Original Article

EGFR mutation is positively correlated with C-Met protein expression: a study of 446 resected lung adenocarcinoma

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Background: *Epidermal growth factor receptor* (*EGFR*) mutation and mesenchymal-epithelial transition factor (C-Met) amplification are known factors for primary resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs) in advanced primary lung adenocarcinoma. However, little is known about the relationship between high expression of C-Met protein and primary *EGFR* mutation. This research aims to investigate the correlation between *EGFR* mutation and C-Met protein expression in resected primary lung adenocarcinoma.

Methods: Four hundred and forty-six surgically resected lung adenocarcinoma between 2013–2015 were collected for *EGFR* mutation analysis by real-time PCR (RT-PCR) and C-Met protein expression by immunohistochemistry (IHC). The relationship between the two biomarkers and clinicopathological features were analyzed.

Results: The positive rate of *EGFR* mutation and C-Met protein expression were 66.4% (296/446) and 96.4% (430/446). *EGFR* mutation was significantly higher in female, mild to moderate differentiation, lepidic, acinar and papillary histological subtypes (P<0.05). C-Met expression was more prominent in female than male (201 *vs.* 123, 45.07% *vs.* 27.57%). *EGFR* mutation was found positively correlated with C-Met protein expression (P<0.05).

Conclusions: *EGFR* mutation and C-Met protein expression are prone to have a female predominance, and are positively correlated with each other in surgically resected lung adenocarcinoma specimens. This finding may be beneficial in explaining some of the resistance mechanisms of *EGFR*-mutated cases, which is worth further study.

Keywords: Lung adenocarcinoma; mesenchymal-epithelial transition factor (C-Met); *epidermal growth factor receptor* (*EGFR*); non-small-cell lung cancer (NSCLC)

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Introduction

Non-small-cell lung cancer (NSCLC) is a leading cause of cancer-related death world-wide. The molecular classification of lung adenocarcinoma and corresponding target therapy have effectively improved the survival status of lung cancer (1). Tyrosine kinase inhibitor (TKI) is the specific targeted therapy, which is the personalized medicine revolution in the treatment of advanced-stage NSCLC, the biomarker-defined indications for targeted therapy include *epidermal growth factor receptor* (*EGFR*)-mutant, *ALK*-rearranged (ALK+), *ROS1*-rearranged or *BRAFV600E*-mutant (2). In recent years, along with the development of immunotherapy, such as anti-programmed cell death 1 (PD-1), tumor mutational burden (TMB), tumor-infiltrating lymphocytes (TILs), which are also the treatment landscape of NSCLC (3). Among many molecular subtypes of lung adenocarcinoma, *EGFR*-mutated lung adenocarcinoma accounts for more than 50% in Chinese patients (4). *EGFR* is one of the four members of ErbB family of tyrosine kinase receptors. Activation of *EGFR* leads to regulating cellular proliferation, differentiation, and survival (5). *EGFR* has been identified as an oncogenic driver of NSCLC, especially *EGFR* mutations and its inhibition with specific TKIs have an important impact on tumor (6). Researches on the efficacy and resistance mechanism of *EGFR* tyrosine kinase inhibitors (EGFR-TKIs) have facilitated the continuing renewal of a series of targeting drugs. However, virtually all advanced lung cancer patients with *EGFR* mutation will inevitably acquire resistance or have primary resistance to EGFR-TKIs. Among these, mesenchymal-epithelial transition factor (C-Met) amplification or exon 14 splice mutation is one of the factors (7). C-Met is a multifunctional transmembrane tyrosine kinase and acts as a receptor for hepatocyte growth factor (8). It has been shown that there is a significant correlation between C-Met amplification and C-Met protein expression (9). In the patients with stage IV or treated with erlotinib after failure of first-line chemotherapy, *EGFR* mutation was correlated with progression-free survival (PFS) and response rate of erlotinib. While C-Met amplification of gene copy number did not show a significant correlation with erlotinib or PFS (10). According to our clinical observation, advanced patient with high C-Met protein expression alone could benefit from crizotinib (11). Nevertheless, in recent years, researchers have paid more attention to mechanisms of *EGFR* T790M-mutant and Met amplifications that responsible for acquired resistance to EGFR-TKIs, while little is known about the high expression of C-Met protein with primary *EGFR* mutation and its significance in lung adenocarcinomas.

In this study, we collected curatively resected lung adenocarcinoma specimens without preoperative neoadjuvant chemotherapy for analysis of *EGFR* mutation and C-Met protein expression, with the aim of exploring C-Met protein expression and its correlation of *EGFR* mutation in lung adenocarcinoma.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2202).

Methods

Case selection

All pathologically diagnosed pulmonary adenocarcinoma surgical resection specimens were consecutively collected from the Department of Pathology of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences from 2013 to 2015. In total, 446 cases were enrolled into the analysis, among which 439 underwent curative intent surgical resection, and the other seven underwent palliative surgery. None of the patients received preoperative adjuvant chemotherapy. Clinicopathological data were extracted from medical archives, including age, gender, and AJCC 7th pathological stage and so on.

Histological review

All 446 archived pathological reports and slides were reviewed by two senior pathologists (HL and LY), according to the 2015 World Health Organization classification of lung tumors (12). Differentiation degree was also included as one of the observing variables which was defined as mild, moderate and poorly degree according to extent of difference between tumor tissue and normal lung tissue. The inclusion criteria for enrolled cases are: (I) underwent surgical resection from 2013 to 2015, (II) the pathological diagnosis of adenocarcinoma, (III) not under preoperative chemoradiotherapy. The exclusion criteria documents of clinicopathological is incompletely.

Experimental methods & positive interpretation standard

Pre experimental preparation

All surgical specimens were routinely fixed in 10% formalin for about 24 h at 10 times the volume of the

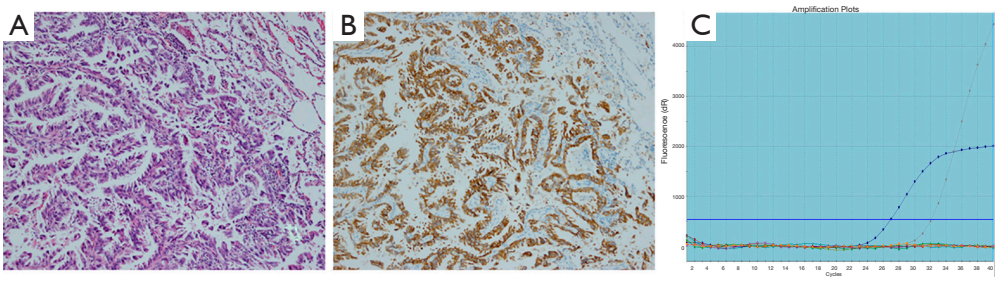

Figure 1 Illustration of histopathological, immunohistochemical and RT-PCR results. (A) One case of lung adenocarcinoma (hematoxylin-eosin staining, original magnification 100×). (B) Showed positive (3+) staining in human C-Met protein (immunohistochemical staining, original magnification 100×). (C) Mutation of *EGFR* exon 21. RT-PCR, real-time PCR; C-Met, mesenchymal-epithelial transition factor; *EGFR, epidermal growth factor receptor.*

tissue liquid, and then embedded in paraffin. Consecutive 4-μm-thick sections and wax roll were prepared for immunohistochemical staining and real-time PCR (RT-PCR), respectively.

C-Met protein expression was determined by immunohistochemistry (IHC). All staining steps were completed on the fully automatic Roche immunohistochemical instruments (Roche Diagnostics, Shanghai, China) according to the recommended standard protocols. C-Met protein was localized primarily in the cytoplasm (*Figure 1*). According to the manufacture's scoring algorithm, intensity was scored according to a four-tier system: including negative (0), no staining or less than 5% staining; weakly positive (1+), 5–25% tumor cells stained; moderately positive (2+), 25–50% tumor cells stained; strongly positive (3+), >50% tumor cells stained. Negative quality control sections were first evaluated to remain unstained before evaluation for immunostaining on every case. For statistical analysis, negative or low expression was defined as 0 and 1+, and high expression was defined as 2+ and 3+.

Genomic DNA was obtained using the QIAamp DNA Mini Tissue kit (Qiagen, Germany). *EGFR* (exon 18-21) mutation tests were performed using a RT-PCR assay (ACCB, Beijing, China), together with the Stratagene Mx3000P (Agilent Technologies Inc., Santa Clara, CA, USA).

Statistical analysis

Independent Chi-square test was used to compare frequency of clinicopathological characters between C-Met high expression and low expression groups, and between *EGFR* mutant and wild type groups. Spearman correlation analysis was made between *EGFR* mutation and C-Met protein expression. The statistical analyses were conducted using SPSS version 24.0 software. Statistical significance was set as $P<0.05$ (two side).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 20/234-2430) and informed consent was taken from all the patients.

Results

Patient characteristics

The 446 lung adenocarcinomas included 181 males (40.58%) and 265 females (59.42%), with a mean age of 57 y. According to the 7th AJCC/UICC staging system, all enrolled patients were classified as stage I (n=161), stage II (n=83), stage III (n=188) and stage IV (n=14), respectively. According to 2015 WHO histological classification, they were adenocarcinoma *in situ* (0.22%, 1/446), minimally invasive adenocarcinoma (0.22%, 1/446), lepidic adenocarcinoma (6.28%, 28/446), acinar adenocarcinoma (53.14%, 237/446), papillary adenocarcinoma (17.26%, 77/446), solid adenocarcinoma (15.92%, 71/446), micropapillary (1.35%, 6/446), mucinous adenocarcinoma (3.81%, 17/446), adenocarcinoma combined squamous carcinoma (1.12%, 5/446), adenocarcinoma combined small cell carcinoma (0.22%, 1/446), enteric adenocarcinoma (0.22%, 1/446) and carcinosarcoma (0.22%, 1/446). As for differentiation degree, they were classified as mild

Table 1 Clinicopathological features of 446 lung adenocarcinomas

Clinicopathological features	Case number (n=446)	Percentage (%)
Age	56.99±10.01	
Gender		
Male	181	40.58
Female	265	59.42
Pathological stage		
Early (I–II)	244	54.71
Progressive (III–IV)	202	45.29
Differentiation level		
Poorly	63	14.13
Moderate	318	71.30
Mild	65	14.57
Major subtypes		
Lepidic	28	6.28
Acinar	237	53.14
Papillary	77	17.26
Solid	71	15.92
Mucinous adenocarcinoma	17	3.81
Special type*	16	3.59

*, Special type includes those cases less than 1% in the enrolled patients, including adenocarcinoma *in situ*, minimally invasive adenocarcinoma, carcinoma combined small cell carcinoma, adenosquamous carcinoma, micropapillary adenocarcinoma, enteric adenocarcinoma and carcinosarcoma.

(n=63), moderate (n=318), and poorly ones (n=65). Other clinicopathological features were listed in *Table 1*.

EGFR mutation and correlation with clinicopathological features

The overall *EGFR* mutation rate was 66.37% (296/446), specifically, with which located in exon 18 (3.04%, 9/296), exon 19 (42.56%, 126/296), exon 20 (3.04%, 9/296), exon 21 (48.31%, 143/296), co-existence in exons 18 and 20 (1/296, 0.33%), co-existence in 18 and 21 (1/296, 0.33%), co-existence in 20 and 21 (6/296, 2%); there's one case with an unknown record of mutated site (1/296, 0.33%). Clinical features were compared by stratifying patients into *EGFR* mutant and *EGFR* wide type groups. Female patients harbored more mutations compared with male patients (41.98% *vs.* 27.92%, P<0.05). The mild and moderate differentiated tumors were more frequently mutated than the poorly differentiated tumors (80% and 69.81% *vs.* 34.92%, P<0.05). The mutation rate was also significantly correlated to lepidic, acinar and papillary histological subtypes (75% *vs.* 70.88% *vs.* 79.22%, P<0.05). However, there was no significant difference in pathological stages (P=0.99) (seen in *Table 2*).

C-Met protein expression and correlation with clinicopathological features

C-Met protein was positively expressed in cytoplasm. Low expression and high expression of C-Met were observed in 27.35% (122/446) and 72.65% (324/446) of the cohort, respectively. The expression of C-Met protein showed a female predominance tendency (201 *vs.* 123, 45.67% *vs.* 27.57%) (seen in *Table 3*). There was no statistical difference in pathological stages, differentiation degrees and histological major subtypes (P>0.05).

Correlation between EGFR mutation and C-Met protein expression

EGFR mutation status showed a significantly positive correlation with C-Met protein expression (r_s=0.095, P=0.044, see in *Table 4*).

Discussion

The molecular classification of lung adenocarcinoma and corresponding target therapy have effectively improved the clinical outcome of lung cancer, especially in patients with *EGFR* sensitive mutations (13). *EGFR* overexpression and/or mutation are associated with tumor cell proliferation, angiogenesis, tumor invasion, metastasis and inhibition of apoptosis. NSCLC patients with high expression of *EGFR* mutation are more prone to recurrence and metastasis (14). Likewise, in our study, 64.53% females had *EGFR* mutation. As there are interactions between the *EGFR* pathway and the estrogen receptor, *EGFR* mutations may be associated with estrogen (15). In adenocarcinomas, *EGFR* mutation correlated with estrogen receptor α expression (P=0.0029 to <0.0001) (16), and the expression of estrogen receptor β (P=0.029) (17). Meanwhile, the study showed a significant correlation of *EGFR* mutation with histological subtypes, which coincides with literatures (18). Ninomiya *et al.* (19) found that the hobnail cell type

Table 2 Correlation between *EGFR* expression and clinicopathological features

Clinicopathological features	EGFR		χ^2	P value
	Wide type (n=150)	Mutant (n=296)		
Age	56.24±10.31	57.37±9.84		0.260
Gender			9.531	0.002
Male	76	105		
Female	74	191		
Pathological stage			1.600×10^{-4}	0.99
Early (I–II)	82	162		
Progressive (III–IV)	68	134		
Differentiation			35.013	2.495×10^{-10}
Poorly	41	22		
Moderate	96	222		
Mild	13	52		
Major subtypes			32.865	4.000×10^{-6}
Lepidic	7	21		
Acinar	69	168		
Papillary	16	61		
Solid	41	30		
Mucinous adenocarcinoma	10	7		
Special type	7	9		

EGFR, epidermal growth factor receptor.

and a micropapillary morphology could predict a higher incidence of *EGFR* mutations in lung adenocarcinomas, meanwhile, Lee *et al*. (20) found *EGFR* mutations were frequent in well to moderately differentiated lung adenocarcinomas. Likewise, the current research showed that mild and moderate differentiated adenocarcinomas were more frequently mutated, and the mutation rate was also significantly correlated to lepidic, acinar and papillary histological subtypes, which indicated the differentiation degree and histological subtypes supported each other.

NSCLC are often intrinsically resistant to certain anticancer drugs, but our knowledge about drug resistance are still far from having a complete understanding of the underlying mechanisms. Currently, there are two specific mechanisms of acquired drug resistance, which includes T790M mutation and *C-Met* amplification, accounting for 50% and 20% of acquired resistant cases, respectively (7,21). Other possible mechanisms include a lack of phosphatase and tensin homolog deleted on chromosome ten (PTEN) (22), down-regulation of BIM (23), up-regulation of Integrin β1 (24), high expression of HGF (25), activation of ALK pathway (26). As for *C-Met* gene, gene amplification was found a mainly cause for EGFR-TKIs resistance which was first discovered by Engelman *et al*. at 2007 (7). Although, biologically, C-Met amplification may not necessarily lead to efficient protein expression for real function execution of the gene, which are possibly influenced by epigenetic factors, although not common. A study of Met protein expression and *C-Met* amplification in 316 surgically resected lung adenocarcinomas found that *C-Met* amplification was significantly associated with Met protein expression (P<0.001) (9). According to NCCN guidelines, the protein overexpression has not been routinely recommended for testing before EGFR-TKIs regimens. Instead, the newly updated NCCN guidelines recommend testing for *C-Met* gene amplification and exon 14 splice site mutation as of crizotinib targeting therapy (27). We experienced one advanced lung adenocarcinoma with C-Met

Table 3 Correlation between C-Met expression and clinicopathological features

Clinicopathological features	Low expression	High expression	χ^2	P value
Age	57.54±9.91	56.78±10.01		0.474
Gender			3.372	0.066
Male	58	123		
Female	64	201		
Pathological stage			0.343	0.558
Early (I–II)	64	180		
Progressive (III–IV)	58	144		
Differentiation			0.314	0.855
Poorly	17	46		
Moderate	89	229		
Mild	16	49		
Major subtypes			4.317	0.505
Lepidic	7	21		
Acinar	63	174		
Papillary	20	57		
Solid	21	50		
Mucinous adenocarcinoma	8	9		
Special type	3	13		

C-Met, mesenchymal-epithelial transition factor.

Table 4 Spearman correlation analysis between *EGFR* mutation and C-Met expression

Spearman correlation	EGRF		r_s	P value
	Wild	Mutant		
C-Met			0.095	0.044
Low expression	50	72		
High expression	100	224		

EGFR, epidermal growth factor receptor; C-Met, mesenchymal-epithelial transition factor; r_s, rank correlation coefficient of spearman.

protein overexpression benefitted from crizotinib (11), which suggests that the detection and analysis of C-Met protein in lung adenocarcinoma may play a role. Awad *et al.* found that patients with *C-Met* exon 14-mutation had a significant likelihood to have concurrent *Met* amplification and C-Met protein overexpression in NSCLC (28), meanwhile, C-Met IHC staining was a positive prognostic biomarker for overall survival in early stage NSCLC (29). In our study, the expression of C-Met protein showed a positive correlation tendency to gender (P=0.066), which is similar to Tsuta's research (30). In another published larger investigation of 1,479 cases from our group, we identified a significant correlation of the expression of C-Met protein and gender (31). In this research, we also found a female concentration trend and positive correlation of both *EGFR* mutation and C-Met expression in lung adenocarcinoma, which was consistent with Nakamura *et al.* (32). Nakamura *et al.* identified phosphor-C-Met correlated with phospho-

Akt (P=0.0381), and phospho-Akt expression was correlated with the expression of phospho-*EGFR* (P=0.0533). As activation of Akt is related to antiapoptotic of tumors, we can speculate that inhibition of the C-Met pathway may provide an alternative therapeutic approach in lung adenocarcinomas with resistance to EGFR inhibitors.

In conclusion, from the current research, we identified that overexpression of C-Met protein was positively correlated with *EGFR* mutation, which indicated that a synergistic effect may exist between EGFR and C-Met in lung adenocarcinoma and may somehow play a role in primary drug resistance of EGFR-TKIs. Still, there are two limits lie in our study. Firstly, we failed to identify EGFR related target therapy due to the insufficiencies of enrolled advanced cases in the curatively surgical specimens. Secondly, since we choose surgical resection specimens to study, the correlation between the therapeutic effect of EGFR-TKIs and the expression of C-Met protein could not be observed, which will be extended for further study.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 20/234-2430) and informed consent was taken from all the patients.

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