Targeting non-small cell lung cancer: Molecular mechanisms and clinical studies (Review)

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Abstract. Over the past two decades, notable advances have been made in the treatment of non-small cell lung cancer (NSCLC), as well as in the elucidation of molecular mechanisms and the development of novel therapeutics (for example, targeted therapy and immunotherapy), whose clinical benefits have been documented. The epidermal growth factor receptor and anaplastic lymphoma kinase are well-known tumor targets; both can promote tumor growth through PI3K/AKT/mTOR pathway. Other oncogenes and tumor suppressor genes such as Kirsten rat sarcoma and tumor protein 53 have also been investigated. The notable immune checkpoints are programmed cell death protein-1/programmed cell death ligand-1 and cytotoxic T-lymphocyte-associated protein 4. However, the overall survival rate of patients with NSCLC is still low due to primary or acquired drug resistance, which is associated with abnormal signaling pathways. In particular, patients with advanced disease who have non-druggable targets or lack an immune response have a poor prognosis, such as the mutation of serine/threonine kinase 11, also known as liver kinase B1 (LKB1). LKB1 impacts cellular energy metabolism and the tumor immune microenvironment, resulting in little benefit from current therapies. Therefore, further research into more effective treatments is warranted to potentially improve the outcomes of patients with NSCLC in the future.

Contents

1. Introduction

Non-small cell lung cancer (NSCLC) comprises ~85% of lung cancer cases and is the leading cause of cancer-related mortality worldwide (mortality, rate, ~22%); however, the mortality rate is continuously declining due to improved treatment strategies (1,2). The global burden of NSCLC varies across regions; for example, compared with the US and the UK, China has a lower cancer incidence rate (~0.04%) but is projected to face a growing lung cancer burden due to population aging and unhealthy lifestyles (3). Based on histopathological tests, NSCLC is mainly screened for adenocarcinoma, squamous cell carcinoma (SCC) and neuroendocrine neoplasm. SCC is associated with smoking and is the second most common histological type of NSCLC, accounting for ~20% of lung cancers worldwide, whereas adenocarcinoma, the most common subtype of NSCLC, is always associated with alterations in tumor driver genes (4). The molecular classification according to driver mutations/fusions includes epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), Kirsten rat sarcoma (KRAS), ROS proto-oncogene 1 (ROS1), proto-oncogene B-Raf, tyrosine-protein kinase (RTK), mesenchymal-epithelial transition (MET), neurotrophic tyrosine receptor kinase and rearranged during transfection (RET) (5). Mutations accumulating in oncogenes and tumor

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suppressor genes of tumors drive the initiation and progression of NSCLC (6). However, over the past two decades, notable progress has been made in research on the molecular mechanism and treatment of advanced NSCLC through the incorporation of novel therapeutic strategies, including various targeted therapies and the effective application of immunotherapies, such as immune checkpoint inhibitors (ICIs) (7). However, not all genetic alterations have druggable molecular targets and majority of patients do not respond to immunotherapy. Furthermore, drug resistance is inevitable for all types of treatments (8). Thus, continuous exploration of the molecular mechanism of NSCLC and tumor evolution is the key to overcoming drug resistance.

Currently, therapy targeting the representative oncogene *EGFR* for patients with NSCLC who are positive for this driver gene has been developed. Simultaneously, approved targeted therapies, such as ALK inhibitors and KRAS G12C inhibitors, have improved the prognosis of patients with NSCLC. For patients with a 'hot' tumor immune microenvironment (TIME), immunotherapy could provide a durable survival benefit. Immune checkpoint inhibition with antibodies against programmed cell death protein-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) has exhibited notable benefits and has revolutionized the treatment of lung cancer (9,10). Other options such as conventional therapies, combination strategies and novel antibody-drug conjugate (ADC) therapy also serve a key role in NSCLC treatment. For example, surgical resection is an effective strategy for patients with stage I-IIIA and selected stage IIIB NSCLC, although certain cases receive surgery with additional neoadjuvant/adjuvant chemotherapy and adjuvant radiotherapy/chemoradiotherapy (11,12). For advanced or metastatic NSCLC without actionable genomic alterations, immunotherapy alone or with chemotherapy is a standard frontline treatment (13). However, patients with *liver kinase B1* (*LKB1*) mutations are always diagnosed at advanced stage and inherently resistant to these therapies. Mutation of the tumor suppressor gene *LKB1* occurs in ~20% of NSCLCs and is associated with a poor prognosis because this subtype has no targetable drugs and lacks therapeutic options (14,15). Thus, developing an effective treatment strategy for *LKB1*-mutant NSCLC is key to improving NSCLC prognosis.

To screen a sufficient and high-quality body of literature with accurate research orientation, the present review developed a literature search strategy based on the databases of PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (http://www.webofknowledge.com). The combined search terms included 'NSCLC, molecular mechanism, oncogene, tumor suppressor gene, targeted therapy, immunotherapy, LKB1, serine/threonine kinase 11 (STK11), clinical trial and drug resistance'. Peer-reviewed original researches, systematic reviews, meta-analyses and phase I-III clinical trial reports published in the past decade were included in the present review. First, a comprehensive overview of NSCLC was presented and its core molecular mechanisms and mainstream therapeutic strategies were systematically summarized. Then, LKB1 was taken as a typical paradigm to elaborate on how to translate insights into tumor molecular mechanisms into clinical breakthroughs for precision treatment of NSCLC.

2. An overview of the molecular mechanisms and therapeutics in NSCLC

As next-generation sequencing (NGS) of DNA has become available, the genetic mutations and alterations associated with cancer initiation have been increasingly identified. Generally, two types of genes with opposite functions have been identified, oncogenes such as *KRAS* and *EGFR*, in which activating mutations promote oncogenesis and tumor-suppressor genes, such as tumor protein 53 (*TP53*) or *LKB1*, whose inactivation results in the loss of function of a gene and promotes oncogenesis (16-18). In this section, the present review addresses the most common and frequently mutated oncogenes and tumor-suppressor genes in NSCLC, as well as the signaling pathways involved and current main treatment options (Fig. 1).

Major driver mutations and alterations

KRAS mutations. According to a pan-cancer analysis, the *Ras* family (*KRAS*, *NRAS* and *HRAS*) was reported to be tumor drivers in up to 25% of all cancer types. *KRAS* mutations rank first among all Ras-mutated cancer types, with a prevalence of 85% (19,20). In NSCLC, *KRAS* mutations occur in 25-30% of lung adenocarcinoma (LUAD) cases, with 98% of the mutations occurring at three mutational hotspots (G12, G13 and Q61) (21). Specifically, while 90% of cases have mutations in codon 12, less common mutations occur in codons 13 (2-6%) and 61 (1%) (22,23). Among the codon 12 mutations, the substitution of glycine with cysteine (KRAS G12C) accounts for 40% of all KRAS mutations in NSCLC, followed by the substitution of glycine with valine/aspartic acid (KRAS G12V/D) and other point mutations, such as G12A/R/S (24). *KRAS* gene mutations lead to the continuous activation of Ras proteins, subsequently activating downstream signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)-AKT-mTOR, Raf-MEK-extracellular signal-regulated kinase (ERK)-mitogen-activated protein kinase (MAPK) and Ras-like pathways, and promoting the proliferation and survival of cancer cells (25). Notably, concurrent molecular alterations, including those in *TP53*, *STK11* and *Kelch-like ECH-associated protein 1* (*KEAP1*), are often detected in patients with *KRAS*-mutant NSCLC. Furthermore, patients harboring *STK11* or *KEAP1* concomitant mutations experienced shorter OS compared with *STK11* or *KEAP1* mutation alone, and several studies have confirmed the negative prognostic impact of *STK11* and *KEAP1* comutations (26,27). Unlike patients with *EGFR* or *ALK* gene mutations, small-molecule inhibitors for patients with NSCLC with *KRAS* mutations, with the exception of those with KRAS G12C mutations, are difficult to design in clinical practice (28). For patients with the KRAS G12C mutation, a disordered switch-II pocket in KRAS G12C allows the design of small-molecule inhibitors (29). Therefore, therapeutic strategies for patients with *KRAS*-mutant NSCLC remain a research hotspot.

EGFR family. The EGFR family, a family of receptor tyrosine kinases, is composed of the EGFR1, EGFR2, EGFR3 and EGFR4 proteins. As a growth factor receptor, EGFR is considered to be involved in the development of cancer because its activation induces cell differentiation and proliferation (30,31). The *EGFR* gene is often mutated in cancer cells. EGFR mutations account for ~50% of LUAD cases in Asian patients,

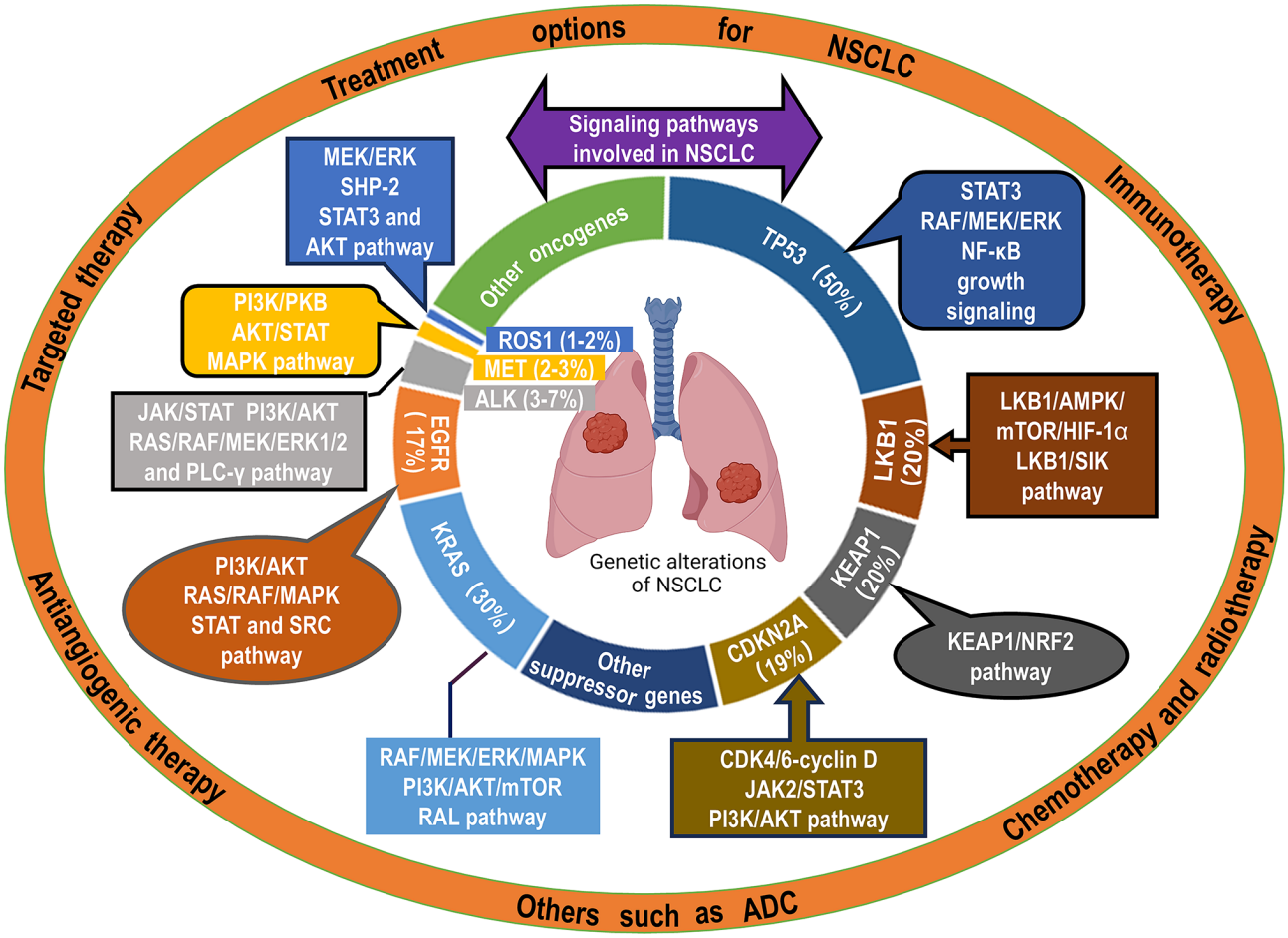

Figure 1. An overview of the molecular mechanisms, signaling pathways and treatment strategies for NSCLC. Mutation rates of the most common oncogenes and tumor suppressor genes occurring in NSCLC, along with the signaling pathways involved and treatments administered. The frequency of genetic alterations is not exclusive; therefore, the total percentage is not 100. ADC, antibody-drug conjugate; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; CDKN2A, CDK inhibitor 2A; MET, mesenchymal-epithelial transition; KEAP1, Kelch-like ECH-associated protein 1; TP53, tumor protein 53; PLC-γ, phospholipase C-γ; HIF-1α, hypoxia-inducible factor-1α; LKB1, liver kinase B1; ALK, anaplastic lymphoma kinase; NRF2, nuclear factor-E2-related factor 2; SHP-2, Src homology region 2 domain-containing phosphatase-2; AMPK, AMP-activated protein kinase; ROS1, ROS proto-oncogene 1; RAL, Ras-like.

whereas they account for 20% of cases in Western patients. Classical EGFR mutations include exon 19 deletions and exon 21 L858R point mutations, whereas uncommon EGFR mutations include G719X, S768I and L861Q (32). EGFR activation initiates intracellular signaling mainly through the following pathways: The Ras/Raf/MAPK, PI3K/AKT, signal transducer and activator of transcription (STAT), Src kinase, stress and autophagy pathways (31). Thus, alterations in EGFR signaling pathways lead to the inhibition of tumor apoptosis and a poor prognosis (33,34). These findings suggested that EGFR is a therapeutic target and supports the development of EGFR-tyrosine kinase inhibitors (TKIs) (35). Furthermore, both the EGFR-MET-targeted bispecific antibody amivantamab and the novel EGFR-TKI mobocertinib have received approval as treatments for patients with advanced NSCLC harboring EGFR exon 20 insertions (36). Although targeted therapy has opened a novel era for lung cancer treatment, drug resistance is inevitable. Of note, EGFR C797S mutation is one of the most notable acquired resistance mechanisms of EGFR-TKIs in NSCLC. The structural changes and its competitive binding with EGFR-TKIs such as osimertinib will lead to drug resistance. The two main subtypes of EGFR C797S mutation include cis- and trans-mutation with EGFR T790M, and their different molecular characteristics result in differential therapeutic responses (37). Therefore, numerous studies have focused on the mechanism of EGFR-TKI resistance and the development of novel drugs (38,39).

Human EGFR 2 (HER2), also known as Erb-b2 receptor tyrosine kinase 2, is another member of the EGFR family. The *HER2* gene, located at chromosome 17q11.2-q12, is a proto-oncogene and belongs to the classical superfamily of receptor tyrosine kinases (40,41). *HER2* mutations, along with HER2 amplification and protein upregulation, are present in patients with NSCLC at a frequency of 2-4% (42). The HER2 alterations also activate the MAPK, PI3K/AKT, protein kinase C and STAT pathways (43,44). Notably, HER2 upregulation was confirmed to be one mechanism of resistance to EGFR-TKIs (45) and HER2 mutations are acquired in 1% of patients receiving EGFR-TKI treatment (35). In contrast to gastric and breast cancer, anti-HER2 agents have not been considered a standard treatment for *HER2*-mutant NSCLC (46). Furthermore, compared with ALK rearrangement, chemotherapy produces notably reduced outcomes in patients with *HER2*-mutant NSCLC (47). However, improved results for

two newly developed HER2-specific TKIs (BAY2927088 and zongertinib) with low EGFR wild-type inhibition were recently reported and these HER2-specific TKIs received the breakthrough therapy designation from the Food and Drug Administration (FDA) for HER2$^+$ NSCLC (48), highlighting the continuous investigation of HER2-targeting agents.

ALK rearrangements. The *ALK* gene, located on chromosome 2, encodes the ALK protein, which has a cytoplasmic receptor kinase segment and an extracellular domain, similar to other receptor tyrosine kinases like EGFR and HER2 (49). Rearrangement is the main type of *ALK* gene mutation and other types include amplification and point mutation (50). As a driver of cancer, *ALK* rearrangement is associated with never smoking, younger age and generally advanced disease, and has been identified in 3-7% of patients with NSCLC (51-53). Rearrangement of the *ALK* gene always occurs with partner genes, such as echinoderm microtubule-associated protein-like 4 (EML4). The *EML4-ALK* fusion represents a novel molecular target and other partner genes, such as *TFG*, *TPR*, *KIF5B*, *KLC1*, *HIP1*, *SQSTM1*, *STRN* and *DCTN1,* have also been described (50). ALK fusion proteins can activate multiple signaling pathways, including Janus kinase (JAK)/STAT, PI3K/AKT, Ras/Raf/MEK/ERK1/2 and phospholipase C-γ, all of which are involved in cellular proliferation and survival (54). According to these findings, ALK-TKIs have been developed as a therapeutic strategy and have exhibited promising results in patients with *ALK*-mutant NSCLC (55,56). In addition to the current FDA-approved ALK-TKIs (crizotinib, ceritinib, alectinib, brigatinib and lorlatinib) (57), other trials of drugs targeting *ALK* rearrangements, such as ensartinib, are still ongoing and have led to favorable OS in patients with crizotinib-resistant NSCLC (58). Thus, drug resistance strategies require further investigation in the future.

MET alterations. The *MET* gene encodes a receptor tyrosine kinase that is involved in multiple oncogenic processes, particularly cell proliferation and tumor growth. The mutations of the *MET* gene include three main types: Protein upregulation, exon 14-skipping (METex14) mutations and gene amplification (59,60). Notably, the most commonly reported oncogenic *MET* mutation is METex14, which is present in 2-3% of patients with NSCLC and coexisting mutations of METex14 with other oncogenic drivers are rare (60-62). MET can activate the ERK/MAPK, PI3K/protein kinase B and JAK/STAT pathways when the MET receptor tyrosine kinase binds to its ligand, hepatocyte growth factor (HGF)/scatter factor (63,64). Thus, anti-MET therapies can be divided into selective/non-selective TKIs and antibodies directly targeting MET or HGF (65). For example, novel agents such as amivantamab, a MET and EGFR bispecific monoclonal antibody, have exhibited promising activity against METex14 NSCLC (66). Similarly, acquired drug resistance is still a challenge for MET-TKIs.

ROS1 rearrangements. *ROS1* is a receptor tyrosine kinase gene that is expressed in 1-2% of NSCLCs, typically in younger and never-smoking patients (67). The *ROS1* gene rarely fuses with other oncogenic driver mutations (<1%), except for several partner genes, such as CD74. Majority of patients with *ROS1*$^+$ NSCLC present with stage IV disease and brain metastases at the initial diagnosis (20-40%) (68,69). Several studies have explored the downstream pathways of ROS1 fusion proteins, including the autophosphorylation of ROS1 and phosphorylation of MEK, Src homology region 2 domain-containing phosphatase-2, STAT3, AKT and ERK (70-72). Notably, the expression of the CD74-ROS1 fusion resulted in autophosphorylation of ROS1 (68). Due to the high degree of homology between ROS and ALK tyrosine kinase domains, *ROS1*-mutant tumors are sensitive to ALK-TKIs (73). Currently, FDA-approved TKIs for patients with NSCLC with *ROS1* rearrangements include crizotinib and entrectinib (74). In addition, repotrectinib can target ROS1 and is a promising second-line therapy for NTRK fusion$^+$ NSCLC (75). ROS1-rearranged NSCLC cases are associated with PD-L1 expression (76); however, ICI monotherapy does not markedly benefit patients with ROS1$^+$ NSCLC (77,78). Therefore, further development of strategies for patients with ROS1-TKI-resistant NSCLC is warranted in future research.

Key tumor suppressor genes

TP53 mutations. The *TP53* gene, which was originally considered an oncogene, is a tumor suppressor gene that was identified in 1979 (79,80). The *TP53* gene is located on chromosome 17 (17p13) and is involved in numerous biological processes, such as DNA repair, apoptosis, senescence and aging (81). *TP53* serves a key role in the tumorigenesis of lung epithelial cells and occurs in ~50% of NSCLC cases (82). *TP53* mutations are associated with the development of lung cancer and are required in maintaining a malignant phenotype (83). Several signals, including DNA damage (genotoxic stress), constitutive activation of growth signaling (oncogenic stress) and other types of stress, can lead to p53 derepression by post-translational modifications (84). The extensive deactivation of TP53 in NSCLC suggests that rebuilding the TP53-mediated pathway in cancerous cells may be an appealing technique for cancer treatment (85). Although several approaches that target TP53 have been applied, patients with NSCLC with TP53 alterations still have a poor prognosis. However, *TP53* mutation is associated with the immune response and could benefit from immunotherapy. Continuous investigations of TP53 biology and treatment strategies are warranted to improve the prognosis of patients with NSCLC.

LKB1 alterations. *STK11/LKB1*, a novel human gene that encodes a serine threonine kinase and is located on chromosome 19p13.3, was first identified in early January 1998 (86,87). LKB1 alterations occur in an extensive variety of cancer types such as NSCLC, hepatocellular carcinoma and colorectal cancer, and the rate in NSCLC can reach 20% (14,88,89). The LKB1 protein acts as a metabolic sensor and controls cellular metabolism (90). The loss of LKB1 inactivates AMP-activated protein kinase (AMPK) and salt-inducible kinase signaling, after which abnormal mTOR and hypoxia inducible factor 1α signaling result in an energy imbalance (91,92). *LKB1* mutations often occur with other driver genes, such as *KRAS*. Different comutations affect the biology of LKB1, with diverse phenotypes (93). Patients with NSCLC with LKB1 loss have a worse prognosis, as chemotherapy and immunotherapy exhibit little efficacy, and no targeted agents are available for this subtype (94). These features make LKB1 a research hotspot. Thus, the present review emphasizes the molecular mechanism and treatment of LKB1 and discusses its relationship with immunotherapy in the following section.

KEAP1 mutations. *KEAP1* was identified in the 1990s and acts as an adaptor for Cul3-based E3 ligases to regulate nuclear factor-E2-related factor 2 (NRF2), and the KEAP1-NRF2 pathway serves a key role in cellular defenses against oxidative and electrophilic stimuli (95-97). *KEAP1* mutations are observed in 10-15% of LUAD cases, with a high frequency of co-occurring mutations in *LKB1* (98). A previous study has demonstrated that *KEAP1* mutation promotes tumor growth mainly through the KEAP1/NRF2 pathway and *KEAP1* is considered a tumor suppressor gene (99). Certain clinical studies have provided evidence that patients with *KEAP1*-mutant NSCLC exhibit a distinct clinicopathological phenotype (100,101). Furthermore, similar to *LKB1* mutation, *KEAP1* mutations in NSCLC are associated with resistance to various therapeutics, including chemotherapy, radiotherapy, TKI treatment and immunotherapy. Although various KEAP1 inhibitors have been described in previous decades, none of them are currently being explored in clinical applications, to the best of our knowledge (101,102). Thus, the development of KEAP1 inhibitors for NSCLC treatment remains challenging and combination immunotherapeutic strategies may be promising in overcoming immune resistance.

Cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) family. The *CDKN2A* gene is also known as *p16INK4a*, which belongs to the INK4 family, with *CDKN2B* (*p15INK4b*) being another key member (103). As a tumor suppressor gene, *CDKN2A* is frequently altered in NSCLC, with an incidence rate of 5.7-19.1% in LUAD (104). As a CDK inhibitor, it encodes the protein p16, which can inhibit CDK and CDK4/6-cyclin D complexes by interacting with the kinase catalytic cleft and distorting the ATP binding site (105). When CDK4/6 phosphorylation is inhibited, the G_1/S transition is prevented (106). CDKN2A inactivation results in the activation of the JAK2/STAT3 pathway and influences PI3K/AKT signaling (107,108). Previous studies have reported that *CDKN2A* mutations in patients with NSCLC are associated with shorter disease-free survival (DFS) and overall survival (OS) compared with its wildtype, with no benefit from ICI treatment (109,110). Therefore, effective strategies targeting CDKN2A/B are urgently needed.

Other tumor genetic mutations, such as RET fusions or rearrangements, and metabolic reprogramming also impact tumor biology, particularly the tumor microenvironment (TME). Thus, the importance of understanding tumor molecular mechanisms is self-evident because these mechanisms influence tumor growth pathways and are key to investigating NSCLC therapeutics.

Dysregulated oncogenic signaling pathways. Alterations in oncogenes/tumor suppressor genes always lead to the development of NSCLC through downstream pathways, including the PI3K/AKT/mTOR, EGF/EGFR, VEGF/VEGFR, Ras/Raf/MAPK, KEAP1/NRF2 and CDK4/6 pathways (35). The abnormal activation of these pathways promotes cell proliferation and inhibits apoptosis, thus resulting in tumor progression. In this section, the present review discusses the classical signaling pathways that are closely associated with NSCLC treatment.

PI3K/AKT/mTOR pathway. The PI3K signaling pathway, one of the most frequently altered pathways in NSCLC, can be activated by members of the EGFR family/insulin and insulin-like growth factor 1 receptors, which are growth factors that are specific to different RTKs (111,112). In NSCLC, *PIK3CA* gene mutation is a common mechanism of PI3K activation (113). The incidence of PIK3CA alterations (*PIK3CA* mutations and amplifications) in lung SCC is higher (33.1 vs. 6.2%) compared with that in LUAD (35,114). Other mechanisms, such as phosphate and tensin homolog mutation, can also result in abnormal activation of the PI3K pathway through the dephosphorylation of phosphatidylinositol-3,4,5-trisphosphate and disruption of further signal transduction (115). After the PI3K signaling pathway is activated, tumors develop and antitumor drug resistance occurs rapidly, leading to disease progression. Notably, the PI3K/AKT pathway also serves a key role in tumors with other known mutations, such as *EGFR*. In addition, the PI3K/AKT/mTOR pathway is constitutively activated in >50% of *EGFR*-mutant lung carcinomas (116). Furthermore, a previous study revealed that the PI3K/AKT/mTOR axis persists as a therapeutic component in KRAS G12D-driven NSCLC (117). Due to the effects of PI3K/AKT signaling and its downstream pathway on tumor development and progression, as well as its potential influence on drug response and resistance, it represents a key target for antitumor therapy in NSCLC.

EGF/EGFR pathway. The alteration of EGFR signaling is a common phenomenon in patients with NSCLC, particularly in patients with LUAD from East Asia, suggesting that it is a key orchestrator of epithelial transformation; it is one of the most prevalent studied targets (118). Dysregulation of EGFR signaling is caused mainly by point mutations, receptor amplification or ligand overproduction (119). Several reviews have described that the EGF/EGFR pathway results in intracellular signaling through the MAPK pathway and the PI3K and STAT pathways (120,121). These downstream signaling pathways lead to increased tumor angiogenesis, tumor cell proliferation and metastasis (35). In addition, alterations in the EGFR pathway inhibit tumor apoptosis due to the activation of its kinase function, thus leading to poor outcomes (34,35). These results suggested that EGFR signaling is a therapeutic target, which could improve the development of antitumor agents. Therefore, small-molecule inhibitors that target EGFR signaling have been used in multiple cancer types, including NSCLC, breast cancer and colorectal cancer (122,123). However, drug resistance develops due to novel mutations, bypass signaling mechanisms and other unknown mechanisms, making research on resistance mechanisms associated with the EGFR pathway a hotspot.

VEGF/VEGFR signaling. Vascular endothelial growth factor (VEGF) belongs to a protein family that serves a key role in regulating angiogenesis. The tumor-associated neovasculature, a hallmark of cancer, is generated through angiogenesis (124,125). In addition to NSCLC, most human tumors upregulate VEGF, whose expression is associated with an increased vascular density, cancer cell invasiveness and metastasis (126). VEGF signaling, which can be regulated by hypoxia and oncogene signaling at multiple levels, is activated mainly through upregulated VEGF expression and its binding to the VEGF receptor (VEGFR) (127,128). Furthermore, the

fibroblast growth factor family is involved in sustaining tumor angiogenesis through proangiogenic signals (129). Thus, the VEGF/VEGFR pathway has been identified as a notable therapeutic target. Bevacizumab was the first monoclonal antibody developed to block VEGF-VEGFR binding and has been reported to be effective against NSCLC as a monotherapy or in combination with platinum-doublet chemotherapy and with EGFR/ALK-TKIs (130,131). Additionally, small-molecule agents that inhibit downstream VEGF/VEGFR signaling can also exert anti-angiogenic and extensive antitumor effects (132).

Ras/Raf/MAPK pathway. The three main members of the MAPK family are ERK, JNK/SAPK and p38 MAPK, which serve key roles in several biological functions, including signal transduction from the extracellular matrix to intracellular organelles (133). The MAPK pathway involves three-kinase cascades: The upstream kinase (MAPKKK) directly phosphorylates MAPKK in response to various extra and intracellular signals and the middle kinase (MAPKK) then phosphorylates and activates MAPK. The MAPK pathway is involved in cell proliferation and differentiation, as well as cell survival and apoptosis. The MAPK pathway is always dysregulated in *Ras*-mutant NSCLC, resulting in uncontrolled cancer cell proliferation and drug resistance (134,135). The Ras/Raf/MAPK pathway serves a key role in this process, making proteins involved in this cascade cancer treatment targets (136). Certain agents that block MAPK signaling, such as Trametinib, have been reported to lead to signal interruption and kinase inhibition (137). Enhancing current understanding on this pathway is key due to its notable functions and the extensive spectrum of crosstalk with other major pathways.

KEAP1/NRF2 pathway. The KEAP1/NRF2 pathway is considered to regulate redox homeostasis and protect cells from oxidative stress. During tumor initiation and progression, this pathway is often hijacked by cancer cells and aberrant KEAP1-NRF2 activity is predominantly observed in NSCLC (138). KEAP1 regulates NRF2 signaling in response to reactive oxygen species (139) and the PI3K signaling pathway also affects this pathway through glycogen synthase kinase 3, which acts as a key mediator (140). Furthermore, KEAP1-NRF2 signaling is involved in crosstalk with other pathways and increasing research has revealed its association with metabolic activities, leading to tumor metabolic reprogramming in lung cancer (141,142). Therefore, the metabolic vulnerability of *KEAP1/NRF2*-mutant NSCLC is a target (143). Furthermore, KEAP1/NRF2 signaling could be used as a prognostic biomarker for a poor prognosis and as a predictive marker for drug resistance (101). *KEAP1/NRF2*-mutant NSCLC is associated with a poor prognosis and resistance to platinum-based chemotherapy, radiotherapy, EGFR-TKI and immune checkpoint inhibitors (144-146). Due to the key role of the KEAP1/NRF2 pathway in NSCLC, novel compounds or repurposed agents that target this pathway are of notable interest for clinical cancer treatment.

Therapeutic strategies for NSCLC. The 5-year survival rate of patients with lung cancer has improved markedly due to the progress in cancer screening and personalized therapy. However, it varies extensively from 8 to 64% in terms of localized differences and tumor stage (147). For patients with early-stage NSCLC, the recommended treatment is surgery, which can markedly improve survival. Furthermore, the 5-year survival rate for patients with clinical stage IA disease can reach 92% and the survival rate for patients with stage I-IIB disease varies from 68 to 53% (9). For patients with distant metastatic lesions, the survival rate is low. For example, up to 40% of patients with stage IV disease develop brain metastases and current treatments for this subgroup have been suggested to lack efficacy due to the intracranial activity of drugs (148). Except classical chemotherapies or radiotherapies, targeted therapies, immunotherapies and anti-angiogenic therapies, other approaches including ADCs, bispecific antibodies, T-cell engagers, cancer vaccines, cellular therapies and external devices are available for patients with advanced NSCLC (149). In this section, the present review discusses the most commonly applied and potential treatments in clinical practice.

Chemotherapies and radiotherapies. For patients with unresectable NSCLC and a good performance status, platinum-based chemotherapy is the cornerstone of treatment and other therapeutic options involve thoracic radiotherapy (150). Although the side effects of chemoradiotherapies are apparent, cytotoxic therapies exert notable effects and have been extensively used in clinical practice: i) As a monotherapy or in combination with immunotherapy/anti-angiogenic therapy in patients with advanced NSCLC who have no actionable molecular target; ii) as an alternative to targeted therapy when drug resistance occurs; iii) and as adjuvant chemotherapy/neoadjuvant therapy in surgical cases. An open phase II study using concurrent cisplatin-oral vinorelbine and radiotherapy reported that comprehensive geriatric assessment was able to select fit elderly patients with locally advanced NSCLCs eligible for concurrent chemoradiotherapy (151). Furthermore, the combination of chemotherapy and thoracic radiation has a survival advantage, with an improvement of four months in median survival (152). However, previous studies have demonstrated that neoadjuvant chemoradiotherapy only improved the downstaging rates and R0 resection rates, with no benefit in terms of OS (153). In addition, postoperative radiotherapy (PORT), an adjuvant type of radiotherapy, can only reduce the rate of local recurrence, with no benefits in terms of DFS and OS (154). Another open-label, randomized, phase III trial demonstrated that conformal PORT cannot be recommended as the standard of care in patients with stage IIIA (N2) NSCLC (NCT00410683) (155). In recent years, radiotherapy has been integrated into neoadjuvant approaches, concurrent chemotherapy and/or immunotherapy due to technological innovations (156). Although chemoresistance which may be caused by impaired DNA repair pathways and inhibition of apoptosis (157), and adverse reactions limit its clinical utility in patients with advanced NSCLC, we hypothesize that the adverse effects of cytotoxic therapies will decrease in the near future with pharmaceutical development and that more patients with advanced lung cancer will benefit from this therapeutic option through toxicity monitoring and patient management.

Targeted therapies. In the era of precision medicine, targeted therapy has advanced the treatment of patients with NSCLC with driver gene alterations. Molecular detection has become a key part of the clinical management of NSCLC. Kinase inhibitors targeting EGFR, ALK, ROS1 and MET are

commonly generated through genetic cues in clinical practice (158). However, >50% of LUAD patients have targetable oncogenic drivers and the use of targeted therapy is associated with improved outcomes (159,160). *EGFR* mutations, which are identified in exon 21 (L858R) or exon 19 (deletions), are the most predominant alterations and occur in 40% of Asian patients, mostly among never-smoking women (32,161). Currently, three generations of EGFR-TKIs are approved by the FDA; however, nearly all patients eventually experience drug resistance and disease progression (162). The common mechanism of acquired resistance to first-generation EGFR-TKIs is a second *EGFR* mutation (T790M), which can be overcome by osimertinib (a third-generation EGFR-TKI). Other resistance mechanisms include bypass or alternative activation, such as MET/HER2 amplification and insulin growth factor receptor 1 activation (163). For patients with *HER2*-mutant NSCLC, only one targeted therapy has been approved by the FDA/European Medicines Agency, trastuzumab deruxtecan, which is an ADC (48). Furthermore, three generations of ALK inhibitors have exhibited promising outcomes. Notably, due to their homologous domains, ALK-TKIs can also target *ROS1*-mutant NSCLCs (73). However, drug resistance inevitably occurs due to alterations in the expression of *ALK* genes, including mutations and amplification, and the upregulation of genes involved in bypass pathways (EGFR and MAPK). The predominant resistance mechanism is secondary *ALK* mutation, such as G1202R (164). Currently, several TKIs, including crizotinib and tepotinib, are on the market or in clinical trials to target MET. Tepotinib is recommended for patients with NSCLC with *MET* exon 14 skipping mutations (165,166). The development of therapeutics to target other potential alterations, such as those in KRAS, has been notably challenging. Several KRAS G12C inhibitors, including sotorasib (AMG510) and adagrasib (MRTX849), have demonstrated notable preclinical and clinical efficacy and gained accelerated approval in 2021 as monotherapies for patients with KRAS G12C NSCLC (29). Notably, all targeted therapies cannot avoid drug resistance, making the next generation of TKIs an emerging issue. Several clinical trials are ongoing; for example, amivantamab plus chemotherapy with and without lazertinib have been used to treat *EGFR*-mutant advanced NSCLC after disease progression on osimertinib (167). Primary results from the phase II SAVANNAH study (NCT03778229) revealed that savolitinib plus osimertinib provide a novel oral targeted treatment approach for patients with *EGFR*-mutated, advanced NSCLC with MET upregulation or amplification following disease progression on osimertinib (168).

Immunotherapies. In addition to targeted therapies for specific gene mutations, the development of immunotherapy, which is based on ICIs, has revolutionized the treatment of patients with non-targetable NSCLC. Since the first immunotherapy drug, nivolumab (anti-PD-1), was approved by the FDA for lung cancer in 2015, several FDA-approved ICIs have been developed that target PD-1/PD-L1 or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in advanced NSCLC (169). These inhibitors are generated upon T-cell activation because CTLA-4-B7.1 suppresses T-cell activation through the regulation of the immunological synapse between T and dendritic cells, and PD-1/PD-L1 hampers immune rejection or the response of T cells to tumor cells (170). Furthermore, the initiation and progression of lung cancer depend on the interaction between cancer cells and the immune system (171). Despite the marked survival outcomes observed in a subset of patients with NSCLC receiving ICI therapy, majority of patients demonstrate primary or secondary resistance to ICIs. Primary resistance is due to extrinsic modulation of TME or intrinsic adaptive changes in cancer cells, resulting in the lack of an immune response. Secondary resistance occurs when the disease progresses after the initial benefit from ICIs, as tumor cells acquire specific alterations that allow them to escape the immune response (172). The mechanisms include impaired antigen presentation, cGMP-AMP synthase-stimulator of interferon genes (STING) pathway dysregulation, tumor antigen loss, metabolic reprogramming in TME, immune cell exhaustion and microbiomes (173). Thus, investigating novel drugs to prevent and overcome immunotherapy resistance is crucial, as these drugs would benefit more patients, such as patients with *LKB1*-mutant NSCLC. Of note, a series of clinical studies focused on overcoming immunotherapy resistance are ongoing. Lifileucel, an autologous tumor-infiltrating lymphocyte monotherapy, was observed to improve the response rate in patients with advanced NSCLC who are resistant to ICIs, including patients with a low TMB and patients with *LKB1* mutations (174). A phase I/II dose-escalation study demonstrated that the TEIPP24 vaccine is a novel immunotherapeutic approach for HLA-A positive checkpoint-resistant NSCLC (NCT05898763) (175). Furthermore, certain studies have described the molecular mechanism of LKB1-mediated immune resistance and proposed possible solutions, and certain clinical studies have also confirmed the poor outcomes of immunotherapy in *LKB1*-mutant NSCLC and verified potential therapeutics for overcoming immune resistance (176,177).

Anti-angiogenic therapies. Abnormal vasculature is a major cancer hallmark and the TME consists of numerous pro-angiogenic factors, including VEGF, which are secreted by tumor or immune cells (178). Thus, antitumor angiogenesis has garnered attention and become one of the most effective cancer treatments (179). Anti-angiogenic agents reduce tumor blood supply by inhibiting VEGF pathway, limiting tumor growth and metastasis. Several agents, such as bevacizumab and ramucirumab, have been developed and applied clinically, often in combination with chemotherapy or other therapies. These combinations have demonstrated promising results, particularly in advanced NSCLC where conventional therapies alone have proven inadequate (180,181). However, notable challenges and limitations persist that hinder its efficacy and application. Safety and tolerability are key considerations in clinical application and common side effects of anti-angiogenic agents include hypertension, proteinuria and gastrointestinal complications (182). Another major challenge is the development of resistance mechanisms, which could be attributed to changes within the TME. Several studies have highlighted that despite initial responses to anti-VEGF therapies, tumors can develop compensatory mechanisms that bypass the effects of these agents, such as upregulating other pro-angiogenic factors or activating alternative signals (183,184). Recent research focuses on novel compounds that can effectively target these alternative pathways, such as the δ-like canonical Notch ligand 4-Notch1 signaling pathway, which serves a notable role in vascular function (185). In the future, the development of novel

agents and selection of appropriate patients for anti-angiogenic therapy is key to maximizing treatment efficacy, highlighting the importance of identifying specific genetic mutations or biomarkers. The integration of biomarkers into clinical practice will facilitate the selection of patients and improve treatment outcomes. Thus, while anti-angiogenic treatments represent a notable advancement in the management of NSCLC, a multi-faceted approach that includes drug development, resistance mechanisms and personalized treatment strategies is key to the treatment of this disease.

Other potential therapeutics. In addition to these classical treatments, novel therapies, such as ADC, are being integrated into treatment guidelines. For example, sacituzumab tirumotecan, a novel TROP2-directed ADC, exhibited notable single-agent activity and manageable tolerability in patients with advanced NSCLC with *EGFR* mutations. Telisotuzumab vedotin, an ADC that targets MET factor (c-Met) protein upregulation, plus osimertinib had promising activity in patients with c-Met protein-upregulating, *EGFR*-mutated non-squamous NSCLC after progression on osimertinib. Patritumab deruxtecan (HER3-DXd), an ADC consisting of a HER3 antibody attached to a topoisomerase I inhibitor, displayed clinical activity in metastatic *EGFR*-mutated NSCLC after disease progression on EGFR-TKI therapy. For HER2-upregulating cases, trastuzumab-deruxtecan has the potential to address the unmet clinical need (186-189). Recently, Scott and Levy (190) discussed the biomarker identification and drug resistance of these ADCs. Bispecific antibodies such as amivantamab, which targets both EGFR and MET, yielded promising efficacy in patients with *EGFR*-mutant NSCLC (191). Ivonescimab is another bispecific antibody which targets PD-1 and VEGF had improved progression-free survival (PFS) in TKI-treated NSCLC (192). Furthermore, first-line treatment with KN046 (a bispecific antibody against PD-L1 and CTLA-4) and chemotherapy is also effective in metastatic NSCLC (193). As a form of active immunotherapy, therapeutic cancer vaccines which include cancer cell vaccine, peptide/protein vaccine and DNA/RNA vaccine could improve survival in patients with advanced NSCLC. For instance, personalized neoantigen peptide vaccination was confirmed to be feasible and safe for patients with advanced NSCLC (194). Furthermore, data from a Phase Ib clinical trial of NEO-PV-01 (a personalized neoantigen-vaccine) supported the safety and immunogenicity in patients with advanced non-squamous NSCLC (195). The limitations of cancer vaccines include lack of standardized design and manufacturing processes, and various barriers in clinical translation. Furthermore, T-cell engagers also demonstrate potential clinical translation value. ACE-05 was a T-cell engager and exhibited promising antitumor efficacy in peripheral blood mononuclear cell-reconstituted humanized mouse harboring human NSCLC tumors (196). Furthermore, Shen *et al* (197) identified a bispecific antibody which was termed 'secretion of T-cell-redirecting bispecific antibodies', could simultaneously binds CD3 on T cells and S15 on tumor cells, resulting in increased activated T cells and inhibition of NSCLC. These strategies potentially provide hope for patients with NSCLC, particularly for those with *LKB1* mutations (Table I). As patients with *LKB1*-mutant NSCLC still have no effective therapeutics, the most promising treatment may be immunotherapy or novel strategies. Thus, the present review emphasizes the molecular mechanism and treatment of *LKB1*-mutant NSCLC next, with a particular focus on immunotherapy and combined therapies.

Barriers to clinical translation and solutions. These approaches are currently hindered by multiple interrelated barriers, such as tumor heterogeneity and adaptive drug resistance, which lead to inconsistent therapeutic responses across patients, along with the mechanisms of antigen escape, bypass pathway activation and epigenetic regulation reducing the efficacy of targeted and immunotherapies in both early and advanced stages. Furthermore, incomplete translational validity of preclinical models limits the predictability of clinical efficacy, as cell or animal models fail to recapitulate the complex TME and genomic co-alterations in human lung cancer. Furthermore, on-target or off-target toxicities of novel agents and poor delivery efficiency to special sites restrict their clinical application (198). Multi-faceted strategies are warranted to address these challenges, for example, developing personalized combinatorial regimens based on multi-omics profiling to overcome drug resistance, optimizing preclinical research systems by establishing patient-derived xenografts and organoid models that mimic human tumor heterogeneity, and integrate artificial intelligence to predict drug sensitivity and clinical outcomes (199), validating and standardizing clinical biomarkers to achieve accurate patient stratification.

3. Focus on LKB1-mutant NSCLC: From mechanisms to clinical breakthroughs

Since the present review acquired knowledge of the molecular mechanisms and treatment options for NSCLC, the *LKB1* gene, for which applicable targeted or immune therapy has not been developed, has gained interest (98). Furthermore, LKB1 affects the prognosis of patients with NSCLC. In the KRYSTAL-1 trial, *LKB1* mutation was associated with shorter survival to adagrasib treatment compared with *LKB1*-wild-type [PFS, 4.2 vs. 11.0 months; hazard ratio (HR), 2.2; P<0.01; OS, 9.8 months vs. not reached; HR, 2.6; P<0.01] (200). Overall, *LKB1* is one of the most common tumor suppressor gene mutations in NSCLC and its molecular regulatory network is complex and unique, which is different from other common mutations. Due to these peculiar characteristics, the present review explores the resistant mechanism of *LKB1* mutation and current potential strategies for patients with NSCLC with *LKB1* mutations. The clinical significance and research value of *LKB1* mutation may provide novel ideas for the treatment of other mutant subtypes of NSCLC in the future.

LKB1 mediates drug resistance mainly through AMPK or STING pathway. Since *LKB1* was identified, previous studies have focused on its biological functions and associations with cancer. LKB1 functions as a metabolic switch, its inactivation suppresses lipid metabolism and abrogates KRAS-induced immunogenicity (177,201). Loss of function of LKB1 has emerged as a major driver of the cold TIME in NSCLC, characterized by low levels of tumor-infiltrating $CD4^+$ and $CD8^+$ T cells, and PD-L1 expression (176,202,203). The immune evasion noted in LKB1-inactivated lung cancer is due to subsequent AMPK inactivation and attenuation of antigen presentation (204). AMPK activation will lead to

Table I. Previous studies about novel treatment strategies for NSCLC.

First author, year	Drug	Treatment type	Trial number	Phase	Patients/model	No. of patients	Outcomes	(Refs.)
Zhao *et al*, 2025	Sacituzumab tirumotecan	ADC	NCT04152499 and NCT05631262	I/II	Advanced NSCLC	107	Encourages single-agent activity with tolerability	(186)
Horinouchi *et al*, 2025	Telisotuzumab vedotin	ADC	NCT02099058	I/Ib	c-Met-upregulating EGFR-mutant non-squamous NSCLC	38	Promising activity of Teliso-V + osimertinib when disease progressed on prior treatment with osimertinib	(187)
Janne *et al*, 2022	Patritumab deruxtecan	ADC	U31402-A-U102	I	Metastatic EGFR-mutated NSCLC	36	Exhibits clinical activity	(188)
Smit *et al*, 2024	Trastuzumab deruxtecan	ADC	NCT03505710	II	HER2-upregulating metastatic NSCLC	90	Supports further investigation of trastuzumab deruxtecan	(189)
Park *et al*, 2021	Amivantamab	Bispecific antibody	NCT02609776	I	NSCLC with EGFR exon 20 insertion	114	Robust and durable responses with tolerable safety	(191)
Investigators *et al*, 2024	Ivonescimab	Bispecific antibody	NCT05184712	III	Progressed EGFR-mutant NSCLC	322	Improvement of PFS with tolerable safety	(192)
Zhao *et al*, 2024	KN046	Bispecific antibody	NCT04054531	II	Metastatic NSCLC	87	Notable efficacy and tolerability	(193)
Li *et al*, 2021	NeoAg peptide	Cancer vaccine	ChiCTR-INR-16009867	I	Advanced NSCLC	24	Feasible and safe personalized vaccination of NeoAg	(194)
Awad *et al*, 2022	NEO-PV-01	Cancer vaccine	NCT03380871	I	Advanced non-squamous NSCLC	38	Safety, feasibility and generation of desired immune responses	(195)
Jang *et al*, 2021	ACE-05	T-cell engager	Preclinical	Preclinical	HCC827 PBMC-reconstituted NCG mice model	0	Demonstrates marked antitumor efficacy and tumor regression	(196)
Shen *et al*, 2025	STAB	Cellular therapy	Preclinical	Preclinical	H460 NSCLC NSG mice model	0	An effective immune cell therapy	(197)

ADC, antibody-drug conjugate; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; STAB, secretion of T-cell-redirecting antibodies; PBMC, peripheral blood mononuclear cells; NeoAg, neoantigen; PFS, progression-free survival; HER2, human EGFR 2; c-Met, mesenchymal-epithelial transition factor; NCT, National Clinical Trial.

the promotion of catabolic processes such as autophagy, which is key to cellular recycling and maintenance (205). This pathway also regulates glucose and lipid metabolism, contributing to the balance between energy intake and expenditure. Dysregulation of this pathway is often implicated in the pathogenesis of cancer (206). *LKB1* mutation also leads to the abnormal activation of poly(ADP-ribose) polymerase-1 (PARP1) and deficiency in the DNA damage repair process. Hyperactivated PARP1 suppresses IFNγ signaling by physically interacting with and increasing the poly(ADP-ribosyl)ation of STAT1 (207). Furthermore, LKB1 inactivation induces the epigenetic repression of STING, thus promoting immune escape in *KRAS*-mutant lung cancer (177,208). Mechanistically, LKB1 deficiency is associated with STING loss, resulting in STING/type I interferon dysfunction and diminished immunotherapy efficacy in NSCLC (209,210). In patients with lymph node metastases, the loss of LKB1 expression is markedly associated with the concurrent loss of STING and p-AMPK in metastatic tumors (209). Notably, LKB1 is also a key regulator of T-cell development, viability and activation. T-cell-specific ablation of LKB1 is associated with blocked thymocyte development and reduced peripheral T cells (211). A recent study revealed that LKB1 deficiency in group 2 innate lymphoid cells, which serve key roles in regulating tumor immunity, leads to an exhausted-like phenotype. Blockade of PD-1 could reverse this phenotype and result in enhanced antitumor immune responses, revealing the antitumor immunity role of LKB1 (212). These results may explain why *LKB1* mutations are associated with poor progresses and immune resistance.

Treatment strategies for LKB1-mutant NSCLC. According to the aberrant pathways induced by LKB1 deficiency, targeting metabolic vulnerabilities with mTOR inhibitors or AMPK agonist could restore metabolic control and inhibit tumor growth. Preclinical studies have demonstrated that *LKB1*-mutant tumors exhibit sensitivity to glutaminase inhibitors and biguanides, which impair glutamine metabolism and mitochondrial respiration, respectively (213,214). Clinical trials are investigating combination therapies of metabolic inhibitors with conventional chemotherapy or targeted agents to overcome resistance (91,215). For patients with *KRAS/LKB1* co-mutant NSCLC, co-inhibition of KRAS and downstream effectors such as MEK, along with metabolic modulators such as autophagy inhibitors, has demonstrated synergistic antitumor effects (216,217). The FDA-approved antibody daratumumab, as an ADC, has been demonstrated to target CD38 in *LKB1*-mutant NSCLC (218). Due to the limited efficacy of single-agent ICIs in *LKB1*-mutant NSCLC, combination therapies have been explored to overcome immune resistance by modulating the TME and enhancing immune activation. A promising strategy involves combining ICIs with chemotherapy or radiotherapy, which can induce immunogenic cell death, and potentiate T-cell priming and infiltration (219). Furthermore, clinical trials are actively investigating various combinations of ICIs with PARP inhibitors, metabolic modulators and other targeted agents such as STAT3 inhibitors and CDK4/6 inhibitors, aiming to remodel the immunosuppressive TME and overcome immune evasion (207,220,221). Beyond conventional immune checkpoint blockade and combination regimens, novel immunotherapeutic modalities are being investigated to address the unique challenges posed by *LKB1*-mutant NSCLC. For example, hyper-interferon-sensitive influenza virus-based *in situ* vaccination has exhibited efficacy in overcoming anti-PD-1 resistance by eliciting robust type I interferon responses and augmenting cytotoxic T-cell activity in murine *LKB1*-mutant NSCLC models (222). Furthermore, adoptive cell therapies targeting tumor antigens are under exploration, with research focusing on enhancing immune recognition and overcoming the immunosuppressive microenvironment characteristic of LKB1 loss. Epigenetic therapies targeting the corepressor of RE1-silencing transcription factor complex have also been developed to reprogram the tumor epigenome, increase immune gene expression and synergize with ICIs to induce durable tumor regressions in *STK11*-mutant tumors (223,224). Collectively, these novel findings make notable breakthroughs and provide potential treatment options for *STK11*-mutant NSCLC in the future.

4. Conclusions and future perspectives

In the present review, the molecular mechanisms and clinical treatments of NSCLC were systematically explained, followed by an example focusing on LKB1. The exploration of molecular mechanisms underlying NSCLC has provided a key theoretical foundation for clinical treatment advancements. With the development of molecular detection, the treatment for patients with NSCLC has undergone marked changes, particularly in the era of targeted therapy and immunotherapy. As more oncogenes or tumor suppressor genes have been identified, the corresponding agents that target these alterations have been continuously developed. However, not all patients benefit from these advancements and key issues such as drug resistance remain pressing hurdles in the clinical management of NSCLC.

In the future, elucidation of cancer-associated signaling pathways remains of paramount importance. Continued research efforts should focus on delineating the complex network of molecular interactions influenced by oncogene, which will facilitate the identification of novel therapeutic targets. Furthermore, the future of managing lung cancer lies in the development of personalized treatment paradigms and integrating biomarker driven approaches will enhance patient stratification, ensuring that therapeutic regimens are optimally matched to individual tumor profiles. Basic research priorities include the following: i) Explore the molecular regulatory network of *LKB1* mutation and its co-mutation in NSCLC; ii) clarify the key downstream effector molecules; and iii) identify the specific TME characteristics of *LKB1*-mutant NSCLC and its crosstalk with immune cells. The development of this field underscores the necessity of a nuanced balance between understanding the underlying biology and translating these insights into effective clinical interventions. Thus, translational research priorities should focus on developing specific *LKB1* mutation detection technologies and multi-omics-based prognostic and predictive biomarkers. Furthermore, it is necessary to optimize the preclinical research model of *LKB1*-mutant NSCLC to improve the consistency between preclinical and clinical results. By targeting comprehensive molecular profiling and embracing a patient-centric framework, clinicians

can potentially improve both survival outcomes and quality of life for patients with NSCLC, particularly those with *LKB1* mutations in the future.

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Competing interests

The authors declare that they have no competing interests.

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