisting of age, gender, smoking history, tumor size, tumoral eIF4E expression, and stromal eIF4E expression were demonstrated to be significant independent predictors of the histological subtype. Our multiple regression analysis model for histo-

**Fig. 1** Detection of eIF4E by immunohistochemistry. A, normal bronchial epithelium; B, normal alveolar epithelium; C, AAH; D, BAC; E, early MX; F, overt MX. Arrowheads indicate normal interstitial lymphocytes. Cells expressing eIF4E show brown staining. ×200.
logical subtype had a high multiple correlation coefficient ($R = 0.798; P < 0.01$).

**Discussion**

In this study, we have clearly demonstrated that eIF4E expression levels are significantly correlated with histological subtypes of peripheral human lung adenocarcinoma and its precursor, AAH. We have also shown that in multivariate analysis, both tumoral and stromal eIF4E expressions in addition to age, gender, smoking history, and tumor size, are significant independent predictors for these histological subtypes.

The current WHO histological classification for lung tumors defines BAC as an adenocarcinoma of the lung that grows in a lepidic fashion along the alveolar septae without invasive growth (2, 6, 8, 11). A considerable proportion of invasive lung adenocarcinomas contains a BAC-like lepidic growth component in the tumor margin, thus most cases are categorized as MX. However, the histological subclassification of cases of invasive lung adenocarcinomas with only a minor BAC-like component is still open to debate. In such cases, some investigators may simply categorize them as MX, whereas others may classify them as one of the non-BAC type invasive lung adenocarcinomas (e.g., acinar, papillary, or solid with mucin formation) according to the predominant histological pattern in the tumor tissue. In this context, it may be more practical for investigators to subclassify invasive lung adenocarcinomas based on the involvement of the BAC-like component in the tumor tissue. Higashiyama et al. (42) proposed a novel classification system based on a semiquantitative analysis of the BAC component area in invasive lung adenocarcinomas and BAC. They found that the tumors with a lesser BAC component had a worse prognosis than tumors with an extensive BAC component and BAC. Carretta et al. (43) divided lung adenocarcinomas composed of BAC and MX into two groups and demonstrated that the tumors with >50% of BAC component, which correspond to BAC and early MX in our study, had a more favorable prognosis than those with ≤50% of BAC component, which correspond to overt MX in our study. Koga et al. (44) also proposed that BAC with an invasive growth component, which is similar to our early MX, should be classified independently from MX because this type of adenocarcinoma had a better prognosis than non-BAC invasive lung adenocarcinomas (composed mainly of papillary adenocarcinoma) and a worse prognosis than BAC. These observations suggest that the presence of a BAC-like component is a critical determinant for the prognosis and histological malignancy of lung adenocarcinoma. In our study, we modified the current WHO criteria for the category of MX based on the predominant histological pattern in the tumor tissue, i.e., early MX was defined as a predominantly bronchioloalveolar pattern with a minor invasive component, and overt MX was defined as a predominantly papillary pattern with a marked invasive component. Because our classification system shares some similarities with the investigators cited above, it seems to be acceptable for evaluating the malignant potential of AAH and small peripheral lung adenocarcinomas. On the basis of all of these considerations, we also postulate that the histological grade is getting worse from AAH, BAC, and early MX to overt MX, although a prognostic study of these four histological subtypes has not been completed.

Many studies during the last decade have found ubiquitous overexpression of eIF4E in a variety of human cancers such as
increased eIF4E expression may facilitate accelerated growth and division of neoplastic cells in BAC. On the basis of these observations, we conclude that dysregulation of cap-dependent translational control occurs during the transition from AAH through probably BAC to invasive lung adenocarcinomas (early MX and overt MX) and that increased tumoral eIF4E expression may confer aggressive neoplastic characteristics such as rapid proliferation, suppression of apoptosis, angiogenesis, invasion, and metastasis. Concomitant with the increase of eIF4E in tumor cells, a progressive increase of eIF4E in stroma cells was also observed in the following order: AAH (lowest expression); BAC; early MX; and overt MX (highest expression; Fig. 2B). Stromal eIF4E expression levels were significantly correlated with tumoral eIF4E expression levels (Fig. 3). Evidence suggests that heterotypic interactions between epithelial tumor cells and stromal cells are important in various stages of tumorigenesis, including tumor growth, desmoplasia, angiogenesis, invasion, and metastasis (45, 46). Therefore, the progressive increase of eIF4E both in tumor cells and stroma cells may be a consequence of heterotypic interactions between these cells. Increased tumoral eIF4E expression may selectively up-transcribe putative downstream targets, including growth promoting factors (e.g., ornithine decarboxylase), angiogenic factors (e.g., FGF-2 and VEGF), cell cycle regulators (e.g., cyclin D1), oncogenes, and proto-oncogenes (e.g., c-Myc and Ras). Increased expression of any of these factors could conceivably cause an amplification of stromal eIF4E expression and, in turn, continue the enhanced translational rates of these proteins, thereby establishing a positive feedback loop for the development of peripheral lung adenocarcinoma.

In AAH tumor cells, eIF4E expression was weak but distinguishably higher than in normal alveolar epithelium (Fig. 1), indicating that dysregulation of cap-dependent translational control may exist in the early stages of lung adenocarcinogenesis. Regarding the specificity of eIF4E expression in noncancerous lesions, alveolar epithelium and interstitial fibroblasts showed undetectable levels of eIF4E, whereas interstitial lymphocytes displayed relatively strong eIF4E expression (Fig. 1). These results are in agreement with those of Rosenwald et al. (38).

Western blot analysis demonstrated a progressive increase of eIF4E from AAH, BAC, and early MX to overt MX (Fig. 4B), largely confirming the results of immunohistochemistry. The only difference noted was that immunohistochemical study revealed an increase of eIF4E in AAH compared with noncancerous lesions (Fig. 1), whereas Western blot analysis did not.

**Table 2 Multiple regression analysis for histological subtype**

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>$R^a$</th>
<th>$\beta^b$</th>
<th>$P$</th>
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<td>Age</td>
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<td>0.162</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Gender</td>
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<td>-0.422</td>
<td>&lt;0.01</td>
</tr>
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<td>Smoking</td>
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<td>0.225</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tumor size</td>
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<td>0.025</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tumoral eIF4E</td>
<td></td>
<td>0.288</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stromal eIF4E</td>
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$^a$ Multiple correlation coefficient.

$^b$ Standardized partial regression coefficient.
detect overexpression of eIF4E in AAH (Fig. 4, A and B). One possible explanation for this variance is that tumoral eIF4E staining in sections of AAH was constitutively positive, but eIF4E was not sufficiently abundant to be detected by Western blot analysis. Another possibility is that the limited numbers of AAH affected the results of Western blot analysis.

Although previous investigations have used Western blotting for the quantification of eIF4E, the assay’s suitability for this purpose remains somewhat controversial. Sorrells et al. (47) reported the intrinsic issue of stromal contamination in preparing protein extracts that represent homogenates of heterogeneous populations of cells, although they used Western blots to demonstrate overexpression of eIF4E in infiltrating ductal carcinoma of the breast and in head and neck squamous cell carcinoma. Rosenwald et al. (38) also reported that tumor samples contain mixed cellular populations, including neoplastic cells and stroma cells, which may variably contribute to protein extracts for Western blotting. In our study, the degree of stromal contamination in the protein extracts was not quantified. However, the results of Western blotting were generally consistent with those of immunohistochemistry.

At this point, it is uncertain whether the progressive increase of tumoral and stromal eIF4E expression is a direct cause of lung adenocarcinogenesis. However, the increased availability or activity of eIF4E seems to be advantageous for malignant cells not only to establish greater protein synthesis but also to achieve more aggressive neoplastic characteristics such as accelerated cell growth, evasion of apoptosis, angiogenesis, and invasion in the development of human peripheral lung adenocarcinoma. Thus, molecular and pharmacological intervention targeting the cap-dependent translation machinery, especially eIF4E, may provide a new therapeutic paradigm for lung adenocarcinoma. Several previous studies support this proposal. Reducing eIF4E expression with antisense RNA or decreasing its function by overexpressing inhibitory eIF4E-binding proteins can abrogate the oncogenic properties of certain tumor cell lines (27, 28, 48). CCI-779, an ester analogue of rapamycin with antitumor activity in several drug-refractory cancers, including non-small cell lung cancer (50, 51).

Although some investigators have suggested a correlation between eIF4E expression and morbidity, others believe that it is possible to achieve more aggressive neoplastic characteristics such as increased tumoral and stromal eIF4E expression is a direct cause of lung adenocarcinogenesis. Several studies support this proposal. Molecular and pharmacological intervention targeting the cap-dependent translation machinery, especially eIF4E, may provide a new therapeutic paradigm for lung adenocarcinoma. Several previous studies support this proposal. Reducing eIF4E expression with antisense RNA or decreasing its function by overexpressing inhibitory eIF4E-binding proteins can abrogate the oncogenic properties of certain tumor cell lines (27, 28, 48). CCI-779, an ester analogue of rapamycin with antitumor activity in several drug-refractory cancers, including non-small cell lung cancer (50, 51).

In conclusion, we have provided evidence that eIF4E may play a pivotal role in the malignant progression of peripheral human lung adenocarcinoma. Elucidating the details of cap-dependent translational control, especially via eIF4E, in lung adenocarcinogenesis may permit earlier diagnosis and aid physicians and scientists in developing more effective treatments.

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