Role of STK11 in ALK-positive non-small cell lung cancer (Review)

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Abstract. Anaplastic lymphoma kinase (ALK) inhibitors have been shown to be effective in treating patients with ALK-positive non-small cell lung cancer (NSCLC), and crizotinib, ceritinib and alectinib have been approved as clinical first-line therapeutic agents. The availability of these inhibitors has also largely changed the treatment strategy for advanced ALK-positive NSCLC. However, patients still inevitably develop resistance to ALK inhibitors, leading to tumor recurrence or metastasis. The most critical issues that need to be addressed in the current treatment of ALK-positive NSCLC include the high cost of targeted inhibitors and the potential for increased toxicity and resistance to combination therapy. Recently, it has been suggested that the serine/threonine kinase 11 (STK11) mutation may serve as one of the biomarkers for immunotherapy in NSCLC. Therefore, the main purpose of this review was to summarize the role of STK11 in ALK-positive NSCLC. The present review also summarizes the treatment and drug resistance studies in ALK-positive NSCLC and the current status of STK11 research in NSCLC.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) being the most common subtype (1). The majority of patients with NSCLC are diagnosed at an advanced, inoperable stage (2) and have an overall 5-year survival rate of just 5% (3). This poor prognosis may be associated with tumor heterogeneity, acquisition and intrinsic resistance to therapeutic agents in NSCLC (4). If the most appropriate treatment is identified early and drug resistance is addressed to a satisfactory degree, patient survival can be significantly improved. Current non-surgical treatments for NSCLC in clinical practice include systemic chemotherapy, radiotherapy, targeted therapy and immunotherapy (IO). In recent years, rapid developments include cellular and molecular biotechnology, and targeted gene therapy and IO are gradually gaining traction (5). Molecular testing is commonly used in NSCLC, and the detection of epidermal growth factor receptor (EGFR), B-Raf proto-oncogene, serine/threonine kinase (BRAF) and MET proto-oncogene, receptor tyrosine kinase (MET) mutations, as well as anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1, receptor tyrosine kinase (ROS1), ret proto-oncogene (RET) and neurotrophic receptor tyrosine kinase 1 (NTRK1) translocations have been incorporated into the diagnostic criteria for NSCLC, and inhibitors of these kinases are now

Key words: non-small cell lung cancer, anaplastic lymphoma kinase-positive, STK11, drug resistance, targeted therapies

Abbreviations: NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; IR, insulin receptor; ALCL, anaplastic large cell lymphoma; EML4, echinoderm microtubule-associated protein like protein 4; CNS, center nervous system; FDA, food and drug administration; AMPK, amp-activated protein kinase; EGFR, epidermal growth factor receptor; MEK, MAP kinase-Erk kinase; ERK, extracellular signal-regulated kinase; NRF2, nuclear related factor 2; NADPH, nicotinamide adenine dinucleotide phosphate; PFS, progression-free survival; OS, overall survival; ORR, objective remission rate; LKB1, liver kinase B1; TMB, tumor mutation burden; ATP, adenosine triphosphate; IO, immunotherapy; STK11, serine/threonine kinase 11; STK11m, STK11 mutation; STK11wt, STK11 wild-type; PD-1, programmed death 1; PD-L1, programmed cell death-ligand 1

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of note, a previous study developed to rearrangement, which leads to by inducing EML4-ALK and exclusive manner with characterised by rearrangements, which occur in a mutually lung carcinogenesis has been found in mice. The transgenic promoter leads to the rapid development of tumors with / (ERK) kinase (MEK) Direct evidence for the oncogenic potential of upon binding to its ligands, pleiotrophin and midkine (25,26). once it is dimerized and activated by autophosphorylation in addition to IO (17–19). The implementation of (PI3K) operation and survival, such as the phosphatidylinositol-3-kinase pathway regulates several different pathways involved in cell prolif-eration and structural activation of ALK. Like in ALC, many different ALK fusions have been identified, but EML4-ALK is the most common variant (24). ALK has been reported to regulate several different pathways involved in cell proliferation and survival, such as the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian targets of rapamycin (mTOR), RAS/RAF/MAP kinase-extracellular signal-regulated kinase (ERK) kinase (MEK)/ERK and JAK/STAT pathways (Fig. 1), once it is dimerized and activated by autophosphorylation upon binding to its ligands, pleiotrophin and midkine (25,26). Direct evidence for the oncogenic potential of EML4-ALK in lung carcinogenesis has been found in mice. The transgenic overexpression of EML4-ALK in type II alveolar cells via the surface activated protein-c or Clara cell secretory protein promoter leads to the rapid development of tumors with features of lung adenocarcinoma (27,28). A total of 3-7% of NSCLC (mainly adenocarcinoma subtypes) cases are characterized by ALK rearrangements, which occur in a mutually exclusive manner with KRAS and EGFR mutations (29,30). Of note, a previous study developed in vivo induction models by inducing EML4-ALK rearrangement, which leads to lung carcinogenesis. These models have shown a sensitivity to ALK inhibition, thus serving as valuable tools to explore the mechanisms of EML4-ALK-induced lung cancer and response to ALK-targeted therapy (31). Of note, ALK-positive NSCLC patients have a healthy weight, are non-smokers or are young (32).

Current targeted therapies for patients with ALK-positive NSCLC Prior to the discovery of the EML4-ALK fusion protein, chemotherapy was the first-line treatment option (33). ALK inhibitors have shown potent clinical activity in patients with NSCLC (34). Three generations of ALK inhibitors have been approved for clinical use (2). Ten years ago, the first-generation ALK inhibitor crizotinib was approved for clinical treatment. Table I documents clinical studies associated with ALK inhibitors (35–46). In a series of subsequent clinical trials, crizotinib demonstrated good clinical efficacy, including in 149 patients with NSCLC and ALK mutations (PROFILE1001), with an objective remission rate (ORR) of 60.8% and progression-free survival (PFS) of 9.7 months in 143 patients evaluated; several other phases of clinical trials also achieved useful results (35) (Table I). However, since crizotinib cannot easily cross the blood-brain barrier, it leads to brain metastases and resistance in patients (24). The rapid development of resistance during the treatment cycle is the main limiting factor associated with crizotinib (47). Since then, progeny ALK inhibitors have demonstrated significant efficacy and better central nervous system (CNS) activity compared with crizotinib (48-50). Among the clinical studies of second-generation ALK inhibitors, the ASCEND series was a series of studies evaluating the safety and efficacy of ceritinib. Based on this series, ceritinib was approved by the food and drug administration (FDA) for clinical treatment in 2014, mainly for patients who were intolerant to crizotinib or whose disease progressed after taking crizotinib in ALK-positive patients (33). As a result, the FDA approved brigatinib for patients who had failed prior ALK inhibitor therapy (33). In the J-Alex study in Japan, alectinib was compared head-to-head with crizotinib. The latest data from this trial demonstrated a PFS of 34.1 and 10.2 months in the alectinib and crizotinib groups, respectively (42). In the global ALEX study, a new record was set with a PFS of 34.8 months for first-line treatment with alectinib (Table I), which was approved for the treatment of pure ALK-positive patients based on the results of the randomized phase III ALEX trial. In addition, alectinib was effective in preventing the development of brain metastasis and significantly reduced the risk of CNS progression in patients by 84% (43,44). The ALTA-1L study was a study comparing the efficacy and safety of brigatinib with those of crizotinib as first-line treatment for patients with ALK-positive metastatic NSCLC (51). The final results showed that when multiple targeted drugs cause resistance, patients can still benefit from brigatinib. Thus, brigatinib has a unique advantage in follow-up therapy. The third-generation ALK inhibitor lorlatinib was found to inhibit both the ALK and ROS1 pathways and overcome the multi-resistance associated with first- and second-generation ALK inhibitors, while also crossing the blood-brain barrier (45). Regarding IO, irrespective of the histological type, patients treated with atezolizumab showed a significantly longer overall survival than platinum-based chemotherapy in patients with NSCLC with a high programmed cell death-ligand 1 (PD-L1) expression, with a significantly superior efficacy (52).

2. Current research advances in ALK-positive NSCLC

ALK and NSCLC. As a receptor tyrosine kinase of the insulin receptor (IR) subfamily, ALK has been found to play an important role in various types of cancer, particularly in anaplastic large cell lymphoma (ALCL), NSCLC and neuroblastoma (21). In 2007, the echinoderm microtubule-associated protein like protein 4 (EML4)-ALK fusion gene was identified in a group of NSCLC patients (22). This fusion is the result of an inversion of the short arm of chromosome 2, where the human EML4 and ALK genes are present (23). EML4 contains a coiled oligomeric structural domain, which mediates the dimerization and structural activation of ALK. Like in ALC, many different ALK fusions have been identified, but EML4-ALK is the most common variant (24). ALK has been reported to regulate several different pathways involved in cell proliferation and survival, such as the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian targets of rapamycin (mTOR), RAS/RAF/MAP kinase-extracellular signal-regulated kinase (ERK) kinase (MEK)/ERK and JAK/STAT pathways (Fig. 1), once it is dimerized and activated by autophosphorylation upon binding to its ligands, pleiotrophin and midkine (25,26). Direct evidence for the oncogenic potential of EML4-ALK in lung carcinogenesis has been found in mice. The transgenic overexpression of EML4-ALK in type II alveolar cells via the surface activated protein-c or Clara cell secretory protein promoter leads to the rapid development of tumors with features of lung adenocarcinoma (27,28). A total of 3-7% of NSCLC (mainly adenocarcinoma subtypes) cases are characterized by ALK rearrangements, which occur in a mutually exclusive manner with KRAS and EGFR mutations (29,30). Of note, a previous study developed in vivo induction models by inducing EML4-ALK rearrangement, which leads to lung carcinogenesis. These models have shown a sensitivity to ALK inhibition, thus serving as valuable tools to explore...
Mechanisms of ALK inhibitor resistance. Although ALK inhibitors are clinically effective, patients still experience various types of drug resistance. This usually occurs in the form of ALK kinase structural domain mutations, ALK site amplification or activation of ‘bypass’ signaling pathways, ~1/3 of which are ALK kinase structural domain mutations (53). The first mutations identified were the L1196M and C1156Y (54), and L1196M is a residue known as the ‘gatekeeper’ that controls the entry of small-molecule ALK inhibitors into a hydrophobic pocket within the catalytic site and can spatially block inhibitor binding (55). Meanwhile, L1196M is the most common mutation in which patients develop resistance to crizotinib (47), while C1156Y develops resistance through other different mechanisms. Cysteine is similar to the catalytically important αC-helix within the structural domain of ALK tyrosine kinase, so its substitution for tyrosine is thought to prevent inhibitor binding by stabilizing the activity of ALK (47). Other resistant mutations that map to the same region with the same mechanism of resistance include I1151Tins, F1174C/L, L1198P, L1198R/P (47, 56, 57) and L1171T (12, 13, 58). Acquired resistance to crizotinib usually emerges after 1 year of treatment. ALK-E1210K mutations have been detected in patients treated with crizotinib (14). Other secondary mutations that occur following crizotinib treatment include L1196M, G1269A, G1202R, S1206Y, G1269A, L1152R, D1203N, I1171T, V1180L and C1156Y (13, 47). The second-generation ALK inhibitors ceritinib, alectinib and brigatinib were found to show a stronger anti-ALK activity compared with crizotinib (16). In addition, they exhibited greater CNS permeability and the ability to target multiple secondary ALK mutations. The direct application of second-generation ALK tyrosine kinase inhibitors has been shown to result in better therapeutic outcomes. In addition to ALK, ceritinib inhibits insulin-like growth factor 1 (IGF1), ROSI and the IR (17, 18). In addition, ceritinib inhibits multiple ALK mutations resistant to crizotinib, including L1196M, G1269A and S1206Y (47). However, C1156Y/T, I1151Tins and L1152P/R mutations have been associated with the emergence of ceritinib resistance (19). Alectinib has a better efficacy against G1269A, L1196M, F1174L and C1156Y mutations (20); however, alectinib treatment has been shown to cause the emergence of resistance mutations (I1171T/N/S, V1180L and G1202R) (14, 58), and the activated bypass signaling pathway to be mediated by hepatocyte growth factor (HGF) and MET (59). Epithelial-mesenchymal transition (EMT) is a potential mechanism of alectinib resistance, characterized by the loss of E-cadherin and increased expression of waveform proteins (60). Brigatinib is a novel inhibitor of ALK, ROSI and EGFR. Brigatinib inhibits crizotinib-resistant mutations, including ALK L1196M and EGFR T790M (51). Lorlatinib can be used to treat all known ALK inhibitor-induced resistance mutations and is the treatment of choice for patients with alectinib resistance (61). The L1198F mutation was recently reported to exhibit resistance to lorlatinib mainly by interfering with drug binding through spatial site block. It has also been reported that L1198F mutation enhances the binding of crizotinib, reduces the effect of C1156Y and enhances susceptibility to crizotinib resistance (62). However, as for how to overcome L1198F mutation, the clinical efficacy and resistance mechanisms of lorlatinib need to be elucidated.

Known mechanisms of resistance include point mutations, fusion gene amplification and bypass signaling through the activation of other oncogenes (Fig. 2) (63), and AMPK, which is closely associated with STK11 mutation and is one of the important pathways in the mechanism of ALK inhibitor resistance (30).

3. Current research progress on STK11

Function of STK11. STK11 is considered an important tumor-suppressor gene with a wide range of metabolic functions (64). It encodes the serine/threonine kinase liver kinase B1 (LKB1), which activates a family of 12
downstream kinases, including AMPK, and plays a role in essential biological functions, including cellular energy regulation (65). It is also involved in several physiological processes, including the regulation of cellular metabolism, cell polarity and DNA damage response (65,66). Tumor cells with inactivated or lost STK11 are unable to activate adenosine monophosphate-activated protein kinases, and are therefore particularly vulnerable to energy stress states (67). STK11 inactivation was initially identified in human tumors associated with Peutz-Jeghers genetic syndrome (68). STK11 also negatively regulates mTOR signaling through its substrate AMPK, and STK11 loss leads to the aberrant activation of mTOR in a variety of tissues. mTOR inhibitor everolimus has been shown to be effective (69,70). STK11/LKB1 loss of function has been found in several cancer types, mainly through somatic alterations in the STK11 gene, such as nonsense mutations, loss of heterozygosity, insertions, intragenic deletions or chromosomal deletions (71-79), while STK11 has been shown to be inactivated through somatic alterations in the STK11 gene, such as nonsense mutations, loss of heterozygosity, insertions, intragenic deletions or chromosomal deletions (71-79), while STK11 inactivation increases sensitivity (93). These findings suggested that STK11 may play a tumor-suppressor or oncogene function. This dual mechanism may explain the lack of a clear association between STK11 alterations and prognosis in lung cancer (100). In vitro studies have shown that STK11 inactivation increases the motility and invasiveness of lung cancer, and facilitates epithelial-to-mesenchymal transition (EMT) in lung cancer, thus enhancing metastatic potential (101,102). In addition, it was shown that STK11/LKB1 inactivation promotes cancer cell growth and survival through the upregulation of hypoxia-inducible factor 1 (HIF-1). The inactivation of STK11/LKB1 in lung cancer cells leads to the upregulation of mTOR signaling, providing a growth advantage associated with mitochondrial dysfunction, due to autophagic injury (103,104). The aberrant activation of the PI3K/AKT/mTOR pathway has been identified in 90% of lung adenocarcinomas and 40% of squamous cell carcinomas (105). The PI3K/AKT/mTOR signaling pathway is mainly activated by receptor tyrosine kinases [e.g. epidermal growth factor receptor (EGFR), insulin-like growth factor receptor 1 (IGFR1), vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR)] and is involved in a variety of biological functions, such as proliferation, differentiation, survival, adhesion, motility, invasion and cellular metabolism (106,107). In addition to the activation of the PI3K/AKT/mTOR pathway by growth factors and insulin, different nutritional and environmental signals,
such as high levels of adenosine triphosphate (ATP), oxygen and elevated serum amino acid levels can also increase the activity of mTOR complex 1 (mTORC1). By contrast, intracellular and environmental stress signals, such as low ATP levels, hypoxia and DNA damage, inhibit mTORC1 activity mainly through AMPK activation (106). mTOR pathway activation has been found to be associated with poor clinical outcomes, invasiveness and metastasis (108-111). It is important to highlight that LKB1, encoded by STK11, is also associated with AMPK, and that LKB1/AMPK may counteract oxidative stress by inhibiting the synthesis of nicotinamide adenine dinucleotide phosphate (NADPH)-consuming fatty acids and increasing the oxidation of NADPH-producing fatty acids (112). At the same time, activated AMPK phosphorylates and activates the transcription factor nuclear related factor 2 (NRF2) (113). NRF2 then activates the transcription of antioxidant genes involved in NADPH production. High NADPH levels, together with autophagy, protect LKB1-savvy cancers from oxidative stress and reactive oxygen species (ROS)-induced chemotherapy (cisplatin, paclitaxel and adriamycin) (114). Thus, the activation of NRF2 is associated with more aggressive lung cancers and reduced patient survival (115). Of note, the activation of the LKB1/autophagy pathway enables circulating tumor cells to resist loss-of-nest apoptosis (116). Thus, cells lacking LKB1 undergo apoptosis in response to metabolic stress because they are unable to respond to energy deficiency and restore homeostasis in vivo (117). The regulation of STK11 expression and its role in cancer cell proliferation remains highly complex (118). For example, recent research has shown that asparagine and aspartic acid can regulate AMPK-mediated p53 activation by physically binding to LKB1 and regulating LKB1 activity. P53 has been reported to control cell survival by generating an auto-amplifying loop through asparagine-aspartate-mediated LKB1-AMPK signaling to regulate asparagine metabolism (118). In lung cancer, STK11/LKB1 alterations are the only marker significantly associated with PD-L1 negativity in patients with high/medium tumor mutation burden (TMB) (119). Both elevated TMB and increased PDL1 expression are associated with IO response (120,121). Kelch like ECH associated protein 1 (KEAP1) mutations or double allelic deletions are enriched in patients with LKB1-mutant NSCLC tumors. NRF2 is a transcriptional factor and KEAP1 is a negative regulator of NRF2 that binds to the antioxidant response element on DNA and initiates the transcription of several genes involved in the regulation of redox homeostasis and cellular detoxification (122). Clinical studies have shown that in KRAS-driven NSCLC, STK11 mutations leading to loss of function are associated with resistance to anti-programmed death 1 (PD-1) monoclonal antibody therapy, but the molecular mechanisms of pathogenesis are not yet clear (123). Despite some uncertainties, STK11 functional status is emerging as a reliable biomarker for predicting a lack of response to anti-PD-1 therapy in NSCLC patients. It has been reported in the literature that STK11 is significantly and significantly associated with decreased survival in meningiomas (124). Although the evidence on the biological role of STK11 is not sufficient, its prognostic significance in advanced NSCLC needs to be confirmed; clarifying the role of STK11 will facilitate the analysis of STK11 mutational status, which may also provide more options for targeted therapy and IO (125). The role and significance of STK11 in NSCLC needs to be further explored.

Current STK11 mutation therapies for NSCLC. Cancer typically evades immune surveillance by aberrantly expressing immune checkpoints (e.g. PD-1) that isolate tumor cells from the host immune system. Immune blockade using monoclonal antibodies against the immune checkpoint PD-1 and its primary ligand PD-L1 can greatly improve survival in advanced NSCLC, with the greatest impact in patients with stage III and first-line stage IV lung cancer (126-128). However, in patients with other types, the response rate was just 20% (129). In a retrospective cohort study, data from the Clinico-Genomic Database were used to identify patients with metastatic NSCLC who received first-line IO (alone or in combination) or chemotherapy in routine clinical practice. The results suggested that in NSCLC, patients with STK11 mutation (STK11m) exhibit poorer overall survival (OS) and PFS compared with patients with STK11 wild-type (STK11wt) receiving IO or chemotherapy. Survival outcomes analyzed by treatment line and type showed that OS and PFS were worse in the IO treatment group for STK11m vs. STK11wt (Table II) (130). The results of the study were not optimistic, which further suggested that STK11 mutations reduce the

Table II. Chemotherapy and immunotherapy for STK11 mutation status in NSCL.

| Variable                  | OS (month) |          | PFS (month) |          |
|---------------------------|------------|----------|-------------|----------|
|                           | STK11m     | STK11wt  | STK11m      | STK11wt  |
| Chemotherapy (130)        |            |          |             |          |
| First-line                | 11.7       | 18.9     | 4.5         | 6.1      |
| Second-line               | 13.1       | 15.2     | 4.2         | 4.5      |
| Immunotherapy (131)       |            |          |             |          |
| First-line                | 14.2       | 20.1     | 4.1         | 5.4      |
| Second-line               | 6.6        | 13.6     | 2.2         | 3.1      |

NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; STK11, serine/threonine kinase 11; STK11m, STK11 mutation; STK11wt, STK11 wild-type.
survival rate of patients with NSCLC. Most importantly, it is unclear whether STK11 can be used as a predictive biomarker to guide treatment selection, and prospective evaluation is still lacking. Therefore, immunotherapy should not be administered to patients with STK11-mutated tumors at the present time (131). At the same time, it has also been reported that LKB1 encoded by the STK11 gene may be associated with radioresistance in patients, and several previous studies have shown the role of LKB1 expression in regulating the response to radiotherapy, based on preclinical experiments (132-134). However, to the best of our knowledge, there are no clinical trials on STK11 mutations, so a comprehensive evaluation of patients with STK11 mutations in NSCLC could not be performed.

4. Conclusions and perspectives

Both STK11 and ALK can regulate tumor proliferation and growth through the mTOR pathway, and STK11 can be oncogenic in NSCLC through the AMPK pathway, which is included in the mechanism of drug resistance in patients with ALK-positive NSCLC. mTOR signaling is known to be a master regulator of homeostasis and to integrate various environmental signals to regulate cell growth, proliferation and metabolism. The deregulation of mTOR signaling, particularly its overactivation, is frequent in human cancer. Recent advances in molecular profiling have identified certain genes involved in encoding the mTOR pathway, including STK11, PIK3CA, PTEN and RPTOR independent companion of MTOR complex 2 (RICTOR), whose amplification or mutation induces mTOR pathway activation. AMPK is a central metabolic sensor that coordinates cell growth and energy balance. In terms of oncogenesis, LKB1 (mentioned previously) can directly phosphorylate and activate AMPK; therefore, in cells with LKB1 mutations, the AMPK protein is oxidized and inactivated, leading to cell death. In terms of drug resistance, if the AMPK pathway is abnormally regulated, patients with ALK-positive NSCLC then become resistant to the drug.

In conclusion, STK11 plays an important role in the treatment and drug resistance of patients with ALK-positive NSCLC. Although there is no definitive evidence on how STK11 affects the prognosis of ALK-positive patients with NSCLC, the results of this review showed that STK11 mutations may reduce the survival of ALK-positive NSCLC patients.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

XCP and JC contributed to the design of this review. WZ, MW, MXM and ZQY reviewed the references. WZ, JC and XCP wrote the manuscript. WZ, LDY, YYC and NL designed and produced the tables and figures. YYC and NL revised the manuscript critically for important intellectual content. NL acquired the funding. YHY analyzed the data and designed the figures. LDY put a lot of effort into revising the manuscript and is listed as co-first author. Data authentication is not applicable. All authors read and approved the manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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ZHOU et al: ROLE OF STK11 IN ALK-POSITIVE NSCLC

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