Original Article

# *PIK3CA* mutation in Chinese patients with lung squamous cell carcinoma

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**Objective:** To investigate *PIK3CA* mutation in Chinese patients with lung squamous cell carcinoma (LSCC) and explore their relationship with clinicopathological profiles.

**Methods:** Tumor samples from 123 cases of LSCC were included in this study. *PIK3CA* mutations in exon 9 and 20 were screened by pyrosequencing and confirmed by clone sequencing or amplification refractory mutation system (ARMS). Denaturing performance liquid chromatography (DHPLC) was employed for evaluation of *EGFR* mutation in exon 19, 21 and *KRAS* mutation.

**Results:** *PIK3CA* mutations were found in 3 (2.4%) patients. The mutation type included E545K, E452Q and H1047R. Of these three patients, one coupled with *EGFR* mutation, and the other two coupled with *PIK3CA* amplification. All the three patients shared the same clinicopathologic characteristics: male, less than 60 years old, had smoke history, stage III and carried wild-type *KRAS*.

**Conclusions:** The frequency of *PIK3CA* mutation is low in Chinese patients with LSCC. The mutational status of *PIK3CA* is not mutually exclusive to *EGFR* mutation.

**Key Words:** Lung squamous cell carcinoma (LSCC); *PIK3CA* mutation; *EGFR* mutation; *KRAS* mutation

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## Introduction

Lung cancer is the most frequent cause of cancer-related death worldwide. Despite therapeutic advances, the overall 5-year survival remains only 15% (1). Novel treatment strategies are, therefore, needed. One promising treatment strategy involves the further subdivision of non-small cell lung cancer (NSCLC) into clinically relevant molecular subsets, according to a classification schema based on specific so-called driver mutations to perform molecular targeted therapies (2,3). For instance, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (gefitinib and erlotinib) and anaplastic lymphoma kinase (ALK) inhibitor (crizotinib) have dramatically improved the response and progression-free survival of NSCLC patients harboring EGFR sensitive mutations and echinoderm microtubule-associated protein like-4 (EML4)-ALK fusion gene (4-6). These mutations occur in genes that encode signaling proteins crucial for cellular proliferation and survival. Mutant oncogenes drive tumor formation and maintenance (7,8). Cancers might rely on the expression of these single-mutant oncogenes for survival. This concept is also called oncogene addiction (2,3). However, these driver mutations mainly cluster in adenocarcinoma. So it is imperative to explore the potential biomarkers for squamous carcinoma.

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB/Akt) signaling pathway plays an important role in cell growth and proliferation initiated by activation of receptor tyrosine kinases and in tumor genesis and

progression (9,10). The PI3K catalytic alpha (PIK3CA) encodes the p110α catalytic subunit of PI3K, which forms a heterodimer with the p85 regulatory subunit and is sequestered to the cell membrane in response to multiple stimuli. Recently, activating mutations of *PIK3CA* gene have been identified in a broad spectrum of tumors. A great majority of somatic mutations in *PIK3CA* are missense mutations clustering in exons 9 and 20 that encode a part of the helical and kinase domains, respectively (11). There is increasing evidence that constitutive activation of the PI3K pathways in lung cancer occurs as a consequence of *PIK3CA* mutation or amplification. However, in Chinese patients with LSCC, little data exist on *PIK3CA* mutations.

*PIK3CA* is a 34 kb gene located on chromosome 3q26.3 that consists of 20 exons coding for 1,068 amino acids yielding a 124 kDa protein (12). *PIK3CA* gene codes for the catalytic subunit p110α of class IA PI3Ks. The first of these mutational reports was published by Samuels *et al*. in 2004 (11). Subsequently, *PIK3CA* mutation is identified in a considerable portion of human primary epithelial cancers, resulting in *PIK3CA* being one of the most commonly mutated oncogenes in human cancers (13,14). *PIK3CA* mutations in human cancers confer a gain of function resulting in increased lipid kinase activity and in constitutive activation of the PI3K-AKT pathway in the absence of growth factor (11,15).

The PI3K/Akt pathway lies in downstream of certain receptor tyrosine kinases, including EGFR. However, the reports about occurrence of *PIK3CA* mutations and its association with *EGFR* mutation and *KRAS* mutation in LSCC were limited. The aims of the present study were to investigate *PIK3CA* mutations in exons 9 and 20 in Chinese patients with LSCC and explore the correlations between *PIK3CA* mutation and *EGFR* or *KRAS* mutations, and the clinicopathologic characteristics.

## Materials and methods

### *Patients and tissue samples*

This retrospective study was conducted in a cohort of 123 patients with LSCC who had treated at the Department of Thoracic Oncology of Beijing Cancer Hospital from June 2003 to September 2011. All patients met the following inclusion criteria: (I) having histologically verified LSCC; (II) the formalin-fixed paraffin-embedded (FFPE) tissue having tumor cell no less than 70%; and (III) having basically clinicopathological information. Both adenosquamous lung cancer patients and those with the second primary cancer were excluded. Survival analysis was calculated from date of diagnosis to date of death or last date of contact for those alive at the time of the analysis. This study was approved by the Institutional Ethic Committee of Beijing Cancer Hospital.

FFPE tissues were obtained before therapy. Serial sections (4 μm) containing representative malignant cells were stained with Hematoxylin-Eosin (H&E) and classified based on the World Health Organization criteria. The tumor samples for molecular analysis were obtained from bronchoscopic biopsy or from computed tomography/ ultrasound-guided needle biopsy, or from percutaneous aspiration (lymph nodes and skin metastasis), or surgery.

### *Detection of EGFR and KRAS mutations*

The genomic DNA was extracted from FFPE tissues using the EZN AFFPE DNA Kits (OMEGA, USA) according to the manufacturers' instructions. We performed denaturing high-performance liquid chromatography (DHPLC) using the Transgenomic Wave Nucleic Acid Fragment Analysis System (Transgenomic, Omaha, NE) for *EGFR* (exon 19 and 21) (16) and *KRAS* (coden 12 and 13) mutation detection. The temperature for analysis was according to the optimal resolution of heteroduplex and homoduplex determined by analyzing the melting behavior of each fragment. We identified mutation profiles by visual inspection of the chromatograms on the basis of the appearance of earlier-eluting (*EGFR* 19 product) or blunt peaks (*EGFR* 21 and *KRAS* product) and corresponding homozygous profiles showed only one peak.

### *Detection of PIK3CA mutation by pyrosequencing*

*PIK3CA* mutation testing has been carried out in our laboratory using conventional PCR followed by pyrosequencing. *PIK3CA* exon 9 is amplified using a forward biotinylated primer, 5'-biotin-CAATGAATTAAGGGAAAATGACAA-3', and a reverse primer, 5'-ACCTGTGACTCCATAGAAAATCTT-3'. *PIK3CA* exon 20 is amplified using a forward biotinylated primer, 5'-biotin-GCAAGAGGCTTTGGAG TATTTCA-3', and a reverse primer, 5'-GTTCAATGC ATGCTGTTTAATTGT-3'. The PCR master mix contains the forward and reverse primers (each 0.2 μmol/L), 2× mix (Promega, USA) 7.5 μL and 20 ng of sample genomic DNA in a total volume of 15 μL. PCR-

 

cycling conditions for *PIK3CA* exon 9 consist of initial denaturing at 95 ℃ for 5 min; 10 cycles of 95 ℃ for 30 s, 52 ℃ for 30 s and 72 ℃ for 50 s; 35 cycles of 95 ℃ for 30 s, 57 ℃ for 30 s and 72 ℃ for 50 s; and final extension at 72 ℃ for 10 min. PCR-cycling conditions for *PIK3CA* exon 20 consist of initial denaturing at 95 ℃ for 5 min; 10 cycles of 95 ℃ for 30 s, 55 ℃ for 30 s and 72 ℃ for 50 s; 35 cycles of 95 ℃ for 30 s, 60 ℃ for 30 s and 72 ℃ for 50 s; and final extension at 72 ℃ for 10 min. The reactions were carried out on an ABI 2,720 Thermocycler (Applied Biosystems). The PCR products were electrophoresed in an agarose gel to confirm successful amplifications before pyrosequencing. The PCR products (each 10 μL) are then sequenced by the Pyrosequencing PyroMark Q24 System (Qiagen, Germany), following the manufacturer's instructions using the pyrosequencing primer for *PIK3CA* exon 9, 5'-TAGAAAATCTTTCTCCTGC-3', and the pyrosequencing primer for *PIK3CA* exon 20, 5'-CCATTTTTGTTGTCCAG-3'. Each sample is sequenced with a separate program of nucleotide dispensation orders: 5'-GTCGAGTGCATTCGAGA-3', designed for detecting mutations at exon 9; and 5'-TCGACGTATCGACTGTG-3' designed for detecting mutations at exon 20. The primers and the dispensation orders enable us to capture all possible mutations of the wild type sequence at exon 9 E542 (GAA), E545 (GAG) and exon 20 H1047 (CAT), G1049 (GGT) of *PIK3CA*.

We confirmed these cases defined as "mutation positive" by pyrosequencing using Amplification Refractory Mutation System (ARMS) or clone sequencing. *PIK3CA* mutation was detected using AmoyDx™ PIK3CA Mutation Detection Kit (Amoy Diagnostics Co., LTD, China.) for E542K, E545K, H1047R, H1047L amino acid mutation detection in accordance with the manufacturer's instructions. For E542Q mutation, clone sequencing was done by selecting 15 sub-clone for each product.

### *Detection of PIK3CA amplification by fluorescence in situ hybridization*

*PIK3CA* gene copy number of the tumor samples, which had *PIK3CA* mutations, was also evaluated by fluorescence *in situ* hybridization (FISH). FFPE tumor materials were cut into 4 μm thick sections and placed onto glass slides. Sections of slides were deparaffinized, pretreated with paraffin pretreatment solution at 95 ℃ for 30 min and digested with protease solution at 37 ℃ for 10-20 min. PIK3CA (Texas Red)/CEN3q (FITC) FISH probe (Abnova, Taiwan) was applied to the sections. The sections were denatured at 75 ℃ for 5 min and then hybridized at 37 ℃ for 48 h. After hybridization, washing was done. The sections were counterstained with 4',6-diamidino-2-phenylindole (DAPI). The samples were analyzed under a 100× oil immersion objective with a fluorescence microscope (OLYMPUS, Japan). At least 100 nuclei per case were evaluated. Signal count ratio of *PIK3CA* to CEP3q more than 2 was defined as amplification.

### *Statistical analysis*

All eligible patients meeting the study inclusion criteria were included in the final statistic analysis. The statistical analyses of categorical variables were done using the Pearson's $\chi^2$ test or the Fisher's exact test where appropriate. All statistical tests were two sided, and a P value less than 0.05 was considered statistically significant. All statistical procedures were performed with SPSS statistical software, version 16.0 (SPSS Inc., Chicago, IL, USA).

## Results

### *Clinical variables*

There were 104 men (84.6%) and 19 women (15.4%), with age at diagnosis ranging from 32 to 83 years (median age, 64.0 years). Patients consisted of 28 non-smokers (22.8%) and 95 smokers (77.2%). Patients had performance status ranging from grade 0 to 3. Performance status was defined according to the Eastern Cooperative Oncology Group. Pathologic staging of lung cancers was determined according to the UICC-AJCC-TNM system (version 7, 2009) (17): 4 (3.3%) had stage I disease, 10 (8.1%) stage II, 19 (15.4%) stage IIIA, 38 (30.9%) stage IIIB, and 52 (42.3%) stage IV. All patients had tissue sample assessable for *EGFR* mutation, *KRAS* mutation and *PIK3CA* mutation detection. The clinicopathologic characteristics of the patients are summarized in *Table 1*.

### *PIK3CA mutation in LSCC*

Tissues of the 123 patients were available for DNA sequencing analysis. *PIK3CA* mutations were found in three patients (2.4%), one in the catalytic domain of *PIK3CA* and two in the helical domain. The mutation included E545K, E452Q, and H1047R. One sample with *PIK3CA* mutation (E545K) also had *EGFR* mutation (L858R), the other two

 

**Table 1** Clinicopathological data of 123 patients

| Characteristics | n (%) |
|---|---|
| Age (year) | |
| Median age | 64.0 [32-83] |
| ≤60 | 43 (35.0%) |
| >60 | 80 (65.0%) |
| Gender | |
| Male | 104 (84.6%) |
| Female | 19 (15.4%) |
| Smoking status | |
| Smoker | 95 (77.2%) |
| Non-smoker | 28 (22.8%) |
| ECOG | |
| 0 | 28 (22.8%) |
| 1 | 85 (69.1%) |
| 2 | 9 (7.3%) |
| 3 | 1 (0.8%) |
| Stage | |
| I | 4 (3.3%) |
| II | 10 (8.1%) |
| IIIA | 19 (15.4%) |
| IIIB | 38 (30.9%) |
| IV | 52 (42.3%) |

coupled with *PIK3CA* amplification. All the three patients with *PIK3CA* mutation share the common clinicopathologic characteristics: male, less than 60 years old, had smoke histology, stage III and carried wild-type *KRAS* (*Table 2*).

### *EGFR and KRAS mutation in LSCC*

The tissues of the 123 patients were available for *EGFR* mutation analysis. *EGFR* mutations were found in 19 patients (15.4%), including 9 in exon 19 and 10 in exon 21. The *EGFR* mutation status was significantly different between smoker and non-smoker groups in our cohort (10.5% *vs.* 32.1%, P=0.013). The frequency of *EGFR* mutation was found higher in women than men, but it was not statistically significant (31.6% *vs.* 12.5%, P=0.077). The incidence of *EGFR* mutation did not show association with age and stage (*Table 3*).

The *KRAS* mutations were identified in 9 (7.3%) of the 123 patients. The *KRAS* mutations were not correlated with age, gender, smoking status and stage of the LSCC (*Table 3*).

## Discussion

The lung adenocarcinoma genome has been characterized extensively (4-8,18-22). However, less is known about specific genetic alterations, especially "driver mutations", in LSCC. In present study, we identified 2.4% of Chinese patients with LSCC harboring *PIK3CA* mutations with the subtype E545K, E452Q and H1047R. The mutational status of *PIK3CA* is not mutually exclusive to *EGFR* mutation. All the *PIK3CA* mutation positive patients shared the same clinicopathologic characteristics, such as male, less than 60 years old, had smoke history, stage III and carried wild-type *KRAS*.

Although *PIK3CA* mutations occur frequently in a variety of human cancers, individual types of epithelial cancers show remarkable variability in their mutational rates, with high rates present in colon cancer, breast cancer, gastric cancer, hepatocellular cancer, brain tumors and ovarian cancer (11,14,23-25). Whereas the rates described in NSCLC are relatively uncommon. Samuels *et al.* reported a low frequency (4.2%) of *PIK3CA* mutations in lung cancer (11). Kawano and his colleagues then confirmed this low frequency (3.4%) in Japanese lung cancer patients and demonstrated that *PIK3CA* mutation incidence was more commonly in squamous cell carcinoma (6.5%) than in adenocarcinoma (1.5%) (26). Okudela *et al.* identified the mutations of *PIK3CA* in 3.6% of lung cancers (27). Lee *et al.* detected *PIK3CA* mutations in 3 of 229 NSCLC (1.3%) (25). Recently, a large samples study was reported. Yamamoto *et al.* analyzed about 700 lung cancer samples and identified *PIK3CA* mutations in 1.6% of all major histology types (28). Stratified by squamous cell carcinoma in the above-mentioned studies, the frequency of *PIK3CA* mutation was 2-7.1%. Our study showed that 2.4% (3/123) of the Chinese LSCC carried mutations in exon 9 and exon 20 of *PIK3CA* gene, which was in good agreement with previous reports, indicating *PIK3CA* mutation is also a rare event in Chinese patients with LSCC. Furthermore, the present data confirm that the prevalence of *PIK3CA* mutations in LSCC doesn't present ethnic difference, unlike mutations in *EGFR* (18).

The high number of observed *PIK3CA* mutations, so-called "hotspot" mutations, map to three sites, E542 and E545 in the helical domain (exon 9) and H1047 in the kinase domain (exon 20). In our study, the three mutated subtypes were observed. *In vitro* and *in vivo* oncogenicity of *PIK3CA* mutants strongly suggests a critical role for these mutated proteins in human malignancies. It was well

 

**Table 2** Clinicopathological data and biomarkers of three patients with PIK3CA mutation

| Case | Gender | Age (year) | Smoking status | Stage | *PIK3CA* mutation | *PIK3CA* amplification | *EGFR* mutation | *KRAS* mutation | OS (month) | Survival status |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Male | 40 | Smoking | IIIB | E545K | NO | L858R | WT | 41.0 | Died |
| 2 | Male | 53 | Smoking | IIIB | E542Q | Amplification | WT | WT | 22.6 | Died |
| 3 | Male | 55 | Smoking | IIIA | H1047R | Amplification | WT | WT | 11.2 | Alive |

OS, overall survival; WT, wild type

**Table 3** Correlation of *EGFR* and *KRSA* mutation with clinicopathological parameters

| | *EGFR* (n=123) | | | *KRAS* (n=123) | | |
|---|---|---|---|---|---|---|
| | Mutation n (%) | Wild type n (%) | P | Mutation n (%) | Wild type n [%] | P |
| Age (year) | | | | | | |
| ≤60 | 8 (18.6) | 35 (81.4) | 0.477 | 0 (0.0) | 43 [100] | 0.055 |
| >60 | 11 (13.8) | 69 (86.2) | | 9 (11.2) | 71 [88.8] | |
| Gender | | | | | | |
| Male | 13 (12.5) | 91 (87.5) | 0.077 | 8 (7.7) | 96 [92.3] | 1.000 |
| Female | 6 (31.6) | 13 (68.4) | | 1 (5.3) | 18 [94.7] | |
| Smoking status | | | | | | |
| Smoker | 10 (10.5) | 85 (89.5) | 0.013 | 7 (7.4) | 88 [92.6] | 1.000 |
| Non-smoker | 9 (32.1) | 19 (67.9) | | 2 (7.1) | 26 [92.9] | |
| Stage | | | | | | |
| I-IIIA | 5 (15.2) | 28 (84.8) | 0.956 | 0 (0.0) | 33 [100] | 0.135 |
| IIIB-IV | 14 (15.6) | 76 (84.4) | | 9 (10.0) | 81 [90.0] | |

documented that these mutations cause an increase in PI3K activity and induce oncogenic cellular transformation when expressed in chicken embryo fibroblasts and in mouse NIH3T3 cells (29,30). In the kinase domain, H1047R is the most common mutation that occurs at the end of the activation loop of the p110 α/p85 α complex. Through the use of somatic cell knockouts, Samuels reported that the mutations of *PIK3CA* result in increased cell signaling, cell growth and invasion. The colorectal cancer cell lines HCT116 containing the hotspot mutation H1047R in exon 20 had a high apoptotic resistance and an increased ability to migrate and metastatize when injected in the tail vein of athymic nude mice (15).

There was one patient with both *PIK3CA* and *EGFR* mutation. The mutational status of *PIK3CA* was not mutually exclusive to *EGFR*, which is similar to previous reports (26,28,31). It has been reported that *PIK3CA* mutations were not correlated with gender, smoking status in Japanese lung cancer patients (26). Yamamoto reported that tumor samples with *PIK3CA* mutation also had *KRAS* mutations (28). However, in our study all the three patients with PIK3CA mutation share the common clinicopathologic characteristics: male, less than 60 years old, had smoke history, stage III and carried wild-type *KRAS*. Two possible reasons may result in the discrepancy between our and other studies. Firstly, the discrepancy in tumor histological subtypes exists. Previous studies investigated whole NSCLC, whereas our study focused on analysis LSCC. Secondly, because the occurrence of *PIK3CA* mutation is a small probabilistic molecular event in LSCC, the positive cases of *PIK3CA* mutation in both our and other studies were limited, even in the study of Yamamoto *et al*., there only were 11 patients with *PIK3CA* mutation, which may contribute to the bias of associations of the *PIK3CA* mutation with clinicopathologic characteristics and other molecular aberrance.

From the diagnostic and therapeutic standpoint, long-term prospective, blinded randomized trials could be performed to determine if the presence or absence of *PIK3CA* mutations have any correlation with clinical

 

outcome in LSCC. This would then allow for the clinician to predict with complete certainty whether or not cancers harboring these mutations would be more or less aggressive and could therefore influence decisions for systemic therapies. The development of targeted therapies creates a need to discriminate tumors accurately by their histological and genetic characteristics. Nevertheless we expect that PIK3CA will become a major molecular target for personalized therapy in LSCC.

In summary, *PIK3CA* mutation occurred in a rare proportion in Chinese patients with primary LSCC, which was similar to Western and Japanese populations. The mutational status of *PIK3CA* is not mutually exclusive to *EGFR* mutation. All the patients with *PIK3CA* mutation shared the same clinicopathologic characteristics: male, less than 60 years old, had smoke history, stage III and carried wild-type *KRAS*.

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