

# The tumor microenvironment in lung cancer: Heterogeneity, therapeutic resistance and emerging treatment strategies (Review)

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**Abstract.** Lung cancer remains a leading cause of cancer-related death. Despite advances in targeted therapies and immunotherapy, treatment outcomes remain suboptimal due to tumor heterogeneity and therapeutic resistance. The tumor microenvironment (TME), a dynamic ecosystem comprising immune cells, stromal components, extracellular matrix and bioactive molecules, serves a critical role in promoting tumor progression and resistance. The present review comprehensively analyzes the molecular mechanisms underlying TME-mediated immune evasion, and resistance to chemotherapy, radiotherapy and immunotherapy. In addition, emerging therapeutic strategies targeting the TME are highlighted, such as immune microenvironment modulation, metabolic and epigenetic interventions, and nanotechnology-based drug delivery systems. By integrating multi-omics datasets and spatial transcriptomics, TME-directed interventions are moving toward biomarker-guided, personalized regimens.

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## 1. Introduction

Lung cancer accounts for 18% of global cancer deaths, with non-small-cell lung cancer (NSCLC) comprising 85% of cases (1). Despite advances in targeted agents and immune checkpoint blockade (ICB), the 5-year survival rate remains at  $\leq 25\%$  (2). Notably, primary or acquired resistance occurs in 50-60% of patients with EGFR mutations within 12-18 months (3) and in  $\geq 30\%$  of patients treated with ICB (4). Intratumoral heterogeneity and clonal evolution are recognized drivers of resistance; however, the tumor microenvironment (TME) is increasingly appreciated as an active factor that imposes metabolic, physical and immunological barriers to therapy (5).

The heterogeneity of NSCLC further complicates treatment. Genomic analyses have revealed distinct molecular subtypes of NSCLC, such as KRAS, BRAF and RET, each requiring tailored therapies (6). However, even within the same subtype, intratumoral heterogeneity drives clonal evolution and therapeutic escape (5). For example, KRAS G12C inhibitors, such as sotorasib, achieve objective response rates (ORRs) of 37%; however, resistance emerges through alternative pathway activation or phenotypic switching (7). Immunotherapy resistance is equally complex, with TME-mediated mechanisms such as T-cell exhaustion, myeloid-derived suppressor cells (MDSCs) and collagen-rich physical barriers impeding immune cell infiltration (8).

The TME has emerged as a critical factor in cancer progression and therapeutic resistance, as supported by both preclinical models and clinical trial data (9-14). Comprising tumor cells, immune cells, stromal components, extracellular matrix (ECM) and bioactive molecules, the TME is a dynamic ecosystem that actively promotes tumor evolution, immune evasion and therapeutic resistance (10). Chronic inflammation within the TME, for example, has been linked to the development of an immunosuppressive environment, which facilitates tumor progression and resistance to immunotherapy (11). Studies have shown that components of the TME, such as tumor-associated macrophages (TAMs), MDSCs and regulatory T cells (Tregs), serve key roles in suppressing antitumor immune responses (12,13). Additionally, the ECM and its degradative enzymes contribute to tumor invasion and metastasis by remodeling the physical structure of the TME (14). Understanding these interactions is crucial for developing

novel therapeutic strategies that target the TME to overcome resistance and improve patient outcomes.

The present review aims to provide a comprehensive analysis of the role of the TME in lung cancer progression and therapeutic resistance. Firstly, the molecular mechanisms underlying TME-mediated immune evasion and resistance to chemotherapy, radiotherapy and immunotherapy were explored. Furthermore, emerging therapeutic strategies targeting the TME, such as immunotherapy combinations, anti-angiogenic therapies and nanoparticle-based drug delivery systems, were critically evaluated, and their potential to overcome resistance and enhance treatment efficacy discussed. The current review will highlight the importance of integrating TME profiling into personalized medicine approaches, and emphasize the need for further research to address the challenges posed by TME heterogeneity and plasticity. By bridging gaps in the current knowledge, the review seeks to inform future research directions and clinical applications in the management of lung cancer.

## 2. Heterogeneity of the lung cancer microenvironment

The heterogeneity of the lung cancer microenvironment arises from the complex interplay of cellular and non-cellular components, as well as emerging factors such as microbiota and neuronal crosstalk (15,16). This heterogeneity poses notable challenges for therapeutic intervention, necessitating a deeper understanding of the dynamic interactions within the TME to develop effective treatment strategies.

*Cellular components.* The TME in lung cancer is characterized by a complex array of immune cells, including TAMs, MDSCs and Tregs, which collectively contribute to an immunosuppressive environment (5) (Fig. 1). TAMs, particularly the M2-polarized subset, secrete interleukin (IL)-10 and transforming growth factor- $\beta$  (TGF- $\beta$ ) to inhibit antitumor immunity and support tumor progression (5). Similarly, MDSCs impair cytotoxic T-cell function via reactive oxygen species and arginase production (17), and Tregs further reinforce immunosuppression through secretion of immunosuppressive cytokines, such as IL-10 and TGF- $\beta$  (18). However, studies have highlighted the heterogeneity of these immune cells within the TME (19,20). For example, it has been suggested that TAMs can exhibit both protumorigenic and antitumorigenic functions depending on their spatial distribution and functional orientation within the tumor (21,22). This heterogeneity complicates therapeutic strategies targeting TAMs, as interventions may need to account for their dual roles (23).

Cancer-associated fibroblasts (CAFs) contribute to tumor progression and therapeutic resistance by remodeling the ECM and secreting growth factors such as TGF- $\beta$  and fibroblast growth factor (FGF) (24) (Fig. 1). Through ECM deposition and cross-linking, CAFs create a physical barrier that impedes drug penetration and immune cell infiltration, while also promoting angiogenesis and metastatic dissemination (25,26). Additionally, the presence of other immune cell subsets, such as natural killer (NK) cells and  $\gamma\delta$  T cells, has been shown to influence tumor outcomes. NK cells, known for their ability to recognize and lyse tumor cells without prior sensitization,

can be impaired in the TME due to factors such as TGF- $\beta$  and programmed death-ligand 1 (PD-L1) expression (27).  $\gamma\delta$  T cells, which are involved in both innate and adaptive immunity, have also been shown to serve a role in shaping the TME and affecting therapeutic responses (28).

*Non-cellular components.* The ECM undergoes dynamic remodeling in the TME, driven by matrix stiffness, collagen crosslinking and protease activity (29). Matrix metalloproteinases (MMPs) and other proteases degrade the ECM, facilitating tumor invasion and metastasis (30). Additionally, increased matrix stiffness can enhance tumor cell proliferation and resistance to therapy by promoting mechanotransduction pathways (30). These changes in the ECM create a physical barrier that limits drug delivery and contributes to therapeutic resistance.

Soluble factors, such as cytokines (for example, IL-6 and TNF- $\alpha$ ), chemokines and growth factors, are critical drivers of TME heterogeneity. IL-6, for example, promotes tumor progression by activating the STAT3 pathway, which enhances cell survival and proliferation (31). TNF- $\alpha$ , while often associated with inflammation, can also contribute to immunosuppression by upregulating PD-L1 expression on tumor cells (31). Growth factors such as vascular endothelial growth factor (VEGF) drive angiogenesis and create an immunosuppressive microenvironment, further complicating therapeutic strategies (32).

*Emerging factors.* Recent studies have identified the presence of intratumoral microbiota within the lung cancer microenvironment, with microbial metabolites influencing oncogenic signaling and immune evasion (33,34). For example, certain bacterial species have been shown to modulate the expression of immune checkpoint molecules, such as PD-L1, thereby enhancing tumor immune evasion (35) (Fig. 1). Furthermore, the role of the gut-lung axis in shaping the lung TME has garnered attention. The gut microbiota can influence systemic immunity and inflammation, which in turn affects the composition and function of the lung microbiota and TME (36). This interplay between the gut and lung may offer novel targets for therapeutic intervention.

Neuronal interactions within the TME have also emerged as a novel area of research (37). Neurotrophic factors and axonogenesis promote tumor innervation, which can enhance tumor growth and metastasis (38). Studies have suggested that neural signaling may influence the secretion of protumorigenic factors, such as TGF- $\beta$ , and create a permissive environment for tumor progression (39,40) (Fig. 1). Additionally, the involvement of neuronal-derived exosomes in transmitting signals that promote tumor cell survival and therapeutic resistance has been revealed (41), highlighting the importance of understanding the bidirectional communication between neurons and tumor cells in shaping the TME.

The heterogeneity of the lung cancer microenvironment, driven by diverse cellular interactions and dynamic non-cellular components, presents a notable barrier to effective therapy. Understanding these complex interactions is essential for developing targeted approaches that can modulate the TME to enhance treatment efficacy. By addressing the dual roles of immune cells, the fibrotic networks created by

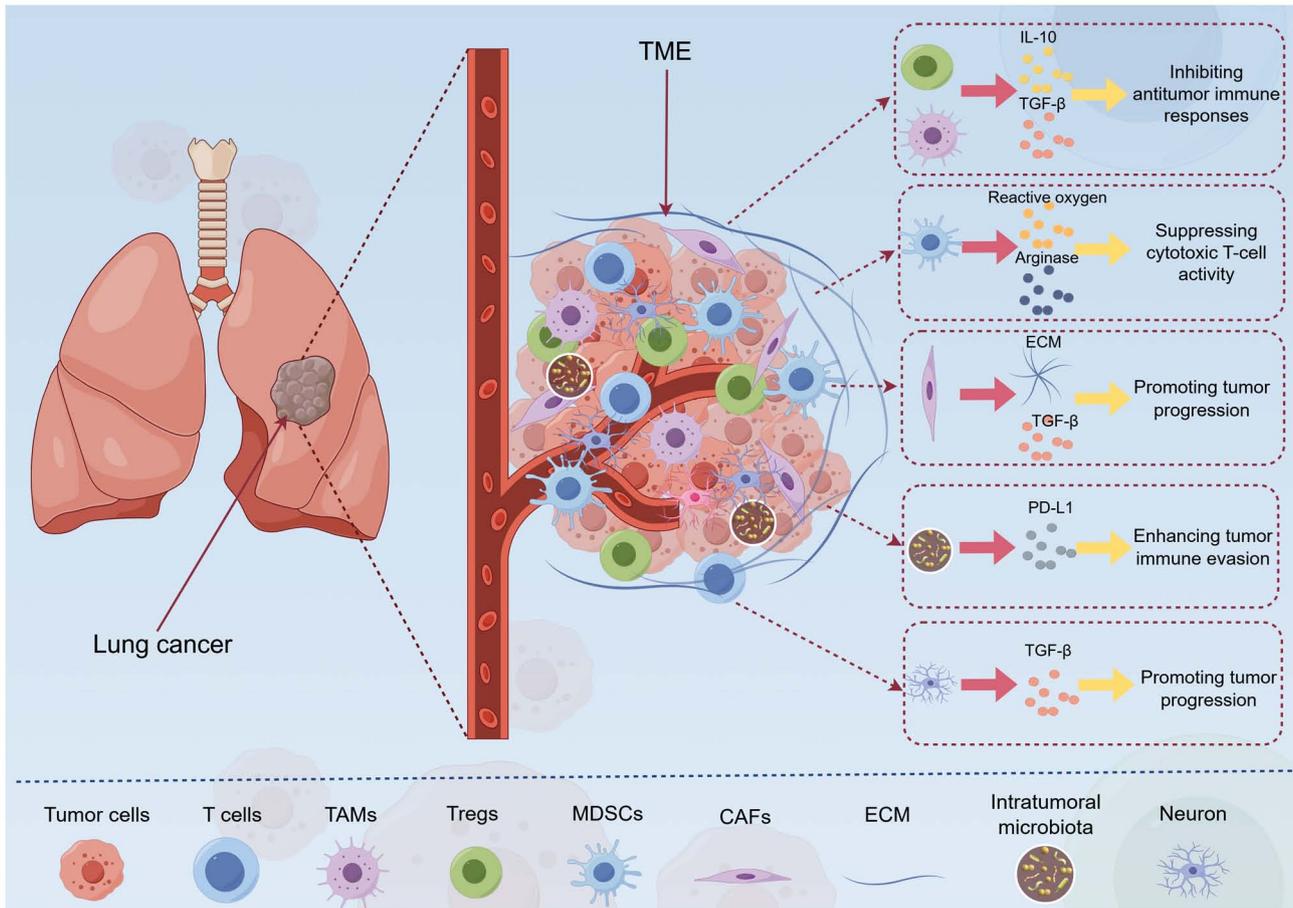


Figure 1. TME composition and interactions in lung cancer. Components of the TME, including immune cells (such as TAMs, MDSCs and Tregs), stromal cells (for example, CAFs and endothelial cells), ECM and soluble factors (cytokines, chemokines and growth factors), are shown, as are the interaction between these components. For example, TAMs secrete IL-10 and TGF- $\beta$ , thus inhibiting antitumor immune responses, and CAFs promote tumor progression by secreting ECM components and growth factors. This figure was created using Figdraw ([www.figdraw.com](http://www.figdraw.com), ID: YTYOW4a999). CAFs, cancer-associated fibroblasts; ECM, extracellular matrix; IL-10, interleukin-10; MDSCs, myeloid-derived suppressor cells; PD-L1, programmed death-ligand 1; TAMs, tumor-associated macrophages; TME, tumor microenvironment; TGF- $\beta$ , transforming growth factor- $\beta$ ; Tregs, regulatory T cells.

CAFs and the physical barriers of the ECM, future therapeutic strategies may be better designed to overcome resistance and improve patient outcomes.

### 3. Dynamic crosstalk in the TME: Mechanisms of progression

The intricate crosstalk within the TME facilitates immune evasion, metabolic reprogramming and epigenetic modulation, thereby creating a permissive niche for tumor growth and therapeutic resistance (12,42). Understanding these dynamic interactions is crucial for developing novel therapeutic strategies that target the TME to enhance treatment efficacy and overcome resistance in lung cancer.

**Immune evasion and checkpoint dysregulation.** The TME facilitates immune evasion through various mechanisms, including the upregulation of immune checkpoint molecules and the polarization of immune cells (11). PD-L1, a well-known immune checkpoint protein, is often upregulated in lung cancer cells, enabling them to suppress T-cell activity and evade immune detection (43,44) (Fig. 2). Previous studies have also highlighted the role of the lymphocyte-activation gene

3 (LAG-3)/fibrinogen-like protein 1 (FGL1) axis and V-type immunoglobulin domain-containing suppressor of T-cell activation (VISTA) in immune evasion. LAG-3, expressed on exhausted T cells, interacts with FGL1, leading to T-cell dysfunction (45). VISTA, another immune checkpoint molecule, contributes to the immunosuppressive environment by inhibiting T-cell activation (46). TAMs serve a notable role in immune evasion by polarizing toward an M2 phenotype. This polarization is driven by cytokines such as colony stimulating factor 1 (CSF-1), which activates CSF-1 receptor signaling in macrophages (47). However, the extent to which these mechanisms contribute to immune evasion may vary among different lung cancer subtypes and patient populations, necessitating further investigation to clarify their roles and potential therapeutic targets.

**Metabolic reprogramming and hypoxia.** Hypoxia is a common feature of the TME, and has marked effects on tumor progression and therapeutic resistance (48) (Fig. 2). Hypoxia-induced autophagy, mediated by hypoxia-inducible factor-1 $\alpha$  and BCL-2/adenovirus E1B 19 kDa protein-interacting protein 3, supports the survival of cancer stem cells (CSCs). CSCs are known for their ability to self-renew and differentiate,

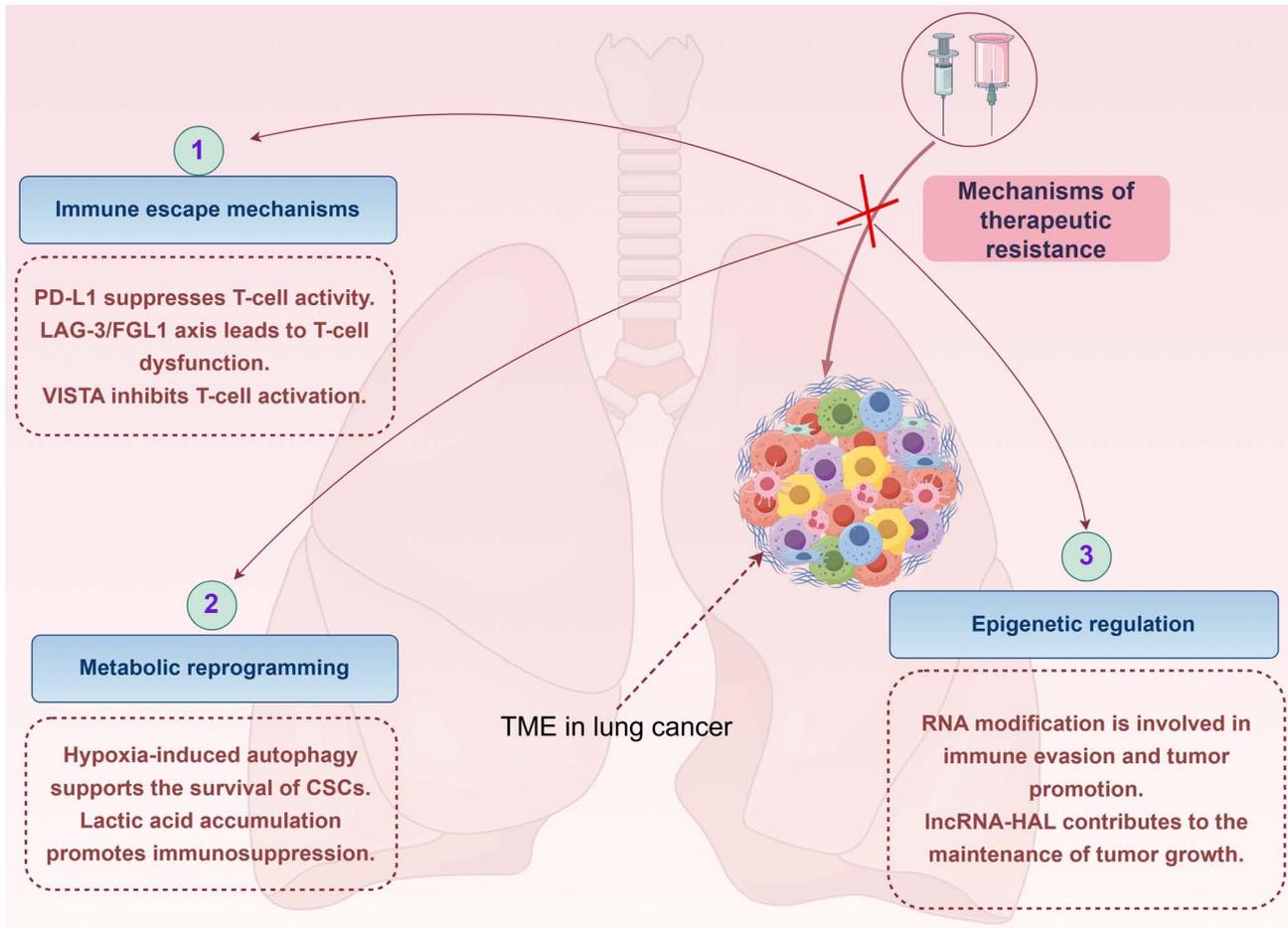


Figure 2. Mechanisms of therapeutic resistance in the TME. The mechanism by which the TME drives treatment resistance is shown, including immune escape mechanisms (such as PD-L1 upregulation, the LAG-3/FGL1 axis and the role of VISTA), metabolic reprogramming (for example, hypoxia-induced autophagy and immunosuppression due to lactic acid accumulation) and epigenetic regulation (such as RNA modification and the role of lncRNAs). This figure was created using Figdraw ([www.figdraw.com](http://www.figdraw.com), ID: STSWAa4006). CSCs, cancer stem cells; FGL1, fibrinogen-like protein 1; LAG-3, lymphocyte-activation gene 3; lncRNA, long non-coding RNA; PD-L1, programmed death-ligand 1; TME, tumor microenvironment; VISTA, V-type immunoglobulin domain-containing suppressor of T-cell activation.

contributing to tumor heterogeneity and resistance to therapy (49). By maintaining CSC survival, hypoxia-induced autophagy ensures a reservoir of cells capable of repopulating the tumor after treatment.

Lactate, a byproduct of anaerobic metabolism, accumulates in the TME under hypoxic conditions and serves a role in promoting immunosuppression (50) (Fig. 2). Lactate-mediated signaling in stromal cells, such as Notch/C-C motif chemokine ligand 5, fosters an immunosuppressive environment by attracting Tregs and inhibiting the function of cytotoxic T cells (51). This metabolic reprogramming not only supports tumor growth but also creates a barrier to effective immune responses, highlighting the complex interplay between metabolic changes and immune modulation in the TME.

**Epigenetic modulation in the TME.** Epigenetic changes within the TME markedly influence tumor progression and therapeutic resistance (42) (Fig. 2). RNA modifications, including m6A, m5C and ac4C, have emerged as critical regulators of mRNA stability and translation. These modifications can affect the expression of immune-related genes, such as *PD-L1*, *STAT1* and *IRF7*, thereby modulating immune cell function

and the overall immune response within the TME (52). For example, m6A methylation of specific mRNA transcripts can enhance their stability and translation efficiency, leading to increased production of proteins involved in immune evasion and tumor promotion (53).

Long non-coding RNAs (lncRNAs) also serve a role in shaping the TME through epigenetic mechanisms (54). Hypoxia-induced lncRNA-HAL has been shown to promote stemness and therapeutic resistance by interacting with chromatin remodeling complexes (55). By altering the epigenetic landscape, lncRNA-HAL contributes to the maintenance of a favorable environment for tumor growth and resistance to treatment (56). Understanding the specific roles of these epigenetic modulators and their interactions within the TME is crucial for developing novel therapeutic strategies aimed at reversing epigenetic changes and enhancing treatment efficacy in lung cancer.

The intricate crosstalk within the TME, involving immune evasion, metabolic reprogramming and epigenetic modulation, creates a complex landscape of resistance mechanisms in lung cancer. By targeting key nodes in these networks, such as immune checkpoint regulation, hypoxia-driven pathways

and epigenetic modifiers, novel therapies can be developed to disrupt the supportive role of the TME in tumor progression. These approaches hold promise for enhancing the effectiveness of existing treatments and addressing the challenge of therapeutic resistance.

**Resistance to targeted therapy.** Resistance to targeted therapies, such as EGFR-tyrosine kinase inhibitors (TKIs), is a notable challenge in lung cancer treatment. One of the key mechanisms underlying this resistance is the activation of alternative signaling pathways. TAMs contribute to resistance against targeted therapies such as EGFR-TKIs by secreting hepatocyte growth factor, which activates the c-MET pathway and bypasses EGFR inhibition (57). Moreover, TAMs and CAFs collaboratively foster a fibrotic niche via ECM remodeling, which physically restricts drug access and activates alternative survival pathways (58,59).

Genetic alterations, including secondary EGFR mutations (such as T790M) and MET amplification, remain key drivers of acquired resistance (60). These changes are often facilitated by a pro-inflammatory TME, which promotes genomic instability and enriches for resistant clones (61).

**Resistance to ICB.** Immune checkpoint inhibitors (ICIs) have revolutionized the treatment landscape for lung cancer, but resistance to these therapies remains a key issue. Resistance to ICIs can be influenced by various factors within the TME (62). For example, the presence of immunosuppressive cells, such as MDSCs and Tregs, can inhibit the activation and function of cytotoxic T cells. These immunosuppressive cells can be recruited and activated by cytokines such as TGF- $\beta$  and IL-10, which are often upregulated in the TME. The dense infiltration of MDSCs and Tregs creates a suppressive milieu that limits the efficacy of ICB (63).

Moreover, physical barriers within the TME, such as a dense ECM and poor vascularization, can prevent immune cells from infiltrating the tumor (64). A recent study demonstrated that the ECM stiffness, mediated by collagen crosslinking and MMPs, can physically impede T-cell migration and reduce the delivery of ICIs to their targets. This structural barrier is further exacerbated by the presence of immunosuppressive cytokines, which collectively contribute to the resistance of tumors to immunotherapy (64).

The interplay between targeted therapeutic resistance and immune evasion is complex and can be influenced by the TME. Metabolic changes induced by targeted therapies can alter the TME and contribute to immune resistance (65). For example, hypoxia resulting from tumor growth can lead to the upregulation of PD-L1 and the recruitment of immunosuppressive cells. Additionally, the release of damage-associated molecular patterns from dying cancer cells during targeted therapy can activate innate immune responses that paradoxically promote immunosuppression.

#### 4. TME-driven therapeutic resistance in lung cancer

Comprehending TME-mediated resistance mechanisms is essential to devise new lung cancer therapies that restore drug sensitivity and prolong patient survival. Future research should focus on assessing the molecular and cellular interactions

within the TME and exploring combination therapies that target multiple resistance pathways simultaneously.

**Immune evasion and resistance mechanisms.** Previous studies have highlighted the role of immune evasion mechanisms in therapeutic resistance (Table I). Utsumi *et al* (66) demonstrated that AXL-mediated drug resistance in ALK-rearranged NSCLC was enhanced by growth-arrest specific protein 6 from macrophages and MMP11-positive fibroblasts, underscoring the importance of cellular interactions within the TME. Moreover, Peyraud *et al* (67) utilized spatially resolved transcriptomics to reveal determinants of primary resistance to immunotherapy in NSCLC with mature tertiary lymphoid structures, suggesting that the spatial organization of immune cells may impact therapy outcomes. However, Nishinakamura *et al* (68) showed that coactivation of innate immune suppressive cells induced acquired resistance against combined Toll-like receptor 7/8 agonist treatment and programmed cell death protein 1 (PD-1) blockade, further illustrating the dynamic nature of immune resistance mechanisms. Notably, large clinical trials, such as KEYNOTE-189, have validated the impact of TME features on immunotherapy response, reinforcing the clinical relevance of these mechanisms (69).

The involvement of specific T-cell subsets in lung cancer resistance mechanisms has garnered attention in previous research.  $\gamma\delta$  T cells, which are part of the innate-like T-cell population, have been shown to serve a dual role in the TME (70). Some studies have indicated that  $\gamma\delta$  T cells can mediate antitumor responses through the secretion of IFN- $\gamma$  and the killing of tumor cells (71,72). However, other research has suggested that  $\gamma\delta$  T cells may also contribute to immunosuppression by producing immunosuppressive cytokines, such as IL-10 and TGF- $\beta$ , in the TME, thereby promoting tumor progression and resistance to therapy (73). For example, Liu *et al* (28) demonstrated that the frequency and function of  $\gamma\delta$  T cells were altered in patients with lung cancer, and these cells may influence the efficacy of immunotherapy. Additionally, tissue-resident memory T cells (Trm) have been identified as key players in local immune responses. Trm cells persist in tissues long-term and can provide immediate protection against tumor recurrence (74). However, in the context of chronic inflammation and an immunosuppressive TME, Trm cells may lose their function or even promote tumor growth. It has been shown that the expression of checkpoint molecules, such as PD-1 and LAG-3, on Trm cells can limit their antitumor activity, contributing to therapeutic resistance (75).

In addition to T-cell subsets, other immune cells such as innate lymphoid cells (ILCs) have been implicated in shaping the TME and influencing therapeutic outcomes. ILCs, including ILC1s, ILC2s and ILC3s, can regulate tumor inflammation and immune responses through the secretion of cytokines. For example, ILC3s have been reported to promote tumor progression by secreting IL-22, which can enhance tumor cell survival and resistance to therapy (76). Furthermore, the interaction between ILCs and other immune cells, such as macrophages and dendritic cells, can modulate the overall immune response in the TME, affecting the efficacy of immunotherapy (77).

Table I. Studies on the TME driving drug resistance in lung cancer.

First author, year	Treatment measures	Study type	Model	Resistance mechanisms	(Refs.)
Utsumi, 2025	AXL inhibition + GAS6/MMP11 blockade	Preclinical	ALK-rearranged NSCLC cell lines	Macrophage-derived GAS6 and fibroblast MMP11 activated AXL to bypass ALK inhibition	(66)
Peyraud, 2025	Spatially resolved transcriptomics	Clinical	NSCLC with tertiary lymphoid structures	Spatial exclusion of CD8 <sup>+</sup> T cells by stromal barriers and immunosuppressive cytokine gradients	(67)
Nishinakamura, 2025	Toll-like receptor agonist + PD-1 blockade	Preclinical	Syngeneic murine models	MDSC recruitment via CCL2/CCR2 axis and Treg activation through TGF- $\beta$ /IL-10 signaling	(68)
Ebid, 2025	Cisplatin + fibroblast crosstalk	<i>In vitro</i>	NSCLC cell lines + fibroblast co-culture	CAF-secreted IL-6 activated STAT3 to upregulate anti-apoptotic BCL-2 family proteins	(78)
Zhang, 2024	LDHA-targeted inhibition	Pan-cancer analysis	NSCLC clinical datasets	Lactate-driven acidosis induced PD-L1 upregulation and impaired T-cell cytotoxicity	(79)
Wang, 2024	POSTN CAF/ACKR1 EC interaction	Single-cell RNA-sequencing	TKI-resistant NSCLC xenografts	CAF-derived POSTN activated endothelial ACKR1 to recruit immunosuppressive neutrophils	(80)
Wang, 2024	SMARCA4 mutation analysis	Preclinical	NSCLC organoids	Chromatin remodeling defects reduced neoantigen presentation and CD8 <sup>+</sup> T-cell infiltration	(81)
Huang, 2024	EGFR-TKI + TGF- $\beta$ blockade	<i>In vivo</i>	EGFR-mutant PDX models	ERK1/2-p90RSK axis enhanced TGF- $\beta$ secretion, promoting T-cell exhaustion and Treg expansion	(82)
Kobayashi, 2024	Bevacizumab + miR-200c delivery	Organoid models	EGFR-mutant NSCLC organoids	EMT-mediated VEGF-independent angiogenesis and ECM remodeling via ZEB1/MMP9 activation	(83)
Tan, 2024	Lung-on-a-chip drug screening	Multi-cellular model	EGFR-TKI-resistant NSCLC	Fibroblast-mediated paracrine HGF/c-MET signaling drove bypass survival pathways	(84)
Pan, 2024	Disulfidoptosis gene targeting	Radio-genomics	Lung adenocarcinoma cohorts	Cysteine metabolism rewiring protected against radiation-induced ferroptosis	(85)
Han, 2024	Osimertinib + anti-angiogenic therapy	Phase II	Osimertinib-resistant NSCLC	VEGFR2/PDGFR $\beta$ crosstalk induced CAF activation and hyaluronan-rich ECM deposition	(86)
Shen, 2023	T1-mapping MRI nanoprobe	Diagnostic study	Patients with multidrug-resistant NSCLC	Hypoxia-induced collagen crosslinking reduced drug permeability and enhanced efflux pumps	(87)
Lu, 2023	STAT3/CD47-SIRP $\alpha$ axis inhibition	Preclinical	EGFR-TKI-resistant PDX models	TAM phagocytosis evasion via CD47 upregulation and STAT3-driven immunosuppressive niche	(88)

ACKR1, atypical chemokine receptor 1; CAF, cancer-associated fibroblast; CCL, C-C motif chemokine ligand; CCR, C-C motif chemokine receptor; EC, endothelial cell; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; GAS6, growth-arrest specific protein 6; HGF, hepatocyte growth factor; ICIs, immune checkpoint inhibitors; IL, interleukin; LDHA, lactate dehydrogenase A; MDSC, myeloid-derived suppressor cell; miR, microRNA; MMP, matrix metalloproteinase; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDX, patient-derived xenograft; PDGFR $\beta$ , platelet-derived growth factor receptor; POSTN, periostin; SIRP $\alpha$ , signal regulatory protein  $\alpha$ ; TAM, tumor-associated macrophage; TME, tumor microenvironment; TGF- $\beta$ , transforming growth factor- $\beta$ ; TKI, tyrosine kinase inhibitor; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2; ZEB1, zinc finger E-box binding homeobox 1.

**Fibroblast-induced resistance and metabolic reprogramming.** Additionally, paracrine signaling mechanisms between tumor cells and CAFs can synergize with the TME to drive resistance (Table I). Ebid *et al* (78) investigated the cross-talk signaling between NSCLC cell lines and fibroblasts, demonstrating that this interaction can attenuate the cytotoxic effect of cisplatin. This previous study highlighted the role of CAFs in mediating chemoresistance. Additionally, Zhang *et al* (79) identified lactate dehydrogenase A as a novel predictor for immunotherapy resistance, linking metabolic reprogramming within the TME to therapy outcomes. Wang *et al* (80) conducted single-cell transcriptomics analysis and revealed an immunosuppressive network between periostin (POSTN) CAFs and atypical chemokine receptor 1 (ACKR1) endothelial cells (ECs) in TKI-resistant lung cancer, providing insights into the cellular and molecular mechanisms underlying resistance to targeted therapies.

**Genetic alterations and resistance.** Additionally, genetic alterations within tumor cells can synergize with the TME to drive resistance (Table I). Wang *et al* (81) showed that SMARCA4 mutations induced tumor cell-intrinsic defects and resistance to immunotherapy, suggesting that genetic alterations within tumor cells may synergize with the TME to drive resistance. Huang *et al* (82) demonstrated that EGFR mutations can induce suppression of CD8<sup>+</sup> T cells and anti-PD-1 resistance via the ERK1/2-p90RSK-TGF- $\beta$  axis, linking genetic alterations to immune evasion mechanisms. Kobayashi *et al* (83) explored the impact of bevacizumab and microRNA (miR)-200c on epithelial-mesenchymal transition (EMT) and EGFR-TKI resistance in EGFR-mutant lung cancer organoids, suggesting that targeting EMT-related pathways may offer a promising strategy to overcome resistance.

**Multicellular models and combination therapies.** Moreover, advanced multicellular models and combination therapies are being explored to better understand and overcome TME-driven resistance (Table I). Tan *et al* (84) evaluated drug resistance for EGFR-TKIs in lung cancer using a multicellular lung-on-a-chip model, allowing for a more accurate simulation of the TME and providing valuable data on resistance mechanisms. Pan *et al* (85) investigated the role of disulfidptosis-related genes in radiotherapy resistance of lung adenocarcinoma, emphasizing the importance of understanding TME-driven resistance across different therapeutic modalities. Han *et al* (86) showed that osimertinib in combination with anti-angiogenesis therapy may be a promising option for osimertinib-resistant NSCLC, highlighting the potential of combination therapies in overcoming resistance mediated by the TME.

**Nanotechnology and resistance management.** Finally, nanotechnology offers innovative approaches to monitor and manage resistance within the TME (Table I). Shen *et al* (87) developed an adaptable nanoprobe integrated with quantitative T1-mapping MRI for accurate differential diagnosis of multidrug-resistant lung cancer, offering a novel option for monitoring and managing resistance within the TME. Lu *et al* (88) showed that reprogramming of TAMs via the STAT3/CD47-signal regulatory protein  $\alpha$  axis promoted acquired resistance to EGFR-TKIs in lung cancer, emphasizing the role of immune cell reprogramming in resistance.

## 5. Challenges and future directions

The heterogeneity of the TME presents notable challenges for the development of effective biomarkers for lung cancer. Spatial transcriptomics has emerged as a powerful tool for mapping immune-stromal interactions among different lung cancer subtypes (89). This technology allows for the simultaneous analysis of multiple cell types and their spatial configurations, providing insights into how immune cells, such as CD8<sup>+</sup> T cells and TAMs, interact with stromal components including CAFs and ECM proteins (90). Studies have shown that the spatial distribution of immune cells within the TME can influence therapeutic responses, with immune-excluded or immune-desert tumors exhibiting poor responses to immunotherapy (90,91). By leveraging spatial transcriptomics, researchers can better characterize the TME landscape and identify key biomarkers that predict treatment outcomes (91). This approach may not only enhance the understanding of TME heterogeneity but also aid in the development of personalized therapeutic strategies.

The integration of single-cell sequencing and artificial intelligence (AI) offers promising options for developing personalized TME-targeted therapies (92). However, translation into clinical practice requires validation through large-scale trials, as exemplified by the ongoing efforts in biomarker-driven studies. Single-cell RNA sequencing (scRNA-seq) has revolutionized the understanding of cellular heterogeneity within the TME, revealing distinct subpopulations of immune cells and their functional states (92). AI algorithms can analyze vast datasets generated from scRNA-seq to predict therapeutic vulnerabilities and optimize treatment combinations. For example, AI models can identify specific immune cell subsets or signaling pathways that are critical for tumor progression and resistance, enabling the design of targeted therapies that disrupt these interactions (93). This approach has shown potential in improving the efficacy of immunotherapy and overcoming resistance in patients with lung cancer (93). However, challenges remain in translating these findings into clinical practice, including the need for standardized protocols and the integration of multiomics data to capture the full complexity of the TME.

Translating TME-targeted therapies into clinical practice faces several barriers, particularly related to off-target effects and delivery systems (19,94,95). TME-modulating agents, such as ICIs and anti-angiogenic drugs, often exhibit off-target effects that can limit their therapeutic efficacy and cause adverse events (96). For example, the secretion of FGL1 by hepatocytes and tumor cells can blunt the efficacy of anti-PD-1 immunotherapy, highlighting the need for strategies to enhance treatment specificity (97). Additionally, optimizing delivery systems to ensure targeted drug delivery and minimize systemic toxicity remains a critical challenge. Nanoparticle-based drug delivery systems and targeted conjugates are being explored as potential solutions to overcome these barriers (98). These approaches aim to enhance the precision of TME-targeted therapies, ensuring that drugs reach their intended targets while minimizing off-target effects. Further research is needed to refine these technologies and evaluate their clinical feasibility in patients with lung cancer.

The complexity of TME heterogeneity poses notable hurdles in developing effective therapeutic strategies. The dynamic nature of the TME, with its diverse cell types and signaling pathways, makes it difficult to identify consistent biomarkers for patient stratification and treatment monitoring (99). For example, the coexistence of immunosuppressive and immunostimulatory signals within the TME can lead to variable responses to immunotherapy, complicating the prediction of treatment outcomes. Recent studies have highlighted the need for a deeper understanding of TME plasticity and the identification of stable biomarkers that can reliably predict therapeutic responses across different patient populations (9,100).

Another critical challenge lies in the technical limitations of advanced imaging and sequencing technologies. While spatial transcriptomics and single-cell sequencing have markedly advanced the understanding of TME heterogeneity, these techniques require highly specialized equipment and expertise, limiting their widespread adoption in clinical settings. Furthermore, the integration of multiomics data remains a complex task, as it necessitates sophisticated bioinformatics tools and standardized protocols to ensure data comparability and reproducibility.

In addition, addressing the challenges posed by TME heterogeneity and developing personalized TME-targeted therapies requires a multidisciplinary approach that integrates advanced technologies, including spatial transcriptomics, single-cell sequencing and AI. Overcoming clinical translation barriers will necessitate innovative strategies to enhance drug specificity and delivery. By addressing these challenges, more effective and personalized treatments may be developed for patients with lung cancer.

## 6. Therapeutic strategies and clinical application of the TME

Therapeutic strategies targeting the TME offer innovative approaches to overcome resistance and improve outcomes in lung cancer treatment (100). By modulating the immune microenvironment (Table II) and targeting metabolic and epigenetic pathways (Table III), researchers and clinicians are developing more effective and personalized treatment regimens. These strategies hold the promise of enhancing the efficacy of existing therapies and addressing the challenges posed by the dynamic and heterogeneous nature of the TME.

### *Immune microenvironment modulation*

**ICIs.** ICIs have revolutionized the treatment landscape of NSCLC by targeting key pathways such as PD-1, PD-L1 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) (101). Large clinical trials, including CHECKMATE-227 and KEYNOTE-024, have established the efficacy of ICIs in improving overall survival, underscoring their clinical importance (102,103). These therapies aim to enhance the antitumor immune response by blocking inhibitory signals that suppress T-cell activity within the TME. PD-1 and PD-L1 inhibitors are the most extensively studied ICIs in NSCLC. Forde *et al* (104) demonstrated the potential of neoadjuvant PD-1 blockade (pembrolizumab) in resectable lung cancer, showing notable tumor regression and increased major histological response rates. In addition, grade  $\geq 3$  adverse events were reported in

<10% of patients, with the most common being fatigue and elevated transaminases. Similarly, Niemeijer *et al* (105) utilized PET imaging to identify PD-1 and PD-L1 expression patterns in patients with NSCLC, providing insights into the spatial distribution of these targets within the TME. However, discrepancies in response rates across studies highlight the need for biomarker-guided patient selection. Zhang *et al* (106) compared the efficacy of anti-PD-1 and anti-PD-L1 therapies in combination with chemotherapy for advanced squamous NSCLC, concluding that both approaches were effective but with varying toxicity profiles. This finding underscores the importance of optimizing treatment combinations based on tumor subtype and patient-specific factors.

Combining ICIs with other therapies, such as radiotherapy or anti-angiogenic agents, has shown promise in enhancing therapeutic efficacy. Nivolumab plus radiotherapy has been reported to yield an ORR of 45%, with grade  $\geq 3$  toxicities in 18% of patients (primarily radiation pneumonitis and lymphopenia) (107). By contrast, low-dose apatinib combined with PD-1 blockade resulted in grade  $\geq 3$  adverse events in 15% of patients, mainly hypertension and hand-foot syndrome (108). These data facilitate comparative risk-benefit assessment across TME-targeted strategies.

Targeting multiple immune checkpoints, such as PD-1 and CTLA-4, has emerged as a strategy to amplify immune responses; however, this approach is often limited by substantial toxicity. Leigh *et al* (109) evaluated the combination of durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA-4) in patients with anti-PD-1/PD-L1-resistant NSCLC, showing only modest activity (ORR: 9%) but grade 3-4 toxicities in 35% of patients. Similarly, the CHECKMATE-227 trial, while demonstrating survival benefit, reported treatment-related adverse events in 76% of patients receiving nivolumab plus ipilimumab, with 33% experiencing grade 3-4 events (103). These findings highlight the challenging risk-benefit balance of dual checkpoint blockade, particularly in heavily pretreated patients, and underscore the need for better patient stratification and toxicity management strategies.

Previous studies have explored innovative combinations, such as personalized neoantigen vaccines. Ott *et al* (110) reported promising results with a neoantigen vaccine combined with anti-PD-1 therapy in patients with advanced melanoma and NSCLC. Similarly, Awad *et al* (111) demonstrated the feasibility of integrating neoantigen vaccines with chemotherapy and anti-PD-1 therapy in non-squamous NSCLC. These approaches leverage tumor antigens to enhance immune recognition, potentially overcoming resistance mechanisms within the TME.

**Immune cells.** Immune cells within the TME serve a critical role in modulating tumor progression and therapeutic resistance in lung cancer. This section focuses on the therapeutic strategies and clinical applications of targeting specific immune cell populations, such as TAMs, tumor-infiltrating lymphocytes (TILs) and chimeric antigen receptor T (CAR-T) cells.

Natural product-based interventions, such as herbal extracts, have shown immunomodulatory potential in preclinical models. Li *et al* (112) demonstrated that the Fuzheng Sanjie recipe could reprogram TAMs and reduce tumor growth in Lewis lung cancer mice. Similarly, Gao *et al* (113) reported

Table II. Studies on immune microenvironment-modulating therapeutic strategies in lung cancer treatment.

First author, year	Intervention/Target	Study type	Model	Clinical value/Treatment outcome	(Refs.)
Forde, 2018	Neoadjuvant PD-1 blockade	Phase II trial	Resectable NSCLC	45% major pathological response; enhanced T-cell clonality and reduced immunosuppressive cells	(104)
Niemeijer, 2018	PD-1/PD-L1 PET imaging	Observational	Advanced NSCLC	Identified spatial heterogeneity of PD-1/PD-L1; associated with ICI response	(105)
Zhang, 2018	Anti-PD-1 vs. anti-PD-L1 + chemo	Retrospective	Squamous NSCLC	Comparable efficacy (ORR: 40-45%); higher pneumonitis risk with anti-PD-L1	(106)
Bozorgmehr, 2019	Nivolumab + radiotherapy	Phase II trial	Advanced NSCLC	Synergistic effect: ORR 45 vs. 29% (monotherapy); increased CD8 <sup>+</sup> T-cell infiltration	(107)
Zhao, 2019	Apatinib + PD-1 blockade	Phase Ib/II	NSCLC	Optimized TME via VEGF inhibition; improved PFS (7.1 vs. 4.2 months)	(108)
Leighl, 2021	Durvalumab + tremelimumab	Phase II trial	PD-1-resistant NSCLC	Modest activity (ORR: 9%); grade 3-4 toxicity in 35% of patients	(109)
Ott, 2020	Neoantigen vaccine + anti-PD-1	Phase Ib trial	Advanced NSCLC	Enhanced tumor-specific T-cell responses; ORR 50% in NSCLC cohort	(110)
Awad, 2022	NEO-PV-01 vaccine + chemotherapy/ICI	Phase I/II	Non-squamous NSCLC	Feasibility confirmed; 2-year OS rate 75% in responders	(111)
Li, 2015	TAM reprogramming (Fuzheng Sanjie)	Preclinical	Lewis lung cancer	Reduced tumor growth via M2-to-M1 polarization; improved CD8 <sup>+</sup> T-cell infiltration	(112)
Li, 2018	Hydroxychloroquine + chemotherapy	Preclinical	NSCLC	Enhanced chemosensitivity; reduced M2-TAMs and increased M1-like macrophages	(113)
Zhang, 2021	EGFR-specific CAR-T cells	Phase I trial	Relapsed NSCLC	Manageable safety; median PFS 4.1 months; 30% disease control rate	(121)

CAR-T, chimeric antigen receptor T; ICI, immune checkpoint inhibitor; LTB4, leukotriene B4; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAMs, tumor-associated macrophages; VEGF, vascular endothelial growth factor.

Table III. Studies on therapeutic strategy that target tumor microenvironment components in lung cancer treatment.

First author, year	Intervention/Target	Study type	Model	Clinical value/Treatment outcome	(Refs.)
Li, 2020	FUT8 inhibition in CAFs	Preclinical	NSCLC	Reduced EGFR core fucosylation; suppressed CAF-mediated tumor proliferation	(128)
Yang, 2020	CAF-derived exosomal miR-210	Preclinical	NSCLC	Promoted metastasis via the PTEN/PI3K/AKT pathway; reversed by miR-210 inhibition	(129)
Chen, 2024	CAF-secreted SERPINE2	Preclinical	NSCLC	Enhanced tumor resistance via exosomal transfer; SERPINE2 knockdown restored chemosensitivity	(130)
Sun, 2024	PRRX1-OLR1 axis in CAFs	Preclinical	NSCLC	Promoted immune suppression; dual targeting reduced MDSC infiltration	(131)
Wang, 2013	Integrin $\beta 1$ inhibition	Preclinical	NSCLC	Suppressed metastasis via ERK1/2 pathway inhibition; reduced ECM adhesion	(133)
Wang, 2013	miR-29c targeting ECM	Preclinical	NSCLC	Inhibited integrin $\beta 1$ /MMP2; reduced lung metastasis in xenografts	(134)
Shie, 2023	Acidosis-induced ECM remodeling	Preclinical	NSCLC	Promoted vasculogenic mimicry; acidosis blockade suppressed metastatic colonization	(138)
Abdel-Hafez, 2024	Inhalable ECM-modulating nanoparticles	Preclinical	NSCLC	Enhanced drug delivery via ECM degradation; improved tumor penetration	(140)
Cai, 2024	Apatinib + chemotherapy/ICI	Phase II trial	KRAS-mutant NSCLC	Improved PFS (8.2 vs. 5.1 months); tumor cavitation linked to anti-angiogenic therapy response	(145)
Zhang, 2024	Anti-angiogenic therapy + RT/ICI	Retrospective	NSCLC brain metastasis	Intracranial ORR 45%; median OS 14.7 months	(146)

FUT8,  $\alpha 1,6$ -fucosyltransferase; CAFs, cancer-associated fibroblasts; ECM, extracellular matrix; ICI, immune checkpoint inhibitor; MDSC, myeloid-derived suppressor cell; miR, microRNA; MMP2, matrix metalloproteinase 2; NSCLC, non-small-cell lung cancer; OLR1, oxLDL receptor 1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRRX1, paired related homeobox 1; RT, radiotherapy.

that ginseng extract altered the behavior of A549 lung cancer cells and TAMs in co-culture systems. However, the translational potential of these natural products is limited by several factors, including undefined active components, batch-to-batch variability, poor bioavailability and a lack of rigorous clinical trial data (114). While these studies provide valuable insights into TME modulation, their clinical applicability remains uncertain without standardized formulations and validation in human trials. Li *et al* (115) showed that hydroxychloroquine could enhance chemosensitivity and promote the transition of M2-TAMs to M1-like macrophages, thereby suppressing tumor growth in NSCLC. However, discrepancies exist in the effectiveness of TAM-targeted therapies, as some studies highlight the challenges of achieving consistent reprogramming of TAMs across different tumor models (47,115).

TILs are a diverse population of immune cells that infiltrate the tumor site and serve a pivotal role in antitumor immune responses (116). CD8<sup>+</sup> T cells, a major subset of TILs, are particularly important for their ability to recognize and kill tumor cells; however, the function of TILs is often suppressed within the immunosuppressive TME (116). Mechanistically, TILs can be inhibited through several pathways. For example, the upregulation of immune checkpoint molecules such as PD-1 and PD-L1 on TILs can lead to T-cell exhaustion, reducing their cytotoxic activity against tumor cells (117). Furthermore, Tregs and MDSCs within the TME can secrete immunosuppressive cytokines, including IL-10 and TGF- $\beta$ , which further suppress the activation and proliferation of TILs (118). Additionally, the metabolic environment of the TME, characterized by hypoxia and high levels of adenosine, can impair TIL function by promoting the expression of inhibitory receptors and reducing the availability of essential nutrients (119).

The spatial distribution and density of TILs within tumors can predict response to immunotherapy. For example, tumors with a high density of CD8<sup>+</sup> TILs in the tumor core tend to respond better to ICIs compared with those with a peripheral distribution of TILs (119). This highlights the importance of understanding not only the presence but also the localization and functional state of TILs in the TME. Sumitomo *et al* (120) investigated the association between PD-L1/PD-L2 expression and TILs in NSCLC, revealing that M2-TAMs and TILs interact to create an immunosuppressive TME. This previous study underscored the importance of targeting both TAMs and TILs to enhance therapeutic outcomes. Furthermore, CAR-T cells have shown promise in hematological malignancies but face notable challenges in solid tumors such as lung cancer. Zhang *et al* (121) performed a Phase I trial of EGFR-specific CAR-T cells in relapsed/refractory NSCLC, demonstrating manageable safety and preliminary efficacy. However, the therapeutic potential of CAR-T in solid tumors is limited by several factors, including on-target/off-tumor toxicity, inadequate tumor infiltration and the immunosuppressive TME (122). Additionally, manufacturing complexity, high costs and the risk of cytokine release syndrome further constrain their widespread clinical application (123). Current research focuses on improving CAR-T design to overcome these barriers, but their role in lung cancer remains investigational.

Emerging evidence has suggested that targeting other immune cells, such as MDSCs, may also enhance therapeutic efficacy. For example, Kong *et al* (124) showed that the Modified Bushen Yiqi formula reduced the chemotactic recruitment of MDSCs in Lewis lung cancer-bearing mice, thereby enhancing antitumor immunity.

#### *Therapies that target TME components*

**CAFs.** CAFs are a critical component of the TME and serve a multifaceted role in promoting tumor progression and therapeutic resistance in lung cancer (125). CAFs contribute to tumor progression through various mechanisms, including promoting cancer cell proliferation, enhancing metastasis and inducing therapeutic resistance (126). Li *et al* (127) demonstrated that  $\alpha$ 1,6-fucosyltransferase regulates the cancer-promoting capacity of CAFs by modifying EGFR core fucosylation in NSCLC. Similarly, Yang *et al* (128) showed that exosomes derived from CAFs containing miR-210 promoted NSCLC migration and invasion through the PTEN/PI3K/AKT pathway.

CAFs are also implicated in therapeutic resistance. Chen *et al* (129) reported that CAFs can transfer SERPINE2 via exosomes, enhancing tumor progression and resistance to treatment in lung cancer. Additionally, Sun *et al* (130) highlighted the role of the paired related homeobox 1-oxLDL receptor 1 axis in supporting CAFs-mediated immune suppression and tumor progression, suggesting potential therapeutic targets.

CAFs influence tumor metabolism and signaling pathways to promote resistance. Wang *et al* (80) revealed an immunosuppressive network between POSTN CAFs and ACKR1 ECs in TKI-resistant lung cancer, emphasizing the role of CAFs in mediating resistance to targeted therapies. Furthermore, studies have shown that CAFs promote glycolysis in NSCLC cells, enhancing DNA damage repair and radioresistance (126,128,129).

**ECM.** The ECM is a critical component of the TME, and serves an important role in lung cancer progression and therapeutic resistance. Targeting the ECM offers promising therapeutic strategies to enhance treatment outcomes. Integrins and MMPs are key mediators of cancer cell adhesion and invasion. Wang *et al* (131) demonstrated that shikonin attenuated lung cancer cell adhesion to the ECM and metastasis by inhibiting integrin  $\beta$ 1 expression and the ERK1/2 signaling pathway. Similarly, Wang *et al* (132) showed that miR-29c suppressed lung cancer cell adhesion to the ECM and metastasis by targeting integrin  $\beta$ 1 and MMP2. These studies highlight the potential of targeting integrins and MMPs to reduce metastasis and improve patient outcomes.

ECM degradation is a critical step in tumor invasion and metastasis. Bi *et al* (133) reported that PRDM14 could promote the migration of human NSCLC cells through ECM degradation *in vitro*. Additionally, Zhang *et al* (134) demonstrated that protein arginine methyltransferase 1 small hairpin RNA inhibited NSCLC cell migration by suppressing EMT, ECM degradation, and Src phosphorylation. These findings underscore the importance of targeting ECM degradation pathways to prevent tumor progression.

ECM remodeling contributes to therapeutic resistance in lung cancer. Wang *et al* (135) revealed that stromal ECM is a microenvironmental cue that can promote resistance to

EGFR-TKIs in lung cancer cells. Furthermore, Shie *et al* (136) showed that acidosis promoted the metastatic colonization of lung cancer via remodeling of the ECM and vasculogenic mimicry. These studies emphasize the role of ECM remodeling in mediating therapeutic resistance and the need for strategies to modulate ECM composition.

Previous studies have explored innovative approaches to target the ECM. Peláez *et al* (137) demonstrated that sterculic acid can alter the expression of adhesion molecules and ECM compounds to regulate the migration of lung cancer cells. Additionally, Abdel-Hafez *et al* (138) investigated inhalable nano-structured microparticles for ECM modulation as a potential delivery system for lung cancer. These approaches offer promising avenues to enhance therapeutic efficacy by modulating the ECM.

**Immune cells.** Emerging evidence has underscored the therapeutic value of targeting immune cell-TME crosstalk. For example, beyond herbal compounds, previous studies have highlighted that modulation of TAM polarity via STAT3 inhibition or CD47-SIRP $\alpha$  axis blockade can resensitize EGFR-TKI-resistant tumors by restoring phagocytic clearance and enhancing T-cell infiltration (88,115). Furthermore, the interaction between immune cells and other TME components, such as CAFs and ECM, can modulate the overall immune response, affecting the efficacy of immunotherapy.

**Anti-angiogenic therapy.** Anti-angiogenic therapy has emerged as a promising strategy in the treatment of lung cancer, targeting the VEGF pathway and other angiogenic factors to normalize tumor blood vessels, alleviate hypoxia and enhance drug delivery (139). The VEGF pathway is a critical target for anti-angiogenic therapy (140). The phase III IMpower150 trial demonstrated that combining atezolizumab, bevacizumab and chemotherapy markedly improved survival in non-squamous NSCLC, providing robust clinical validation (141). Similarly, Qiang *et al* (142) demonstrated the efficacy of first-line chemotherapy combined with immunotherapy or anti-angiogenic therapy in advanced KRAS-mutant NSCLC, showing improved progression-free survival. Similarly, Cai *et al* (143) reported tumor cavitation in patients with NSCLC receiving anti-angiogenic therapy with apatinib, highlighting the potential of this approach in specific patient populations.

Combining anti-angiogenic therapy with other modalities has shown promise in enhancing therapeutic efficacy. Zhang *et al* (146) evaluated the combination of anti-angiogenic therapy, radiotherapy and PD-1 inhibitors in patients with driver gene-negative NSCLC brain metastases, demonstrating improved outcomes. Additionally, Song *et al* (145) reported the efficacy of PD-1 inhibitors combined with anti-angiogenic therapy in NSCLC with brain metastases, further supporting the benefits of multi-modal approaches.

Despite initial success, resistance to anti-angiogenic therapy remains a challenge. Studies have identified mechanisms, such as upregulation of compensatory pro-angiogenic factors (for example, basic FGF, platelet-derived growth factor and VEGF-C) and recruitment of bone marrow-derived endothelial progenitor cells as key contributors to resistance (146,147). Furthermore, tumor heterogeneity and the TME serve notable roles in mediating resistance, necessitating strategies to overcome these limitations.

**Novel therapeutic approaches: Antibody-drug conjugates (ADCs) and bispecific antibodies.** In addition to the aforementioned therapies, novel approaches such as ADCs and bispecific antibodies are emerging as promising strategies in the treatment of lung cancer. ADCs are engineered molecules that combine the specificity of antibodies with the potency of cytotoxic drugs. They selectively deliver chemotherapy agents to cancer cells expressing specific antigens, thereby minimizing off-target effects (141). For example, enfortumab vedotin, an ADC targeting Nectin-4, has shown notable efficacy in patients with advanced NSCLC. In a phase I/II trial, an ORR of 41% and a median duration of response of 10.5 months was demonstrated (141). Another ADC, sacituzumab govitecan, which targets Trop-2, has also exhibited promising results in early-phase trials for NSCLC (6). These ADCs represent a novel frontier in personalized lung cancer therapy by leveraging antigen specificity to enhance treatment efficacy and reduce systemic toxicity. Bispecific antibodies, which can simultaneously bind to two different antigens, offer unique advantages in cancer immunotherapy. They can redirect immune cells to tumor cells or modulate immune checkpoints more effectively. For example, bispecific antibodies targeting PD-L1 and TGF- $\beta$  have been developed to overcome immunosuppression in the TME (148). Preclinical studies have shown that these bispecific antibodies can enhance T-cell activation and tumor cell killing (148,149). Additionally, bispecific T-cell engagers are being explored to redirect T cells to cancer cells expressing specific antigens, such as EGFR or HER2, which are frequently upregulated in lung cancer (149,150). Early clinical trials have indicated that bispecific antibodies can achieve tumor regression in a subset of patients with refractory NSCLC, highlighting their potential as next-generation immunotherapies (148-150).

These emerging therapies, including ADCs and bispecific antibodies, are expected to markedly impact the treatment landscape of lung cancer by addressing the limitations of current targeted therapies and immunotherapies. Further clinical research is warranted to optimize their application and combination strategies in the context of the TME.

## 7. Conclusion

In conclusion, the TME drives drug resistance in lung cancer through immune evasion, metabolic reprogramming and epigenetic modulation. While targeting TME components shows promise, several challenges remain. Immune-based strategies, such as dual checkpoint blockade and CAR-T therapy, are limited by toxicity and poor efficacy in solid tumors. Natural product interventions face translational hurdles due to undefined mechanisms and a lack of clinical validation. Emerging technologies, such as spatial transcriptomics and nanodrug delivery, offer potential solutions but require further optimization for clinical application. Future research should prioritize not only multiomics integration but also rigorous preclinical models and well-designed clinical trials to distinguish promising research possibilities from preliminary findings.

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**Authors' contributions**

LiL contributed to the literature review on the heterogeneity of the lung cancer microenvironment. LY wrote the part about the role of the tumor microenvironment in treatment resistance. HL and TS were involved in the literature search and analysis, as well as in the writing of the manuscript. LihL, as the corresponding author, oversaw the entire review process, provided critical guidance and revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

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**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Wéber A, Morgan E, Vignat J, Laversanne M, Pizzato M, Runggay H, Singh D, Nagy P, Kenessey I, Soerjomataram I and Bray F: Lung cancer mortality in the wake of the changing smoking epidemic: A descriptive study of the global burden in 2020 and 2040. *BMJ Open* 13: e065303, 2023.
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 74: 229-263, 2024.
3. Oxnard GR, Arcila ME, Sima CS, Riely GJ, Chmielecki J, Kris MG, Pao W, Ladanyi M and Miller VA: Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: Distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res* 17: 1616-1622, 2011.
4. Miyata H, Shigetoh H, Ikeya T, Ashizawa T, Iizuka A, Kikuchi Y, Maeda C, Kanematsu A, Yamashita K, Urakami K, *et al*: Localization of epidermal growth factor receptor-mutations using PNA: DNA probes in clinical specimens from patients with non-small cell lung cancer. *Sci Rep* 15: 11314, 2025.
5. Son B, Lee S, Youn H, Kim E, Kim W and Youn B: The role of tumor microenvironment in therapeutic resistance. *Oncotarget* 8: 3933-3945, 2017.
6. Yu H, Zhang W, Xu XR and Chen S: Drug resistance related genes in lung adenocarcinoma predict patient prognosis and influence the tumor microenvironment. *Sci Rep* 13: 9682, 2023.
7. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, Italiano A, Schuler M, Borghaei H, Barlesi F, *et al*: Sotorasib for lung cancers with KRAS p.G12C mutation. *N Engl J Med* 384: 2371-2381, 2021.

8. Said SS and Ibrahim WN: Cancer resistance to immunotherapy: Comprehensive insights with future perspectives. *Pharmaceutics* 15: 1143, 2023.
9. Glaviano A, Lau HS, Carter LM, Lee EHC, Lam HY, Okina E, Tan DJJ, Tan W, Ang HL, Carbone D, *et al*: Harnessing the tumor microenvironment: Targeted cancer therapies through modulation of epithelial-mesenchymal transition. *J Hematol Oncol* 18: 6, 2025.
10. Tian Y, Yang Y, He L, Yu X, Zhou H and Wang J: Exploring the tumor microenvironment of breast cancer to develop a prognostic model and predict immunotherapy responses. *Sci Rep* 15: 12569, 2025.
11. Tan Z, Xue H, Sun Y, Zhang C, Song Y and Qi Y: The role of tumor inflammatory microenvironment in lung cancer. *Front Pharmacol* 12: 688625, 2021.
12. Liu Y, Liang J, Zhang Y and Guo Q: Drug resistance and tumor immune microenvironment: An overview of current understandings (Review). *Int J Oncol* 65: 96, 2024.
13. Heydenreich B, Bellinghausen I, Lorenz S, Henmar H, Strand D, Würtzen PA and Saloga J: Reduced in vitro T-cell responses induced by glutaraldehyde-modified allergen extracts are caused mainly by retarded internalization of dendritic cells. *Immunology* 136: 208-217, 2012.
14. Mai Z, Lin Y, Lin P, Zhao X and Cui L: Modulating extracellular matrix stiffness: A strategic approach to boost cancer immunotherapy. *Cell Death Dis* 15: 307, 2024.
15. Chen K, Luo L, Li Y and Yang G: Reprogramming the immune microenvironment in lung cancer. *Volume* 16: 1684889, 2025.
16. Chandra R, Ehab J, Hauptmann E, Gunturu NS, Karalis JD, Kent DO, Heid CA, Reznik SI, Sarkaria IS, Huang H, *et al*: The current state of tumor Microenvironment-specific therapies for Non-small cell lung cancer. *Cancers (Basel)* 17: 1732, 2025.
17. He ZN, Zhang CY, Zhao YW, He SL, Li Y, Shi BL, Hu JQ, Qi RZ and Hua BJ: Regulation of T cells by myeloid-derived suppressor cells: Emerging immunosuppressor in lung cancer. *Discov Oncol* 14: 185, 2023.
18. Lim JU, Lee E, Lee SY, Cho HJ, Ahn DH, Hwang Y, Choi JY, Yeo CD, Park CK and Kim SJ: Current literature review on the tumor immune micro-environment, its heterogeneity and future perspectives in treatment of advanced non-small cell lung cancer. *Transl Lung Cancer Res* 12: 857-876, 2023.
19. Genova C, Dellepiane C, Carrega P, Sommariva S, Ferlazzo G, Pronzato P, Gangemi R, Filaci G, Coco S and Croce M: Therapeutic implications of tumor microenvironment in lung cancer: Focus on immune checkpoint blockade. *Front Immunol* 12: 799455, 2021.
20. Cao Q, Li C, Li Y, Kong X, Wang S and Ma J: Tumor microenvironment and drug resistance in lung adenocarcinoma: Molecular mechanisms, prognostic implications, and therapeutic strategies. *Discov Oncol* 16: 238, 2025.
21. Chu X, Tian Y and Lv C: Decoding the spatiotemporal heterogeneity of Tumor-associated macrophages. *Mol Cancer* 23: 150, 2024.
22. Mei S, Zhang H, Hirz T, Jeffries NE, Xu Y, Baryawno N, Wu S, Wu CL, Patnaik A, Saylor PJ, *et al*: Single-cell and spatial transcriptomics reveal a Tumor-associated macrophage subpopulation that mediates prostate cancer progression and metastasis. *Mol Cancer Res* 23: 653-665, 2025.
23. Ashrafi A, Akter Z, Modareszadeh P, Modareszadeh P, Berisha E, Alemi PS, Chacon Castro MDC, Deese AR and Zhang L: Current landscape of therapeutic resistance in lung cancer and promising strategies to overcome resistance. *Cancers (Basel)* 14: 4562, 2022.
24. Guo T and Xu J: Cancer-associated fibroblasts: A versatile mediator in tumor progression, metastasis, and targeted therapy. *Cancer Metastasis Rev* 43: 1095-1116, 2024.
25. Wu C, Gu J, Gu H, Zhang X, Zhang X and Ji R: The recent advances of cancer associated fibroblasts in cancer progression and therapy. *Front Oncol* 12: 1008843, 2022.
26. Papavassiliou KA, Sofianidi AA, Gogou VA and Papavassiliou AG: Drugging the tumor microenvironment epigenome for therapeutic interventions in NSCLC. *J Cancer* 16: 1832-1835, 2025.
27. Tong L, Jiménez-Cortegana C, Tay AHM, Wickström S, Galluzzi L and Lundqvist A: NK cells and solid tumors: Therapeutic potential and persisting obstacles. *Mol Cancer* 21: 206, 2022.
28. Liu J, Wu M, Yang Y, Wang Z, He S, Tian X and Wang H:  $\gamma\delta$  T cells and the PD-1/PD-L1 axis: A love-hate relationship in the tumor microenvironment. *J Transl Med* 22: 553, 2024.

29. Mancini A, Gentile MT, Pentimalli F, Cortellino S, Grieco M and Giordano A: Multiple aspects of matrix stiffness in cancer progression. *Front Oncol* 14: 1406644, 2024.
30. Henke E, Nandigama R and Ergün S: Extracellular matrix in the tumor microenvironment and its impact on cancer therapy. *Front Mol Biosci* 6: 160, 2019.
31. Marrugal Á, Ojeda L, Paz-Ares L, Molina-Pinelo S and Ferrer I: Proteomic-based approaches for the study of cytokines in lung cancer. *Dis Markers* 2016: 2138627, 2016.
32. Zhang A, Miao K, Sun H and Deng CX: Tumor heterogeneity reshapes the tumor microenvironment to influence drug resistance. *Int J Biol Sci* 18: 3019-3033, 2022.
33. Li X, Shang S, Wu M, Song Q and Chen D: Gut microbial metabolites in lung cancer development and immunotherapy: Novel insights into gut-lung axis. *Cancer Lett* 598: 217096, 2024.
34. Li J, Shi B, Ren X, Hu J, Li Y, He S, Zhang G, Maolan A, Sun T, Qi X, *et al.*: Lung-intestinal axis, Shuangshen granules attenuate lung metastasis by regulating the intestinal microbiota and related metabolites. *Phytomedicine* 132: 155831, 2024.
35. Ankudavicius V, Nikitina D, Lukosevicius R, Tilinde D, Salteniene V, Poskiene L, Miliauskas S, Skieceviciene J, Zemaitis M and Kupcinskas J: Detailed characterization of the Lung-gut microbiome axis reveals the link between PD-L1 and the microbiome in Non-Small-cell lung cancer patients. *Int J Mol Sci* 25: 2323, 2024.
36. Dong Q, Chen ES, Zhao C and Jin C: Host-Microbiome interaction in lung cancer. *Front Immunol* 12: 679829, 2021.
37. Hunt PJ, Andújar FN, Silverman DA and Amit M: Mini-review: Trophic interactions between cancer cells and primary afferent neurons. *Neurosci Lett* 746: 135658, 2021.
38. Hernandez S, Serrano AG and Solis Soto LM: The role of nerve fibers in the tumor Immune microenvironment of solid tumors. *Adv Biol (Weinh)* 6: 2200046, 2022.
39. Li X, Peng X, Yang S, Wei S, Fan Q, Liu J, Yang L and Li H: Targeting tumor innervation: Premises, promises, and challenges. *Cell Death Discov* 8: 131, 2022.
40. Yang Y, Ye WL, Zhang RN, He XS, Wang JR, Liu YX, Wang Y, Yang XM, Zhang YJ and Gan WJ: The role of TGF- $\beta$  signaling pathways in cancer and its potential as a therapeutic target. *Evid Based Complement Alternat Med* 2021: 6675208, 2021.
41. Jiang C, Zhang N, Hu X and Wang H: Tumor-associated exosomes promote lung cancer metastasis through multiple mechanisms. *Mol Cancer* 20: 117, 2021.
42. Yang J, Xu J, Wang W, Zhang B, Yu X and Shi S: Epigenetic regulation in the tumor microenvironment: Molecular mechanisms and therapeutic targets. *Signal Transduct Target Ther* 8: 210, 2023.
43. Yu W, Hua Y, Qiu H, Hao J, Zou K, Li Z, Hu S, Guo P, Chen M, Sui S, *et al.*: PD-L1 promotes tumor growth and progression by activating WIP and  $\beta$ -catenin signaling pathways and predicts poor prognosis in lung cancer. *Cell Death Dis* 11: 506, 2020.
44. Xiao K, Zhang S, Peng Q, Du Y, Yao X, Ng II and Tang H: PD-L1 protects tumor-associated dendritic cells from ferroptosis during immunogenic chemotherapy. *Cell Rep* 43: 114868, 2024.
45. Shi AP, Tang XY, Xiong YL, Zheng KF, Liu YJ, Shi XG, Lv Y, Jiang T, Ma N and Zhao JB: Immune checkpoint LAG3 and its ligand FGL1 in cancer. *Front Immunol* 12: 785091, 2021.
46. Villarroel-Espindola F, Yu X, Datar I, Mani N, Sanmamed M, Velcheti V, Syrigos K, Toki M, Zhao H, Chen L, *et al.*: Spatially resolved and quantitative analysis of VISTA/PD-1H as a novel immunotherapy target in human Non-small cell lung cancer. *Clin Cancer Res* 24: 1562-1573, 2018.
47. Wang S, Wang J, Chen Z, Luo J, Guo W, Sun L and Lin L: Targeting M2-like tumor-associated macrophages is a potential therapeutic approach to overcome antitumor drug resistance. *NPJ Precis Oncol* 8: 31, 2024.
48. Li Y, Zhao L and Li XF: Hypoxia and the tumor microenvironment. *Technol Cancer Res Treat* 20: 15330338211036304, 2021.
49. Zaarour RF, Azakir B, Hajam EY, Nawafleh H, Zeinelabdin NA, Engelsen AST, Thiery J, Jamora C and Chouaib S: Role of Hypoxia-mediated autophagy in tumor cell death and survival. *Cancers (Basel)* 13: 533, 2021.
50. Sasidharan Nair V, Saleh R, Toor SM, Cyprian FS and Elkord E: Metabolic reprogramming of T regulatory cells in the hypoxic tumor microenvironment. *Cancer Immunol Immunother* 70: 2103-2121, 2021.
51. Li X, Yan X, Wang Y, Kaur B, Han H and Yu J: The Notch signaling pathway: A potential target for cancer immunotherapy. *J Hematol Oncol* 16: 45, 2023.
52. Luo H, Liu L, Liu X, Xie Y, Huang X, Yang M, Shao C and Li D: Interleukin-33 (IL-33) promotes DNA damage-resistance in lung cancer. *Cell Death Dis* 16: 274, 2025.
53. Boo SH and Kim YK: The emerging role of RNA modifications in the regulation of mRNA stability. *Exp Mol Med* 52: 400-408, 2020.
54. Guo Y, Xie Y and Luo Y: The role of Long Non-coding RNAs in the tumor immune microenvironment. *Front Immunol* 13: 851004, 2022.
55. Jiang J, Lu Y, Zhang F, Huang J, Ren XL and Zhang R: The emerging roles of long noncoding RNAs as hallmarks of lung cancer. *Front Oncol* 11: 761582, 2021.
56. Entezari M, Ghanbarirad M, Taheriazam A, Sadrkhanloo M, Zabolian A, Goharrizi MASB, Hushmandi K, Aref AR, Ashrafzadeh M, Zarrabi A, *et al.*: Long non-coding RNAs and exosomal lncRNAs: Potential functions in lung cancer progression, drug resistance and tumor microenvironment remodeling. *Biomed Pharmacother* 150: 112963, 2022.
57. Tian Z, Cen L, Wei F, Dong J, Huang Y, Han Y, Wang Z, Deng J and Jiang Y: EGFR mutations in non-small cell lung cancer: Classification, characteristics and resistance to third-generation EGFR-tyrosine kinase inhibitors (Review). *Oncol Lett* 30: 375, 2025.
58. Parente P, Parcesepe P, Covelli C, Olivieri N, Remo A, Pancione M, Latiano TP, Graziano P, Maiello E and Giordano G: Crosstalk between the tumor microenvironment and immune system in pancreatic ductal adenocarcinoma: Potential targets for new therapeutic approaches. *Gastroenterol Res Pract* 2018: 7530619, 2018.
59. Reichel D, Tripathi M and Perez JM: Biological effects of nanoparticles on macrophage polarization in the tumor microenvironment. *Nanotheranostics* 3: 66-88, 2019.
60. Coelho MA, Strauss ME, Watterson A, Cooper S, Bhosle S, Illuzzi G, Karakoc E, Dinçer C, Vieira SF, Sharma M, *et al.*: Base editing screens define the genetic landscape of cancer drug resistance mechanisms. *Nature Genetics* 56: 2479-2492, 2024.
61. Wen Y, Zhu Y, Zhang C, Yang X, Gao Y, Li M, Yang H, Liu T and Tang H: Chronic inflammation, cancer development and immunotherapy. *Front Pharmacol* 13: 1040163, 2022.
62. Qian FF and Han BH: Mechanisms of resistance to immune checkpoint inhibitors and strategies to reverse drug resistance in lung cancer. *Chin Med J (Engl)* 133: 2444-2455, 2020.
63. Bagchi S, Yuan R and Engleman EG: Immune checkpoint inhibitors for the treatment of cancer: Clinical impact and mechanisms of response and resistance. *Annu Rev Pathol* 16: 223-249, 2021.
64. Zhang M and Zhang B: Extracellular matrix stiffness: Mechanisms in tumor progression and therapeutic potential in cancer. *Exp Hematol Oncol* 14: 54, 2025.
65. Benvenuto M and Focaccetti C: Tumor microenvironment: Cellular interaction and metabolic adaptations. *Int J Mol Sci* 25: 3642, 2024.
66. Utsumi T, Mizuta H, Seto Y, Uchibori K, Nishio M, Okamoto I and Katayama R: AXL-Mediated drug resistance in ALK-rearranged NSCLC enhanced by GAS6 from macrophages and MMP11 positive fibroblasts. *Cancer Sci* 116: 1034-1047, 2025.
67. Peyraud F, Guégan JP, Rey C, Lara O, Odin O, Del Castillo M, Vanhersecke L, Coindre JM, Clot E, Brunet M, *et al.*: Spatially resolved transcriptomics reveal the determinants of primary resistance to immunotherapy in NSCLC with mature tertiary lymphoid structures. *Cell Rep Med* 6: 101934, 2025.
68. Nishinakamura H, Shinya S, Irie T, Sakihama S, Naito T, Watanabe K, Sugiyama D, Tamiya M, Yoshida T, Hase T, *et al.*: Coactivation of innate immune suppressive cells induces acquired resistance against combined TLR agonism and PD-1 blockade. *Sci Transl Med* 17: adk3160, 2025.
69. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, *et al.*: Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 378: 2078-2092, 2018.
70. Cheng M and Hu S: Lung-resident  $\gamma\delta$  T cells and their roles in lung diseases. *Immunology* 51: 375-384, 2017.
71. Subhi-Issa N, Tovar Manzano D, Pereiro Rodriguez A, Sanchez Ramon S, Perez Segura P and Ocaña A:  $\gamma\delta$  T cells: Game changers in immune cell therapy for cancer. *Cancers (Basel)* 17: 1063, 2025.
72. Lv J, Liu Z, Ren X, Song S, Zhang Y and Wang Y:  $\gamma\delta$ T cells, a key subset of T cell for cancer immunotherapy. *Front Immunol* 16: 1562188, 2025.
73. Jin C, Lagoudas GK, Zhao C, Bullman S, Bhutkar A, Hu B, Ameh S, Sandel D, Liang XS, Mazzilli S, *et al.*: Commensal microbiota promote lung cancer development via  $\gamma\delta$  T cells. *Cell* 176: 998-1013.e16, 2019.

74. Dhodapkar MV and Dhodapkar KM: Tissue-resident memory-like T cells in tumor immunity: Clinical implications. *Semin Immunol* 49: 101415, 2020.
75. Hofmann M, Thimme R and Schamel WW: PD-1 and LAG-3: Synergistic fostering of T cell exhaustion. *Signal Transduct Target Ther* 9: 291, 2024.
76. Ducimetière L, Vermeer M and Tugues S: The interplay between innate lymphoid cells and the tumor microenvironment. *Front Immunol* 10: 2895, 2019.
77. Yuan X, Rasul F, Nashan B and Sun C: Innate lymphoid cells and cancer: Role in tumor progression and inhibition. *Eur J Immunol* 51: 2188-2205, 2021.
78. Ebid N, Sharaky M, Elkhoely A, El Morsy EM and Saad SY: Cross-talk signaling between non-small cell lung cancer cell lines and fibroblasts attenuates the cytotoxic effect of cisplatin. *J Biochem Mol Toxicol* 39: e70201, 2025.
79. Zhang Q, Luo Y, Qian B, Cao X, Xu C, Guo K, Wan R, Jiang Y, Wang T, Mei Z, *et al*: A systematic pan-cancer analysis identifies LDHA as a novel predictor for immunological, prognostic, and immunotherapy resistance. *Aging (Albany NY)* 16: 8000-8018, 2024.
80. Wang Z, Yan N, Sheng H, Xiao Y, Sun J and Cao C: Single-cell transcriptomic analysis reveals an immunosuppressive network between POSTN CAFs and ACKR1 ECs in TKI-resistant lung cancer. *Cancer Genomics Proteomics* 21: 65-78, 2024.
81. Wang Y, Meraz IM, Qudratullah M, Kotagiri S, Han Y, Xi Y, Wang J and Lissanu Y: SMARCA4 mutation induces tumor cell-intrinsic defects in enhancer landscape and resistance to immunotherapy. *bioRxiv*: Jun 22, 2024 doi: 10.1101/2024.06.18.599431
82. Huang H, Zhu X, Yu Y, Li Z, Yang Y, Xia L and Lu S: EGFR mutations induce the suppression of CD8<sup>+</sup> T cell and anti-PD-1 resistance via ERK1/2-p90RSK-TGF- $\beta$  axis in non-small cell lung cancer. *J Transl Med* 22: 653, 2024.
83. Kobayashi N, Katakura S, Fukuda N, Somekawa K, Kaneko A and Kaneko T: The impact of bevacizumab and miR200c on EMT and EGFR-TKI resistance in EGFR-mutant lung cancer organoids. *Genes (Basel)* 15: 1624, 2024.
84. Tan J, Zhu L, Shi J, Zhang J, Kuang J, Guo Q, Zhu X, Chen Y, Zhou C and Gao X: Evaluation of drug resistance for EGFR-TKIs in lung cancer via multicellular lung-on-a-chip. *Eur J Pharm Sci* 199: 106805, 2024.
85. Pan X, Qian H, Sun Z, Yi Q, Liu Y, Lan G, Chen J and Wang G: Investigating the role of disulfidptosis related genes in radiotherapy resistance of lung adenocarcinoma. *Front Med (Lausanne)* 11: 1473080, 2024.
86. Han R, Guo H, Shi J, Zhao S, Jia Y, Liu X, Liu Y, Cheng L, Zhao C, Li X and Zhou C: Osimertinib in combination with anti-angiogenesis therapy presents a promising option for osimertinib-resistant non-small cell lung cancer. *BMC Med* 22: 174, 2024.
87. Shen A, Sun Y, Wang G, Meng X, Ren X, Wan Q, Lv Q, Wang X, Ni J, Li M, *et al*: An adaptable nanoprobe integrated with quantitative T1-Mapping MRI for accurate differential diagnosis of Multidrug-resistant lung cancer. *Adv Healthc Mater* 12: e2300684, 2023.
88. Lu J, Li J, Lin Z, Li H, Lou L, Ding W, Ouyang S, Wu Y, Wen Y, Chen X, *et al*: Reprogramming of TAMs via the STAT3/CD47-SIRP $\alpha$  axis promotes acquired resistance to EGFR-TKIs in lung cancer. *Cancer Lett* 564: 216205, 2023.
89. Yuan Y: Spatial heterogeneity in the tumor microenvironment. *Cold Spring Harb Perspect Med* 6: a026583, 2016.
90. Wang Y, Liu B, Min Q, Yang X, Yan S, Ma Y, Li S, Fan J, Wang Y, Dong B, *et al*: Spatial transcriptomics delineates molecular features and cellular plasticity in lung adenocarcinoma progression. *Cell Discovery* 9: 96, 2023.
91. Zhang JT, Zhang J, Wang SR, Yan LX, Qin J, Yin K, Chu XP, Wang MM, Hong HZ, Lv ZY, *et al*: Spatial downregulation of CD74 signatures may drive invasive component development in part-solid lung adenocarcinoma. *iScience* 26: 107699, 2023.
92. Zhang J, Song C, Tian Y and Yang X: Single-cell RNA sequencing in lung cancer: Revealing phenotype shaping of stromal cells in the microenvironment. *Front Immunol* 12: 802080, 2021.
93. Joo MS, Pyo KH, Chung JM and Cho BC: Artificial intelligence-based non-small cell lung cancer transcriptome RNA-sequence analysis technology selection guide. *Front Bioeng Biotechnol* 11: 1081950, 2023.
94. Xie L, Xie D, Du Z, Xue S, Wang K, Yu X, Liu X, Peng Q and Fang C: A novel therapeutic outlook: Classification, applications and challenges of inhalable micron/nanoparticle drug delivery systems in lung cancer (Review). *Int J Oncol* 64: 38, 2024.
95. Hu M and Huang L: Strategies targeting tumor immune and stromal microenvironment and their clinical relevance. *Adv Drug Deliv Rev* 183: 114137, 2022.
96. Qian W, Zhao M, Wang R and Li H: Fibrinogen-like protein 1 (FGL1): The next immune checkpoint target. *J Hematol Oncol* 14: 147, 2021.
97. Wang J, Sanmamed MF, Datar I, Su TT, Ji L, Sun J, Chen L, Chen Y, Zhu G, Yin W, *et al*: Fibrinogen-like Protein 1 Is a Major Immune Inhibitory Ligand of LAG-3. *Cell* 176: 334-347, e12, 2019.
98. Miao L, Wang Y, Lin CM, Xiong Y, Chen N, Zhang L, Kim WY and Huang L: Nanoparticle modulation of the tumor microenvironment enhances therapeutic efficacy of cisplatin. *J Control Release* 217: 27-41, 2015.
99. Runa F, Hamalian S, Meade K, Shisgal P, Gray PC and Kelber JA: Tumor microenvironment heterogeneity: Challenges and opportunities. *Curr Mol Biol Rep* 3: 218-229, 2017.
100. Guan XY, Guan XL and Jiao ZY: Improving therapeutic resistance: Beginning with targeting the tumor microenvironment. *J Chemother* 34: 492-516, 2022.
101. Lu J and Ramirez RA: The role of checkpoint inhibition in Non-small cell lung cancer. *Ochsner J* 17: 379-387, 2017.
102. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csósz T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, *et al*: Pembrolizumab versus chemotherapy for PD-L1-positive Non-small-cell lung cancer. *N Engl J Med* 375: 1823-1833, 2016.
103. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, Park K, Alexandru A, Lupinacci L, de la Mora Jimenez E, *et al*: Nivolumab plus ipilimumab in advanced Non-Small-Cell lung cancer. *N Engl J Med* 381: 2020-2031, 2019.
104. Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, Zahurak M, Yang SC, Jones DR, Broderick S, *et al*: Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med* 378: 1976-1986, 2018.
105. Niemeijer AN, Leung D, Huisman MC, Bahce I, Hoekstra OS, van Dongen GAMS, Boellaard R, Du S, Hayes W, Smith R, *et al*: Whole body PD-1 and PD-L1 positron emission tomography in patients with non-small-cell lung cancer. *Nat Commun* 9: 4664, 2018.
106. Zhang Y, Zhou H and Zhang L: Which is the optimal immunotherapy for advanced squamous non-small-cell lung cancer in combination with chemotherapy: Anti-PD-1 or anti-PD-L1? *J Immunother Cancer* 6: 135, 2018.
107. Bozorgmehr F, Hommertgen A, Krisam J, Lasitschka F, Kuon J, Maenz M, Huber PE, König L, Kieser M, Debus J, *et al*: Fostering efficacy of anti-PD-1-treatment: Nivolumab plus radiotherapy in advanced non-small cell lung cancer-study protocol of the FORCE trial. *BMC Cancer* 19: 1074, 2019.
108. Zhao S, Ren S, Jiang T, Zhu B, Li X, Zhao C, Jia Y, Shi J, Zhang L, Liu X, *et al*: Low-Dose apatinib optimizes tumor microenvironment and potentiates antitumor effect of PD-1/PD-L1 blockade in lung cancer. *Cancer Immunol Res* 7: 630-643, 2019.
109. Leighl NB, Redman MW, Rizvi N, Hirsch FR, Mack PC, Schwartz LH, Wade JL, Irvin WJ, Reddy SC, Crawford J, *et al*: Phase II study of durvalumab plus tremelimumab as therapy for patients with previously treated anti-PD-1/PD-L1 resistant stage IV squamous cell lung cancer (Lung-MAP substudy S1400F, NCT03373760). *J Immunother Cancer* 9: e002973, 2021.
110. Ott PA, Hu-Lieskovan S, Chmielowski B, Govindan R, Naing A, Bhardwaj N, Margolin K, Awad MM, Hellmann MD, Lin JJ, *et al*: A Phase Ib Trial of Personalized Neoantigen Therapy Plus Anti-PD-1 in Patients with Advanced Melanoma, Non-small Cell Lung Cancer, or Bladder Cancer. *Cell* 183: 347-362.e24, 2020.
111. Awad MM, Govindan R, Balogh KN, Spigel DR, Garon EB, Bushway ME, Poran A, Sheen JH, Kohler V, Esaulova E, *et al*: Personalized neoantigen vaccine NEO-PV-01 with chemotherapy and anti-PD-1 as first-line treatment for non-squamous non-small cell lung cancer. *Cancer Cell* 40: 1010-1026.e11, 2022.
112. Li JH, Tian F, Qiu CS, Chen WJ, Xu DX, Yang LQ and Li RJ: Relevant studies on effect of Fuzheng Sanjie recipe in regulating immune microenvironment remodeling of TAMs in Lewis lung cancer mice. *Zhongguo Zhong Yao Za Zhi* 40: 1161-1165, 2015 (In Chinese)
113. Gao J, Bi L, Jiang YC, Yang Y, Li BY and Chen WP: Effect of water extract of ginseng on biological behaviors of lung cancer A549 cells and the expression of F-actin in Co-culture system of TAMs and A549 cells. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 37: 345-350, 2017 (In Chinese).

114. Wen X, Wang Y, Su C, You Y, Jiang Z, Zhu D and Fan Q: Integrating Multi-omics technologies with traditional Chinese medicine to enhance cancer research and treatment. *QJM*: Apr 29, 2025 (Epub ahead of print). doi: 10.1093/qjmed/hcaf103.
115. Li Y, Cao F, Li M, Li P, Yu Y, Xiang L, Xu T, Lei J, Tai YY, Zhu J, *et al.*: Hydroxychloroquine induced lung cancer suppression by enhancing chemo-sensitization and promoting the transition of M2-TAMs to M1-like macrophages. *J Exp Clin Cancer Res* 37: 259, 2018.
116. Sarnaik AA, Hwu P, Mulé JJ and Pilon-Thomas S: Tumor-infiltrating lymphocytes: A new hope. *Cancer Cell* 42: 1315-1318, 2024.
117. Stachowiak M, Becker WJ, Olkhanud PB, Moreno PA, Markowicz S, Berzofsky JA and Sarnowska E: Cancer cells accelerate exhaustion of persistently activated mouse CD4+ T cells. *Oncoimmunology* 14: 2521392, 2025.
118. Stachowiak M, Becker WJ, Olkhanud PB, Moreno PA, Markowicz S, Berzofsky JA and Sarnowska E: Mechanisms underlying immunosuppression by regulatory cells. *Front Immunol* 15: 1328193, 2024.
119. Mastelic-Gavillet B, Navarro Rodrigo B, Décombaz L, Wang H, Ercolano G, Ahmed R, Lozano LE, Ianaro A, Derré L, Valerio M, *et al.*: Adenosine mediates functional and metabolic suppression of peripheral and tumor-infiltrating CD8+ T cells. *J Immunother Cancer* 7: 257, 2019.
120. Sumitomo R, Huang CL, Fujita M, Cho H and Date H: Differential expression of PD-L1 and PD-L2 is associated with the tumor microenvironment of TILs and M2 TAMs and tumor differentiation in non-small cell lung cancer. *Oncol Rep* 47: 73, 2022.
121. Zhang Y, Zhang Z, Ding Y, Fang Y, Wang P, Chu W, Jin Z, Yang X, Wang J, Lou J and Qian Q: Phase I clinical trial of EGFR-specific CAR-T cells generated by the piggyBac transposon system in advanced relapsed/refractory non-small cell lung cancer patients. *J Cancer Res Clin Oncol* 147: 3725-3734, 2021.
122. Sterner RC and Sterner RM: CAR-T cell therapy: Current limitations and potential strategies. *Blood Cancer J* 11: 69, 2021.
123. Labanieh L and Mackall CL: CAR immune cells: Design principles, resistance and the next generation. *Nature* 614: 635-648, 2023.
124. Kong Q, Zhu H, Gong W, Deng X, Liu B and Dong J: Modified Bushen Yiqi formula enhances antitumor immunity by reducing the chemotactic recruitment of M2-TAMs and PMN-MDSCs in Lewis lung cancer-bearing mice. *J Ethnopharmacol* 319: 117183, 2024.
125. Chen C, Hou J, Yu S, Li W, Wang X, Sun H, Qin T, Claret FX, Guo H and Liu Z: Role of cancer-associated fibroblasts in the resistance to antitumor therapy, and their potential therapeutic mechanisms in non-small cell lung cancer. *Oncol Lett* 21: 413, 2021.
126. Feng H, Cao B, Peng X and Wei Q: Cancer-associated fibroblasts strengthen cell proliferation and EGFR TKIs resistance through aryl hydrocarbon receptor dependent signals in non-small cell lung cancer. *BMC Cancer* 22: 764, 2022.
127. Li F, Zhao S, Cui Y, Guo T, Qiang J, Xie Q, Yu W, Guo W, Deng W, Gu C and Wu T:  $\alpha$ 1,6-Fucosyltransferase (FUT8) regulates the cancer-promoting capacity of cancer-associated fibroblasts (CAFs) by modifying EGFR core fucosylation (CF) in non-small cell lung cancer (NSCLC). *Am J Cancer Res* 10: 816-837, 2020.
128. Yang F, Yan Y, Yang Y, Hong X, Wang M, Yang Z, Liu B and Ye L: MiR-210 in exosomes derived from CAFs promotes non-small cell lung cancer migration and invasion through PTEN/PI3K/AKT pathway. *Cell Signal* 73: 109675, 2020.
129. Chen Y, Zhu S, Yang L, Lu Y and Ye X: Cancer-associated fibroblasts (CAFs) regulate lung cancer malignant progression by transferring SERPINE2 (PN1) via exosomes. *Curr Mol Med* 25: 1025-1037, 2025.
130. Sun Y, Ying K, Sun J, Wang Y, Qiu L, Ji M, Sun L and Chen J: PRRX1-OLR1 axis supports CAFs-mediated lung cancer progression and immune suppression. *Cancer Cell Int* 24: 247, 2024.
131. Wang H, Wu C, Wan S, Zhang H, Zhou S and Liu G: Shikonin attenuates lung cancer cell adhesion to extracellular matrix and metastasis by inhibiting integrin  $\beta$ 1 expression and the ERK1/2 signaling pathway. *Toxicology* 308: 104-112, 2013.
132. Wang H, Zhu Y, Zhao M, Wu C, Zhang P, Tang L, Zhang H, Chen X, Yang Y and Liu G: miRNA-29c suppresses lung cancer cell adhesion to extracellular matrix and metastasis by targeting integrin  $\beta$ 1 and matrix metalloproteinase2 (MMP2). *PLoS One* 8: e70192, 2013.
133. Bi HX, Shi HB, Zhang T and Cui G: PRDM14 promotes the migration of human non-small cell lung cancer through extracellular matrix degradation in vitro. *Chin Med J (Engl)* 128: 373-377, 2015.
134. Zhang T, Cui G, Yao YL, Guo Y, Wang QC, Li XN and Feng WM: Inhibition of nonsmall cell lung cancer cell migration by protein arginine methyltransferase 1-small hairpin RNA through inhibiting Epithelial-mesenchymal transition, extracellular matrix degradation, and src phosphorylation in vitro. *Chin Med J (Engl)* 128: 1202-1208, 2015.
135. Wang Y, Zhang T, Guo L, Ren T and Yang Y: Stromal extracellular matrix is a microenvironmental cue promoting resistance to EGFR tyrosine kinase inhibitors in lung cancer cells. *Int J Biochem Cell Biol* 106: 96-106, 2019.
136. Shie WY, Chu PH, Kuo MY, Chen HW, Lin MT, Su XJ, Hong YL and Chou HE: Acidosis promotes the metastatic colonization of lung cancer via remodeling of the extracellular matrix and vasculogenic mimicry. *Int J Oncol* 63: 136, 2023.
137. Peláez R, Ochoa R, Pariente A, Villanueva-Martínez Á, Pérez-Sala Á and Larráyoiz IM: Sterculic acid alters adhesion molecules expression and extracellular matrix compounds to regulate migration of lung cancer cells. *Cancers (Basel)* 13: 4370, 2021.
138. Abdel-Hafez SM, Gallei M, Wagner S and Schneider M: Inhalable nano-structured microparticles for extracellular matrix modulation as a potential delivery system for lung cancer. *Eur J Pharm Biopharm* 204: 114512, 2024.
139. Frezzetti D, Gallo M, Maiello MR, D'Alessio A, Esposito C, Chicchinelli N, Normanno N and De Luca A: VEGF as a potential target in lung cancer. *Expert Opin Ther Targets* 21: 959-966, 2017.
140. Villaruz LC and Socinski MA: The role of Anti-angiogenesis in non-small-cell lung cancer: An update. *Curr Oncol Rep* 17: 26, 2015.
141. Socinski MA, Nishio M, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodríguez-Abreu D, Moro-Sibilot D, Thomas CA, *et al.*: IMpower150 final overall survival analyses for atezolizumab plus bevacizumab and chemotherapy in First-line metastatic nonsquamous NSCLC. *J Thorac Oncol* 16: 1909-1924, 2021.
142. Qiang H, Wang Y, Zhang Y, Li J, Zhang L, Du H, Ling X, Cao S, Zhou Y, Zhong R and Zhong H: Efficacy of first-line chemotherapy combined with immunotherapy or anti-angiogenic therapy in advanced KRAS-mutant non-small cell lung cancer. *Transl Oncol* 53: 102317, 2025.
143. Cai Q, Hu K, Dong S, Li X, Hu S, Deng W and Ou W: Tumor cavitation in patients with non-small-cell lung cancer receiving anti-angiogenic therapy with apatinib. *Transl Lung Cancer Res* 13: 1708-1717, 2024.
144. Zhang X, Sun Q, Chen R, Zhao M, Cai F, Cui Z and Jiang H: Efficacy and safety of combining anti-angiogenic therapy, radiotherapy, and PD-1 inhibitors in patients with driver gene-negative non-small cell lung cancer brain metastases: A retrospective study. *BMC Cancer* 24: 1492, 2024.
145. Song JQ, Wang X, Zeng ZM, Liang PA, Zhong CY and Liu AW: Efficacy of PD-1 Inhibitors combined with anti-angiogenic therapy in driver gene mutation negative non-small-cell lung cancer with brain metastases. *Discov Med* 35: 321-331, 2023.
146. Itatani Y, Kawada K, Yamamoto T and Sakai Y: Resistance to Anti-angiogenic therapy in Cancer-alterations to Anti-VEGF pathway. *Int J Mol Sci* 19: 1232, 2018.
147. Bergers G and Hanahan D: Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer* 8: 592-603, 2008.
148. Wu Y, Yan Y, Guo Y, Niu M, Zhou B, Zhang J, Zhou P, Chu Q, Mei Q, Yi M and Wu K: Anti-TGF- $\beta$ /PD-L1 bispecific antibody synergizes with radiotherapy to enhance antitumor immunity and mitigate radiation-induced pulmonary fibrosis. *J Hematol Oncol* 18: 24, 2025.
149. Huehls AM, Coupet TA and Sentman CL: Bispecific T-cell engagers for cancer immunotherapy. *Immunol Cell Biol* 93: 290-296, 2015.
150. Si Y, Pei X, Wang X, Han Q, Xu C and Zhang B: An Anti-EGFR/anti-HER2 bispecific antibody with enhanced antitumor activity against acquired Gefitinib-resistant NSCLC cells. *Protein Pept Lett* 28: 1290-1297, 2021.

