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Review Article

The Tumor Microenvironment in Lung Cancer: Molecular Mechanisms, Immune Interactions, and Emerging Therapeutic Strategies

Mondem Bhavana[1], Akshima Thakur[1]

[1]*Departmet of Biotechnology, Thapar Institute o Engineering and Technology, Patiala, India*
Correspondence should be addressed to mbhavana_phd2@thapar.edu

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Abstract

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for approximately 2.48 million new cases and 1.82 million deaths in 2022. The tumor microenvironment (TME) has emerged as a critical determinant of tumor progression, immune evasion, and therapeutic response in both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). This comprehensive review systematically examines the cellular and molecular architecture of the lung cancer TME, emphasizing the dynamic interplay between malignant cells, cancer-associated fibroblasts, tumor-associated macrophages, regulatory T cells, myeloid-derived suppressor cells, and other stromal components. We discuss the molecular signaling pathways that drive TME remodeling, including NF-κB, TGF-β, PI3K/AKT/mTOR, and hypoxia-inducible factor (HIF)-mediated adaptations. The review further explores mechanisms of immune evasion, therapeutic resistance, and metabolic reprogramming within the TME, highlighting recent advances in single-cell and spatial transcriptomics that have transformed our understanding of intratumoral heterogeneity. We critically evaluate emerging therapeutic strategies targeting the TME, including immune checkpoint inhibitors, combination immunotherapies, CAR-T cell approaches, anti-angiogenic agents, and nanomedicine-based interventions. Additionally, we discuss the clinical translation of TME-derived biomarkers, liquid biopsy approaches, and the integration of artificial intelligence for precision oncology. Finally, we identify current challenges, research gaps, and future directions for TME-targeted therapies. This review provides a framework for understanding the complex ecosystem of the lung cancer TME and highlights the translational potential of TME-centered therapeutic strategies for improving patient outcomes.

Keywords: Lung cancer; tumor microenvironment; immunotherapy; immune checkpoint inhibitors; cancer-associated fibroblasts

1. Introduction

Lung cancer represents one of the most formidable challenges in oncology, constituting the leading cause of cancer incidence and mortality on a global scale. According to GLOBOCAN 2022 estimates, lung cancer accounted for approximately 2.48 million new cases (12.4% of all cancers) and 1.82 million deaths (18.7% of all cancer deaths) worldwide, underscoring the urgent need for innovative therapeutic approaches [1,2].

The disease is broadly classified into two major histological categories: non-small cell lung cancer (NSCLC), comprising approximately 85% of cases, and small cell lung cancer (SCLC), accounting for the remaining 15% [3]. NSCLC is further subdivided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, each exhibiting distinct molecular profiles, clinical behaviors, and therapeutic vulnerabilities [4].

Despite significant advances in targeted therapies and immunotherapy, the 5-year overall survival rate for lung cancer remains below 25%, with most patients presenting at advanced stages where curative options are limited [5]. The recognition that tumor progression is not solely driven by cancer cell-autonomous mechanisms but is profoundly influenced by the surrounding tumor microenvironment (TME) has transformed our understanding of cancer biology and treatment resistance [6]. The TME comprises a complex ecosystem of malignant and non-malignant cells, including immune cells, cancer-associated fibroblasts (CAFs), endothelial cells, extracellular matrix (ECM) components, and a milieu of soluble factors that collectively shape tumor evolution, immune evasion, and therapeutic response [7,8].

Historically, the concept of the TME was first proposed by Stephen Paget in his "seed and soil" hypothesis over a century ago, suggesting that tumor growth depends on favorable interactions with the host microenvironment [9]. Modern TME research has evolved dramatically, particularly with the advent of single-cell and spatial transcriptomics technologies that enable unprecedented resolution of cellular heterogeneity and intercellular communication networks [10,11]. In lung cancer, the TME has been shown to play pivotal roles in driving immune suppression, promoting angiogenesis, facilitating metastatic dissemination, and mediating resistance to both chemotherapy and immunotherapy [12,13].

The overarching objectives of this review are to provide a comprehensive synthesis of current knowledge regarding the lung cancer TME, to elucidate the molecular and cellular mechanisms underlying TME-driven tumor progression and therapy resistance, and to critically evaluate emerging therapeutic strategies that target the TME. We further discuss how multi-omics integration, artificial intelligence, and biomarker development are accelerating the translation of TME research into clinical practice, ultimately aiming to improve outcomes for patients with lung cancer.

2. Overview of the Lung Cancer Tumor Microenvironment

2.1 Definition and Components of the TME

The tumor microenvironment is defined as the cellular and non-cellular environment that surrounds tumor cells, encompassing a diverse array of components that collectively influence cancer initiation, progression, and therapeutic response [14]. In lung cancer, the TME consists of multiple interacting cell types, including stromal cells (CAFs, pericytes), immune cells (T lymphocytes, B lymphocytes, natural killer cells, macrophages, neutrophils, dendritic cells, myeloid-derived suppressor cells, regulatory T cells), endothelial cells, and the extracellular matrix [15,16]. Non-cellular components include cytokines, chemokines, growth factors, extracellular vesicles, metabolites, and the extracellular matrix scaffold, which together create a dynamic and often immunosuppressive milieu that favors tumor growth [17].

2.2 Dynamic Nature of the TME

The lung cancer TME is not a static entity but evolves continuously throughout tumor progression, from premalignant lesions to invasive carcinoma and metastatic dissemination [18]. Early-stage lung adenocarcinoma is characterized by immune cell infiltration, particularly CD8+ tissue-resident memory T cells predominantly aggregating at the tumor parenchyma-stroma interface [19]. As tumors progress to locally advanced stages, immune cell reprogramming occurs, with a shift toward immune suppression, reduction in CD8+ resident memory T cells, and predominant M2 polarization of tumor-associated macrophages [20]. In advanced metastatic disease, immune exhaustion and heterogeneity become prominent features, with increased proportions of exhausted T cells in peripheral blood and metastatic lesions [21]. This temporal evolution of the TME has profound implications for therapeutic interventions and highlights the need for dynamic monitoring strategies.

2.3 Cellular and Non-Cellular Components

The cellular landscape of the lung cancer TME exhibits remarkable heterogeneity. Recent single-cell RNA sequencing analyses of advanced NSCLC tumors have identified at least 11 major cell types, demonstrating unique TME subtypes for endothelial cells, fibroblasts, tumor-associated macrophages, regulatory T cells, dendritic cells, and polymorphonuclear leukocytes [22]. Two major TME community patterns have been characterized: the CP2E pattern (immune-activated) containing cancer-associated myofibroblasts, pro-inflammatory macrophages, and exhausted CD8+ T cells; and the N3MC pattern (immune-cold) comprising non-inflammatory macrophages, myeloid dendritic cells, and normal myofibroblasts [23]. Notably, N3MC tumors were associated with superior overall survival compared to CP2E tumors, underscoring the clinical relevance of TME classification.

Non-cellular components, including the extracellular matrix, soluble factors, and metabolites, play equally important roles in shaping TME biology. The ECM provides structural support and biochemical signals that influence cell behavior, while the metabolic milieu—characterized by hypoxia, acidosis, and nutrient deprivation—creates a hostile environment for antitumor immune cells while supporting cancer cell survival [24,25].

2.4 Intercellular Communication Networks

Intercellular communication within the lung cancer TME occurs through multiple mechanisms, including direct cell-cell contact, paracrine signaling via cytokines and chemokines, and indirect communication through extracellular vesicles and exosomes [26]. Cell-cell interaction assays have revealed several unique interactions between tumor cells and TME components through multiple signaling pathways, with tumor-associated macrophages prominently suppressing T-cell function, potentially contributing to immune evasion [22]. The complexity of these communication networks is further amplified by the reciprocal crosstalk between cancer cells and stromal components, whereby tumor cells actively remodel the TME while stromal cells provide signals that promote tumor progression and therapy resistance [27].

2.5 Role of the TME in Tumor Progression

The lung cancer TME actively promotes tumor progression through multiple mechanisms. Chronic inflammation within the TME drives the development of an immunosuppressive environment that facilitates tumor growth and resistance to therapy [28]. Components such as tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells serve key roles in suppressing antitumor immune responses, while the ECM and its degradative enzymes contribute to tumor invasion and metastasis by remodeling the physical structure of the TME [29,30]. Understanding these mechanisms is crucial for developing novel therapeutic strategies that target the TME to overcome resistance and improve patient outcomes.

3. Cellular Components of the Lung Cancer TME

3.1 Tumor Cells

Tumor cells themselves are central architects of the TME, secreting a diverse array of factors that recruit and reprogram stromal and immune cells to support tumor growth [31]. Lung cancer cells exhibit significant intratumoral heterogeneity, with genomic analyses revealing distinct molecular subtypes characterized by driver mutations in EGFR, KRAS, BRAF, ALK, ROS1, and other oncogenes [32]. This genetic diversity contributes to phenotypic plasticity and the ability of tumor cells to adapt to changing microenvironmental conditions. Furthermore, tumor cells can undergo epithelial-mesenchymal transition (EMT), acquiring migratory and invasive properties that facilitate metastatic dissemination while simultaneously remodeling the surrounding TME to create an immunosuppressive niche [33].

3.2 Cancer-Associated Fibroblasts (CAFs)

Cancer-associated fibroblasts represent one of the most abundant stromal cell types in the lung cancer TME and play multifaceted roles in tumor progression [34]. CAFs secrete numerous protumorigenic factors, including growth factors, cytokines, and chemokines, creating a favorable environment for cancer cell proliferation and survival. Recent single-cell transcriptomics studies have identified distinct CAF subpopulations, including matrix-associated CAFs (mCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs), each with specialized functions [35]. Thrombospondin-2-positive CAFs (THBS2+ CAFs) have been identified as key biomarkers of progression, associated with reduced immune infiltration and poor response to immunotherapy in early-stage lung adenocarcinoma [36]. Importantly, CAFs contribute to immune evasion by physically excluding T cells from tumor regions and secreting immunosuppressive molecules such as TGF-β, IL-6, and CXCL12 [37].

3.3 Tumor-Associated Macrophages (TAMs)

Tumor-associated macrophages are the most abundant immune cells in the lung cancer TME and exhibit remarkable plasticity, existing along a spectrum from pro-inflammatory M1-like to immunosuppressive M2-like phenotypes [38]. In NSCLC, TAMs predominantly display an M2-like phenotype that promotes tumor growth, angiogenesis, and immune suppression through secretion of IL-10, TGF-β, and expression of PD-L1 [39]. Galectin-3 has been shown to interact with triggering receptor expressed on myeloid cells 2 (TREM2), inhibiting TREM2-mediated phagocytosis and converting TREM2+ macrophages to immunosuppressive TAMs, thereby reducing antigen presentation and co-stimulation [40]. The inositol-requiring enzyme 1α (IRE1α)-X-box binding protein 1 signaling pathway also plays a vital role in lung cancer by promoting immune-suppressing cell accumulation and weakening antitumor immune responses [41].

3.4 Dendritic Cells

Dendritic cells (DCs) are professional antigen-presenting cells that play critical roles in initiating and regulating antitumor immunity [42]. In lung cancer, the TME contains multiple DC subsets, including conventional DC1 (cDC1), conventional DC2 (cDC2), and plasmacytoid DCs, each with distinct functions in antigen presentation and T-cell activation [43]. However, the immunosuppressive TME impairs DC maturation and function, leading to defective antigen presentation and inadequate T-cell priming [44]. Strategies to enhance DC function or deliver tumor antigens directly to DCs represent active areas of therapeutic development.

3.5 Neutrophils

Neutrophils are increasingly recognized as important contributors to lung cancer progression and immune regulation [45]. Tumor-associated neutrophils (TANs) can adopt either antitumor (N1) or protumor (N2) phenotypes, analogous to the M1/M2 polarization of macrophages [46]. In the lung cancer TME, neutrophils promote tumor progression through secretion of matrix metalloproteinases, reactive oxygen species, and neutrophil extracellular traps (NETs), which facilitate tumor cell migration, invasion, and metastasis [47]. Adenosine A2A receptor activation in TAMs promotes CXCL5 secretion, which augments NETosis by TANs and suppresses CD8+ T-cell activity, creating a feedforward loop of immunosuppression [48].

3.6 Natural Killer Cells

Natural killer cells are innate lymphoid cells that provide rapid antitumor immunity without prior sensitization [49]. In lung cancer, NK cell function is often impaired by the immunosuppressive TME, including the effects of TGF-β, IL-10, and prostaglandin E2 [50]. Despite this, NK cells remain an attractive target for immunotherapy, with strategies to enhance their activity—including checkpoint inhibitors targeting NKG2A (such as monalizumab) and cytokine stimulation—being actively investigated in clinical trials [51].

3.7 Myeloid-Derived Suppressor Cells (MDSCs)

Myeloid-derived suppressor cells represent a heterogeneous population of immature myeloid cells that accumulate in the lung cancer TME and potently suppress antitumor immunity [52]. MDSCs inhibit T-cell function through multiple mechanisms, including depletion of L-arginine via arginase-1, production of reactive oxygen and nitrogen species, and induction of regulatory T cells [53]. The paired related homeobox 1 (PRRX1)-OLR1 axis in CAFs promotes immune suppression by enhancing MDSC infiltration, highlighting the interconnected nature of TME-mediated immunosuppression [54].

3.8 Regulatory T Cells

Regulatory T cells (Tregs) are a subset of CD4+ T cells that maintain immune homeostasis and prevent autoimmunity but are co-opted by tumors to suppress antitumor immunity [55]. In lung cancer, Tregs accumulate in the TME through chemokine-mediated recruitment (particularly via CCL22 and CCL17) and local expansion [56]. Tregs suppress effector T-cell function through multiple mechanisms, including secretion of IL-10 and TGF-β, expression of immune checkpoint molecules CTLA-4 and PD-1, and metabolic disruption via CD39/CD73-mediated adenosine production [57].

3.9 Cytotoxic T Lymphocytes

Cytotoxic CD8+ T lymphocytes are the primary effectors of antitumor immunity and the main targets of immune checkpoint inhibitor therapy [58]. In lung cancer, the presence of tumor-infiltrating CD8+ T cells is generally associated with improved prognosis and better response to immunotherapy [59]. However, the TME promotes T-cell exhaustion, characterized by progressive loss of effector function, upregulation of inhibitory receptors (PD-1, CTLA-4, LAG-3, TIM-3), and ultimately, T-cell dysfunction [60]. Understanding the mechanisms that regulate T-cell exhaustion and developing strategies to reinvigorate exhausted T cells remain critical research priorities.

3.10 B Cells

B cells and tertiary lymphoid structures (TLS) have emerged as important components of the lung cancer immune landscape [61]. TLS are organized lymphoid aggregates that form within tumors and adjacent tissues, resembling secondary lymphoid organs with germinal centers containing B cells, T cells, and follicular dendritic cells [62]. The presence of TLS in NSCLC has been associated with improved prognosis and enhanced response to immunotherapy, suggesting that B cells and humoral immunity contribute to antitumor responses [63]. In early-stage lung adenocarcinoma, TLS formation begins with CD_4+ T-cell and B-cell aggregation around precancerous epithelium, representing an active immune response that may be harnessed therapeutically [64].

4. Immune Interactions Within the Tumor Microenvironment

4.1 Antitumor Immunity

Antitumor immunity in lung cancer involves a coordinated response across multiple immune cell types, beginning with the recognition of tumor-associated antigens by professional antigen-presenting cells, particularly dendritic cells [65]. Cross-presentation of tumor antigens by cDC1 cells to naive CD8+ T cells in draining lymph nodes initiates the priming of cytotoxic T-cell responses [66]. Activated CD8+ T cells traffic to tumor sites, where they recognize and kill cancer cells expressing specific antigen-MHC class I complexes [67]. Concurrently, CD_4+ T helper cells provide essential support through cytokine production and licensing of antigen-presenting cells, while natural killer cells contribute innate antitumor immunity against MHC-deficient tumor variants [68,69].

4.2 Immune Surveillance

The concept of cancer immune surveillance posits that the immune system continuously monitors and eliminates nascent transformed cells, thereby preventing tumor development [70]. In the lung, where constant exposure to environmental carcinogens creates a high risk of malignant transformation, immune surveillance is particularly critical [71]. The "3E" model proposed by Dunn and colleagues describes three phases of tumor-immune interactions: elimination (immune surveillance), equilibrium (tumor dormancy), and escape (tumor progression) [72]. In the equilibrium phase, the immune system controls but does not completely eliminate tumor cells, which can persist for extended periods before eventually escaping immune control.

4.3 Immune Editing

Cancer immunoediting represents the process by which the immune system shapes tumor immunogenicity through selective pressure, resulting in the emergence of tumor variants that can evade immune recognition [73]. In lung cancer, immunoediting manifests as loss of tumor antigens, downregulation of MHC class I molecules, and selection for tumor cell variants with reduced immunogenicity [74]. Recent studies have demonstrated that CD8+ T-cell-excluded lung tumors have higher expression and HLA-I presentation efficiency of tumor-associated antigens, with enrichment of predicted neoantigens, while the HLA-II peptidome mirrors immune cell composition [75]. Understanding the mechanisms of immune editing is essential for designing immunotherapeutic strategies that can overcome tumor adaptation.

4.4 Immune Suppression Mechanisms

The lung cancer TME employs multiple mechanisms to suppress antitumor immunity. In 2024, Galassi and colleagues introduced a comprehensive "3C" paradigm identifying three primary strategies of immune evasion: camouflage (hiding from immune recognition), coercion (forcing immune cells into suppressive phenotypes), and cytoprotection (shielding tumor cells from immune attack) [76]. Peroxiredoxin-2 (PRDX2) has been identified as strongly expressed in lung cancer and directly linked to survival; PRDX2 modulates Galectin-9 expression through phosphorylation of $HDAC_3$, impairing T-cell cytotoxic activity and facilitating immune evasion [77,78]. Interleukin-9 (IL-9) has also been shown to prevent apoptosis of lung cancer cells while suppressing antitumor immune responses by altering T-cell subpopulation function [79].

4.5 Cytokine Networks

Cytokine networks within the lung cancer TME form a complex regulatory system that balances pro- and anti-inflammatory signals [80]. Pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α promote tumor progression through activation of oncogenic signaling pathways and recruitment of immunosuppressive cells [81]. Conversely, immunosuppressive cytokines including TGF-β, IL-10, and VEGF directly inhibit effector T-cell function and promote regulatory T-cell differentiation [82]. The net balance of these cytokine signals determines the overall immune status of the TME and influences response to immunotherapy [83].

4.6 Chemokine Signaling

Chemokines play crucial roles in organizing the cellular composition of the lung cancer TME through directed cell migration [84]. Chemokine ligand 4 (CCL4) is significantly upregulated in lung cancer and interacts with its receptor CCR5 to decrease antitumor immune responses by recruiting cells that release immunosuppressive molecules including IL-10 and TGF-β [85]. T-cell exhaustion and elevated CCL4 expression are tightly associated with the lung cancer microenvironment, and elevated CCL4 expression correlates with overexpression of immune checkpoint markers, indicating potential collaboration with the PD-1/PD-L1 pathway to enhance immune evasion [86]. Other important chemokine axes include CXCL12-CXCR4, CCL2-CCR2, and CXCL8-CXCR1/2, each contributing to immune cell recruitment and tumor progression [87,88].

4.7 Immune Cell Crosstalk

The functional state of any given immune cell in the lung cancer TME is determined by its interactions with multiple other cell types [89]. TAMs suppress T-cell function through PD-L1 expression and metabolic competition, while CAFs physically exclude T cells from tumor regions and secrete immunosuppressive factors [90]. Regulatory T cells suppress dendritic cell maturation and effector T-cell function, creating a feedforward loop of immunosuppression [91]. Understanding these complex intercellular interactions is essential for designing effective combination therapies that can disrupt multiple immunosuppressive mechanisms simultaneously [92].

4.8 Tumor-Induced Immune Dysfunction

Beyond immune suppression, the lung cancer TME actively induces immune dysfunction in effector cells [93]. T-cell exhaustion is characterized by progressive loss of proliferative capacity, effector cytokine production, and cytotoxic potential, accompanied by epigenetic reprogramming that renders exhausted T cells resistant to reactivation [94]. Dendritic cells in the TME display impaired maturation, reduced costimulatory molecule expression, and defective antigen presentation [95]. These dysfunctional states are maintained by persistent antigen exposure, immunosuppressive cytokines, and metabolic constraints within the TME, necessitating therapeutic strategies that address these underlying drivers [96].

5. Molecular Mechanisms Driving TME Remodeling

5.1 Genetic Alterations

Genetic alterations in lung cancer cells profoundly influence the composition and function of the TME [97]. Oncogenic driver mutations in EGFR, KRAS, BRAF, and ALK not only promote cancer cell proliferation and survival but also actively remodel the TME through secretion of growth factors, cytokines, and chemokines [98]. Tumor suppressor mutations, particularly in TP53 and STK11/LKB1, have been associated with distinct TME phenotypes characterized by enhanced immunosuppression and reduced response to immunotherapy [99]. Recent studies have demonstrated that STK11 mutations create a non-T cell-inflamed TME, which reduces responsiveness to immune checkpoint inhibitors, while KEAP1 mutations drive hyperactivation of the NRF2 pathway, promoting immune evasion through metabolic reprogramming [100,101].

5.2 Epigenetic Modifications

Epigenetic modifications play critical roles in regulating TME remodeling in lung cancer [102]. Aberrant DNA methylation, histone modifications, and chromatin remodeling regulate oncogene activation and tumor suppressor silencing, some of which have emerged as predictive biomarkers for immunotherapy [103]. Hypermethylation of STAT5A has been associated with immune cell depletion in lung squamous cell carcinoma, enriching immune-cool tumors accompanied by decreased dendritic cell and effector signatures [104]. Furthermore, epigenetic reprogramming contributes to the phenotypic plasticity of stromal cells, including CAFs and TAMs, enabling dynamic adaptation to changing microenvironmental conditions [105].

5.3 Growth Factor Signaling

Growth factor signaling pathways are central mediators of TME remodeling in lung cancer [106]. The epidermal growth factor receptor (EGFR) pathway not only drives cancer cell proliferation but also induces secretion of VEGF, IL-8, and other factors that promote angiogenesis and immune suppression [107]. Platelet-derived growth factor (PDGF) signaling in CAFs promotes proliferation and cytokine production that stimulates polymorphonuclear myeloid-derived suppressor cell migration, contributing to the immunosuppressive microenvironment [108]. Fibroblast growth factor (FGF) signaling has been implicated in resistance to anti-angiogenic therapy and immunotherapy, highlighting the interconnected nature of growth factor signaling networks in the TME [109].

5.4 Inflammatory Pathways

Chronic inflammation is a hallmark of the lung cancer TME and drives the recruitment and activation of immunosuppressive cell populations [110]. The NF-κB signaling pathway serves as a master regulator of inflammatory responses, promoting the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules that facilitate immune cell recruitment and activation [111]. In NSCLC, NF-κB is frequently activated by both tumor-intrinsic mechanisms (oncogenic signaling, genotoxic stress) and tumor-extrinsic factors (cytokine stimulation, microbial products), creating a self-sustaining inflammatory environment that promotes tumor progression [112].

5.5 NF-κB Signaling

NF-κB signaling in the lung cancer TME operates through both canonical and non-canonical pathways [113]. The canonical pathway is initiated by various extracellular stimuli through different receptors, including TLRs, TNFRs, TCRs, and BCRs, leading to activation of the IKK complex and subsequent degradation of IκB inhibitors, allowing NF-κB dimers to translocate to the nucleus and regulate gene transcription [114]. The non-canonical pathway is activated by members of the TNFR superfamily and specifically engages NF-κB-inducing kinase (NIK) to activate IKKα [115]. Both pathways converge on the regulation of genes involved in cell survival, proliferation, inflammation, and immune modulation, making NF-κB a central node in TME biology and an attractive therapeutic target [116].

5.6 JAK/STAT Signaling

The JAK/STAT signaling pathway transduces signals from numerous cytokines and growth factors to regulate gene expression programs that influence immune cell function and tumor progression [117]. In lung cancer, JAK/STAT signaling is frequently dysregulated, with $STAT_3$ and STAT6 activation promoting immunosuppressive phenotypes in TAMs and CAFs [118]. $STAT_3$ activation in tumor cells induces expression of immunosuppressive factors including IL-10, TGF-β, and VEGF, while simultaneously upregulating anti-apoptotic proteins that enhance cancer cell survival [119]. Targeting JAK/STAT signaling represents a promising strategy for TME remodeling, with several JAK inhibitors currently under investigation in clinical trials [120].

5.7 PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR pathway is a critical regulator of cell metabolism, proliferation, and survival that is frequently activated in lung cancer [121]. Beyond its tumor cell-autonomous effects, PI3K/AKT/mTOR signaling actively remodels the TME by promoting VEGF expression and angiogenesis, regulating immune cell function, and controlling cellular metabolism [122]. AKT recruits mTOR upon interaction of TGFβRII and TGFβRI with the p85 subunit of PI3K, integrating TGF-β signaling with metabolic regulation [123]. Hyperactivation of this pathway has been associated with resistance to both targeted therapies and immunotherapy, highlighting its importance as a therapeutic target [124].

5.8 MAPK Signaling

The MAPK signaling cascade, particularly the RAS-RAF-MEK-ERK axis, is one of the most frequently activated pathways in lung cancer, particularly in KRAS-mutant tumors [125]. MAPK signaling promotes tumor progression through regulation of cell proliferation, survival, and migration, while also influencing the TME through modulation of cytokine and chemokine expression [126]. TGF-β can induce MAPK activation, which in turn increases PD-L1 expression and enhances immunosuppression, contributing to resistance to immunotherapy [127]. The intersection of MAPK signaling with immune regulation makes it an important target for combination therapeutic strategies [128].

5.9 TGF-β Signaling

Transforming growth factor-β (TGF-β) is a pleiotropic cytokine with multifaceted roles in lung cancer TME remodeling [129]. TGF-β signaling occurs through both canonical SMAD-dependent and non-canonical SMAD-independent pathways, including PI3K/AKT, MAPK, and Rho-like GTPase signaling [130]. In the TME, TGF-β promotes immune evasion by inhibiting T-cell activation and proliferation, enhancing regulatory T-cell differentiation, and promoting M2 polarization of macrophages [131]. TGF-β also drives CAF activation, ECM deposition, and EMT, contributing to tumor invasion and therapeutic resistance [132]. Blockade of TGF-β signaling in CAFs has been shown to facilitate intratumoral T-cell infiltration and enhance tumor regression in combination with anti-PD-L1 antibody immunotherapy [133].

5.10 Wnt/β-Catenin Pathway

The Wnt/β-catenin signaling pathway plays important roles in lung cancer TME remodeling, particularly in the regulation of immune cell function and tumor-stromal interactions [134]. β-catenin activation in tumor cells has been associated with immune exclusion phenotypes characterized by reduced T-cell infiltration and resistance to immunotherapy [135]. The Wnt pathway also regulates CAF activation and ECM remodeling, contributing to the physical barriers that impede immune cell infiltration [136]. Cross-talk between Wnt signaling and other pathways, including PI3K/AKT and TGF-β, further amplifies its effects on TME composition and function [137].

6. Angiogenesis, Hypoxia, and Metabolic Reprogramming

6.1 Tumor Angiogenesis

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is an essential process for tumor growth and metastasis in lung cancer [138]. The angiogenic switch is driven by the imbalance between pro-angiogenic factors, primarily vascular endothelial growth factor (VEGF), and anti-angiogenic factors [139]. In NSCLC, tumor-associated macrophages promote angiogenesis through secretion of VEGF, MMP7, MMP9, and MMP12, which induce basement membrane degradation and facilitate endothelial cell migration and tube formation [140]. The resulting tumor vasculature is often disorganized, leaky, and functionally abnormal, creating regions of poor perfusion and hypoxia that further exacerbate tumor progression and therapeutic resistance [141].

6.2 VEGF Signaling

VEGF signaling represents the primary driver of tumor angiogenesis in lung cancer [142]. VEGF family members, including VEGF-A, VEGF-B, VEGF-C, and VEGF-D, bind to cognate VEGF receptors (VEGFR-1, VEGFR-2, VEGFR-3) on endothelial cells to promote proliferation, migration, and survival [143]. Bevacizumab, a monoclonal antibody targeting VEGF-A, has demonstrated clinical efficacy in combination with chemotherapy for nonsquamous NSCLC, normalizing tumor vasculature and reducing hypoxia [144]. However, resistance to anti-angiogenic therapy frequently develops through alternative angiogenic pathways, EMT-mediated VEGF-independent angiogenesis, and ECM remodeling via ZEB1/MMP9 activation [145].

6.3 Hypoxia-Induced Responses

Hypoxia is a defining feature of the lung cancer TME that profoundly impacts tumor biology and therapeutic response [146]. Regions of low oxygen tension develop as tumor growth outstrips the oxygen supply from the abnormal vasculature, creating microenvironmental conditions that select for more aggressive tumor phenotypes [147]. Hypoxia promotes cancer stem cell maintenance through activation of hypoxia-inducible factors, supports tumor cell survival via autophagy-mediated pathways, and enhances resistance to both chemotherapy and radiation therapy [148]. The acidic microenvironment resulting from hypoxia-associated metabolic reprogramming decreases the proliferation of polymorphonuclear leukocytes and cytotoxic T lymphocytes while increasing the recruitment of regulatory T cells, generating an immunosuppressive milieu [149].

6.4 HIF Signaling

Hypoxia-inducible factor-1α (HIF-1α) is the master transcriptional regulator of cellular responses to hypoxia and plays a central role in lung cancer TME remodeling [150]. Under normoxic conditions, HIF-1α is hydroxylated by prolyl hydroxylase domain proteins and targeted for proteasomal degradation; however, under hypoxic conditions, HIF-1α stabilizes, dimerizes with HIF-1β, and translocates to the nucleus to activate transcription of hundreds of target genes [151]. HIF-1α induces expression of VEGF for angiogenesis, glycolytic enzymes for metabolic adaptation, and immune checkpoint molecules including PD-L1 for immune evasion [152]. HIF-1α also induces MMP-2 and MMP-9 expression, which degrade the ECM and facilitate tumor invasion and metastasis while altering ECM composition to create physical barriers to immune cell infiltration [153].

6.5 Metabolic Competition

Metabolic competition within the lung cancer TME represents a critical mechanism of immune suppression and tumor progression [154]. Cancer cells exhibit high metabolic demands, consuming glucose, amino acids, and lipids at rates that create nutrient-depleted conditions detrimental to immune cell function [155]. The resulting competition for limited resources impairs T-cell activation, proliferation, and effector function, while simultaneously supporting the immunosuppressive activities of regulatory T cells, TAMs, and MDSCs, which have adapted to thrive in nutrient-poor conditions [156]. This metabolic asymmetry contributes to the establishment and maintenance of an immunosuppressive TME that favors tumor progression [157].

6.6 Aerobic Glycolysis

Aerobic glycolysis, also known as the Warburg effect, represents a metabolic shift in which cancer cells preferentially metabolize glucose to lactate even in the presence of adequate oxygen [158]. HIF-1α drives this metabolic reprogramming by upregulating glycolytic enzymes including hexokinase 2, phosphofructokinase, and lactate dehydrogenase A, enabling cancer cells to survive and proliferate in hypoxic environments while generating biosynthetic precursors for rapid cell division [159]. The glycolytic phenotype is not limited to cancer cells; CAFs also exhibit enhanced glycolysis, creating a metabolic symbiosis that supports tumor growth and shapes the TME [160].

6.7 Lactate-Mediated Immunosuppression

Lactate, the end product of anaerobic glycolysis, accumulates to high concentrations in the lung cancer TME and functions as a critical immunosuppressive metabolite [161]. Elevated lactate decreases extracellular pH, creating an acidic environment that impairs cytotoxic T-cell and NK cell function while promoting regulatory T-cell and TAM-mediated immunosuppression [162]. Lactate also boosts IL-8 and VEGF production to facilitate angiogenesis and induces the degradation of the ECM through activation of matrix metalloproteinases, supporting tumor cell migration and metastasis [163]. Lactate-driven acidosis has been shown to induce PD-L1 upregulation and impair T-cell cytotoxicity, linking metabolic reprogramming directly to immune evasion [164]. Furthermore, lactate-stimulated CAFs promote secretion of IL-6, which suppresses cytotoxic immune cell activity, creating a feedforward loop of immunosuppression [165].

6.8 Nutrient Deprivation Mechanisms

Beyond glucose and lactate, nutrient deprivation of amino acids and lipids in the TME contributes to immune dysfunction and tumor progression [166]. Tryptophan depletion by indoleamine 2,3-dioxygenase (IDO) expressed by tumor cells and myeloid cells generates kynurenine metabolites that suppress T-cell proliferation and promote regulatory T-cell differentiation [167]. Arginine depletion by arginase-1 expressed by MDSCs and TAMs impairs T-cell receptor signaling and proliferation [168]. These metabolic checkpoints represent potential therapeutic targets, with IDO inhibitors and arginase inhibitors being investigated in clinical trials for lung cancer [169].

7. Extracellular Matrix and Mechanobiology

7.1 ECM Components

The extracellular matrix of the lung cancer TME undergoes extensive remodeling, creating a scaffold that supports tumor growth, invasion, and immune evasion [170]. The ECM consists of structural proteins (collagens, elastin, laminin), glycoproteins (fibronectin, tenascin), proteoglycans, and glycosaminoglycans (hyaluronan) [171]. In lung cancer, collagen deposition is significantly increased, with COL11A1+ CAFs and SPP1+ macrophages identified as key contributors to immune evasion at the tumor boundary, inhibiting T-cell infiltration [172]. Decellularized metastatic lung tumors display distinct ECM structures, including a surrounding capsule, an interior dense ECM, and partially empty cavities where cancer cells reside [173].

7.2 Matrix Remodeling

ECM remodeling in lung cancer is a dynamic process mediated by the concerted actions of tumor cells, CAFs, and immune cells [174]. Matrix-associated CAFs (mCAFs) are specialized fibroblast subpopulations that produce and organize ECM components, creating a desmoplastic stroma that physically excludes immune cells and restricts drug delivery [175]. ECM-based "matreotypes" and a 28-gene matrix-risk signature have been defined to predict progression of squamous carcinoma in situ, with ECM-High subtypes correlated with poorer prognosis and immuno-stromal remodeling [176]. The cooperative roles of angiogenesis and mCAFs in promoting early lung adenocarcinoma invasion have been delineated through integrated spatial transcriptomics and single-cell analyses [177].

7.3 Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that degrade ECM components, facilitating tumor cell invasion and metastasis [178]. HIF-1α induces MMP-2 and MMP-9 expression, which degrade the ECM and create physical barriers to immune cell infiltration while releasing sequestered growth factors that further support angiogenesis and tumor progression [179]. MMP activity is tightly regulated by tissue inhibitors of metalloproteinases (TIMPs), and the balance between MMPs and TIMPs determines the extent of ECM remodeling [180]. In NSCLC, MMP9 expression is associated with TAM recruitment and poor prognosis, highlighting the clinical relevance of MMP-mediated ECM remodeling [181].

7.4 Tumor Stiffness

Increased tumor stiffness, resulting from collagen crosslinking and hyaluronan accumulation, is a hallmark of the lung cancer TME with profound effects on tumor biology and therapy response [182]. The ECM from lung carcinoma macrometastases is more than 4-fold stiffer than healthy lung ECM (1.79 ± 1.32 kPa vs. 0.42 ± 0.09 kPa), with stark increases in fibronectin deposition [183]. Tumor stiffness activates mechanotransduction signaling pathways in cancer and stromal cells, promoting proliferation, survival, and invasive behavior [184]. Importantly, ECM stiffness physically impedes T-cell migration and reduces the delivery of immune checkpoint inhibitors to their targets, representing a structural barrier to immunotherapy efficacy [185].

7.5 Mechanotransduction

Mechanotransduction is the process by which cells convert mechanical stimuli into biochemical signals, playing critical roles in lung cancer progression and TME remodeling [186]. Protein mechanosensors, including integrins, focal adhesion proteins, mechano-stimulated ion channels, and cytoskeletal proteins, detect mechanical cues from the ECM and transduce signals to intracellular effectors [187]. The transcriptional coactivators YAP (yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif) serve as master integrators of mechanical signals, becoming activated in response to matrix stiffness and promoting oncogenic transcriptional programs [188]. YAP/TAZ activation drives cancer cell proliferation, survival, EMT, and stemness, while simultaneously remodeling the TME through regulation of CAF activation and cytokine production [189].

7.6 Cell Migration and Invasion

Mechanobiological mechanisms are intimately linked to cancer cell migration and invasion in lung cancer [190]. ECM stiffness and topology guide cancer cell movement through contact guidance and durotaxis, with cells preferentially migrating toward stiffer substrates [191]. CAF-derived mechanical forces create tracks in the ECM that facilitate cancer cell invasion, while TAMs degrade basement membrane components to create portals for intravasation [192]. The mechanical interplay between cancer cells and the TME thus creates a permissive environment for local invasion and subsequent metastatic dissemination [193].

7.7 Metastatic Dissemination

Metastatic dissemination in lung cancer involves multiple steps—local invasion, intravasation, circulation, extravasation, and colonization—each influenced by TME mechanics and composition [194]. For metastasis to occur, cancer cells must interact with the ECM to invade local tissues, a process facilitated by ECM stiffening and remodeling [195]. Distinct ECM structures at metastatic sites, including surrounding capsules and interior dense matrices, create specialized niches that support cancer cell survival and proliferation [196]. Understanding the mechanical and molecular determinants of metastatic spread is essential for developing therapies that can prevent or target established metastases [197].

8. Immune Evasion and Therapy Resistance

8.1 Immune Checkpoint Molecules

Immune checkpoint molecules are inhibitory receptors expressed on immune cells that maintain self-tolerance and prevent autoimmunity but are co-opted by tumors to evade immune destruction [198]. Beyond the well-characterized PD-1/PD-L1 and CTLA-4 axes, emerging checkpoints including LAG-3, TIM-3, TIGIT, VISTA, and CD73 contribute to immune evasion in lung cancer [199]. LAG-3, expressed on exhausted T cells, interacts with its ligand FGL1 (fibrinogen-like protein 1), leading to T-cell dysfunction [200]. VISTA contributes to the immunosuppressive environment by inhibiting T-cell activation [201]. These multiple checkpoint pathways provide both challenges and opportunities for therapeutic intervention [202].

8.2 PD-1/PD-L1 Axis

The PD-1/PD-L1 axis represents the most successfully targeted immune checkpoint pathway in lung cancer [203]. PD-L1 expression on tumor cells and immune cells is upregulated by multiple mechanisms, including IFN-γ signaling, oncogenic pathways, and hypoxia-induced HIF-1α activation [204]. HIF-1α directly influences immune evasion by regulating PD-L1 expression on tumor cells and immune cells, impairing T-cell activity and leading to immunosuppression [205]. PD-1/PD-L1 blockade has demonstrated significant clinical efficacy across multiple lung cancer indications, with PD-L1 tumor proportion score (TPS) serving as a predictive biomarker for patient selection [206].

8.3 CTLA-4 Pathway

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is an inhibitory receptor expressed on activated T cells and regulatory T cells that competes with CD28 for binding to B7 molecules (CD80/CD86) on antigen-presenting cells, thereby dampening T-cell activation [207]. Dual CTLA-4 and PD-1/PD-L1 blockade has been investigated as a strategy to enhance antitumor immunity, with a recent individual patient data meta-analysis demonstrating significantly improved overall survival in patients with PD-L1 TPS less than 1% and in those with STK11-mutated tumors [208]. However, the increased toxicity associated with dual immune checkpoint blockade necessitates careful patient selection and biomarker-guided treatment decisions [209].

8.4 LAG-3 and TIM-3

Lymphocyte-activation gene 3 (LAG-3) and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) are emerging immune checkpoint targets in lung cancer [210]. LAG-3 expression on exhausted T cells contributes to progressive loss of effector function, and LAG-3 inhibitors are being evaluated in combination with PD-1/PD-L1 blockade [211]. TIM-3 expression is associated with reduced activity of antigen presentation pathways and impaired T-cell function, with TIM-3+ cells predominantly localized within precancerous lesions and adjacent tumor regions, identifying TIM-3 as a potential biomarker for lung adenocarcinoma precancer interception [212]. Dual checkpoint blockade strategies targeting LAG-3 or TIM-3 in combination with PD-1/PD-L1 inhibitors represent promising approaches to overcome resistance [213].

8.5 Tumor Heterogeneity

Intratumoral heterogeneity is a major driver of therapeutic resistance in lung cancer, encompassing both genetic and phenotypic diversity within primary tumors and metastatic lesions [214]. Genomic analyses have revealed extensive spatial and temporal heterogeneity, with distinct molecular subtypes coexisting within the same tumor [215]. This heterogeneity extends to the TME, where different tumor regions may harbor distinct immune cell compositions and functional states [216]. Multi-omics analyses integrating whole-exome sequencing, RNA-seq, single-cell RNA-seq, and DNA methylation profiling have demonstrated that LUAD progression and spatial heterogeneity are driven primarily by non-genetic, plastic transcriptional state shifts and TME reprogramming rather than new driver mutations [217].

8.6 Drug Resistance Mechanisms

Drug resistance in lung cancer arises through multiple TME-mediated mechanisms that span immune escape, metabolic reprogramming, and epigenetic modulation [218]. Resistance to immune checkpoint blockade is influenced by the presence of immunosuppressive cells such as MDSCs and Tregs, which inhibit the activation and function of cytotoxic T cells [219]. Physical barriers within the TME, including a dense ECM and poor vascularization, prevent immune cells from infiltrating the tumor and reduce the delivery of therapeutic agents to their targets [220]. Metabolic changes induced by targeted therapies can alter the TME and contribute to immune resistance, creating a complex interplay between targeted therapeutic resistance and immune evasion [221].

8.7 Acquired Resistance

Acquired resistance to immunotherapy develops in patients who initially respond but later experience disease progression, affecting 52-57% of patients receiving first-line ICI treatment and 32-64% receiving second-line treatment [222]. Mechanisms underlying acquired resistance include loss of tumor antigens and neoantigen expression, alterations in antigen presentation machinery, activation of oncogenic signaling pathways, impaired IFN-γ signaling, and upregulation of alternative immune checkpoints [223]. Acquired resistance to PD-1 blockade in NSCLC is characterized by elevated IFN-γ signaling, immune dysfunction, and mutations in antigen presentation machinery, which contribute to immune evasion [224].

8.8 TME-Mediated Therapeutic Failure

The lung cancer TME actively mediates therapeutic failure through multiple interconnected mechanisms [225]. AXL-mediated drug resistance in ALK-rearranged NSCLC is enhanced by growth-arrest specific protein 6 from macrophages and MMP11-positive fibroblasts, underscoring the importance of cellular interactions within the TME [226]. Spatially resolved transcriptomics has revealed that determinants of primary resistance to immunotherapy in NSCLC include spatial exclusion of CD8+ T cells by stromal barriers and immunosuppressive cytokine gradients [227]. Additionally, coactivation of innate immune suppressive cells induces acquired resistance against combined Toll-like receptor 7/8 agonist treatment and PD-1 blockade, further illustrating the dynamic nature of immune resistance mechanisms [228].

9. Emerging Therapeutic Strategies Targeting the TME

9.1 Immune Checkpoint Inhibitors

Immune checkpoint inhibitors have transformed the treatment landscape for lung cancer, with multiple agents targeting PD-1, PD-L1, and CTLA-4 now approved across various indications [229]. Pembrolizumab, nivolumab, atezolizumab, cemiplimab, and durvalumab have demonstrated significant clinical benefit as monotherapy or in combination with chemotherapy for advanced NSCLC [230]. In SCLC, atezolizumab and durvalumab in combination with chemotherapy have improved survival outcomes, expanding the role of immunotherapy beyond NSCLC [231]. The perioperative use of nivolumab in resectable NSCLC has also shown significant improvement in event-free survival and pathological complete response rates, representing a paradigm shift toward earlier application of immunotherapy [232].

9.2 Combination Immunotherapies

Combination approaches targeting multiple immune checkpoint pathways are being actively investigated to overcome resistance and improve response durability [233]. The combination of PD-1/PD-L1 inhibitors with CTLA-4 inhibitors has demonstrated enhanced efficacy in specific subgroups, particularly patients with PD-L1 TPS less than 1% and those with STK11 mutations [234]. Novel combinations incorporating LAG-3 inhibitors (such as relatlimab), TIM-3 inhibitors, and TIGIT inhibitors (such as vibostolimab) with PD-1/PD-L1 blockade are currently in clinical development [235]. Bispecific antibodies targeting PD-1/CTLA-4 (cadonilimab, MEDI5752) and PD-L1/CTLA-4 (KN046) have shown promising early results, potentially offering improved efficacy with manageable toxicity profiles [236].

9.3 CAR-T Cell Therapies

Chimeric antigen receptor (CAR)-T cell therapy, while highly successful in hematological malignancies, faces significant challenges in lung cancer due to the immunosuppressive TME, poor CAR-T cell infiltration into tumor tissue, and the scarcity of truly tumor-specific antigens [237]. Current research is focused on identifying suitable target antigens in NSCLC, including EGFR, mesothelin (MSLN), mucin 1 (MUC1), carcinoembryonic antigen (CEA), and PD-L1 [238]. Innovative approaches to enhance CAR-T cell efficacy in solid tumors include armored CAR-T cells secreting cytokines or checkpoint inhibitors, combination with TME-modulating agents, and regional delivery strategies [239].

9.4 Cancer Vaccines

Therapeutic cancer vaccines aim to enhance adaptive antitumor immune responses by introducing tumor-specific antigens to activate the host immune system [240]. Nucleic acid-based vaccines, including mRNA vaccines and DNA vaccines, have emerged as particularly promising approaches due to their ability to deliver multiple antigens simultaneously, inducing both humoral and cell-mediated immune responses [241]. Personalized neoantigen vaccines, designed based on individual tumor mutation profiles, represent a precision immunotherapy approach that is being evaluated in combination with immune checkpoint inhibitors for NSCLC [242]. Despite promising preclinical data, clinical translation of cancer vaccines has been challenging due to the immunosuppressive TME and relatively low immunogenicity, necessitating combination strategies to enhance efficacy [243].

9.5 Cytokine-Based Therapies

Cytokine-based therapies aim to modulate the immune landscape of the lung cancer TME to promote antitumor immunity [244]. Interleukin-2 (IL-2) therapy has shown limited efficacy in lung cancer due to toxicity and preferential expansion of regulatory T cells; however, modified IL-2 variants with enhanced selectivity for effector T cells are under development [245]. Type I interferons promote antitumor immunity through enhancement of antigen presentation and T-cell activation, with ongoing investigations of interferon combination strategies [246]. Novel cytokine engineering approaches, including cytokine-antibody fusions and masked cytokines that activate only in the TME, represent innovative strategies to enhance efficacy while reducing systemic toxicity [247].

9.6 Anti-Angiogenic Agents

Anti-angiogenic agents targeting VEGF signaling have demonstrated clinical efficacy in lung cancer, particularly in combination with immunotherapy [248]. Bevacizumab in combination with atezolizumab and chemotherapy (the IMpower150 regimen) showed improved overall survival compared to bevacizumab plus chemotherapy in EGFR/ALK wild-type nonsquamous NSCLC, leading to FDA approval [249]. More recently, ivonescimab, a bispecific antibody targeting PD-1 and VEGF, has demonstrated clinical efficacy comparable to pembrolizumab in advanced NSCLC with positive PD-L1 expression in the first-line setting [250]. The combination of anti-angiogenic agents with immunotherapy is hypothesized to promote vascular normalization, enhance immune cell infiltration, and improve therapeutic efficacy [251].

9.7 Targeting CAFs

Therapeutic strategies targeting cancer-associated fibroblasts include elimination approaches, functional reprogramming, and phenotypic conversion [252]. FAP-targeted CAR-T cells, bispecific antibodies as T-cell engagers, and antibody-drug conjugates targeting FAP or LRRC15 are being developed to selectively deplete protumorigenic CAFs [253]. Reprogramming strategies aim to convert tumor-promoting CAFs to quiescent or tumor-suppressive states using all-trans retinoic acid (ATRA), vitamin D analogs, or TGF-β signaling blockade [254]. Notably, Meflin+ CAFs in NSCLC have been associated with prolonged survival and favorable response to immune checkpoint therapy, and the synthetic retinoid Am80 induces Meflin expression in CAFs, enhancing the effect of immune checkpoint therapy [255].

9.8 TAM Reprogramming Strategies

Repolarizing tumor-associated macrophages from an immunosuppressive M2-like phenotype to an antitumor M1-like phenotype represents a promising therapeutic strategy [256]. CCL2 inhibition by upstream silencing of the PIM1 proto-oncogene in NSCLC cells has been shown to abrogate TAM polarization to an M2-like state and recruitment to the TME, while augmenting the antitumor activity of PD-1 inhibitors in murine models [257]. A2AR inhibition by the small molecule CPI-444 and CXCR2 inhibition by SB225002 have demonstrated the ability to abrogate tumor growth and suppress CXCL5 expression in preclinical models [258]. Nanocarrier-based approaches, including superparamagnetic iron oxide nanoparticles, have been shown to repolarize TAMs and reshape the lung TME [259].

9.9 Nanomedicine Approaches

Nanomedicine offers innovative solutions for targeting the lung cancer TME through enhanced drug delivery, TME remodeling, and combination immunotherapy [260]. Nanoparticle-based delivery systems exploit the enhanced permeability and retention (EPR) effect for passive targeting or utilize ligand-specific interactions for active targeting of tumor cells or stromal components [261]. Nanocarriers can reprogram TAMs from an immunosuppressive M2 phenotype to an antitumor M1 phenotype, deliver innate immune agonists such as STING agonists directly to lung tumors, and encapsulate TGF-β receptor inhibitors to enhance anti-PD-1 therapy [262]. Carrier-free nanomedicines composed entirely of active pharmaceutical ingredients represent a next-generation platform with ultra-high drug loading and enhanced tumor-targeting efficiency [263].

9.10 Personalized TME-Targeted Therapy

The recognition that TME composition varies substantially between patients and tumor types has driven interest in personalized TME-targeted therapeutic strategies [264]. Single-cell and spatial transcriptomics analyses enable detailed characterization of individual patient TMEs, identifying specific immunosuppressive mechanisms that can be targeted with precision [265]. Biomarker-driven approaches, such as the use of PD-L1 expression to guide immunotherapy decisions and the identification of STK11 or KEAP1 mutations to inform combination strategies, represent early steps toward personalized TME-targeted therapy [266]. Future approaches integrating multi-omics profiling with artificial intelligence may enable real-time TME monitoring and adaptive therapeutic strategies [267].

10. Single-Cell, Spatial, and Multi-Omics Approaches

10.1 Single-Cell RNA Sequencing

Single-cell RNA sequencing (scRNA-seq) has revolutionized our understanding of lung cancer TME heterogeneity by enabling transcriptomic profiling at single-cell resolution [268]. Wu and colleagues analyzed advanced NSCLC tumors from 42 patients and 90,406 cells, identifying 11 major cell types and demonstrating unique TME subtypes for multiple components including endothelial cells, fibroblasts, TAMs, Tregs, dendritic cells, and polymorphonuclear leukocytes [269]. ScRNA-seq has also enabled the discovery of rare subpopulations such as exhausted T cells and transitional alveolar epithelial states that are critical for prognosis and therapeutic response [270]. These studies have provided unprecedented insights into cellular diversity and intercellular communication networks within the lung cancer TME [271].

10.2 Spatial Transcriptomics

Spatial transcriptomics technologies preserve the positional context of gene expression, enabling the mapping of cell types and molecular states within intact tissue sections [272]. The combination of spatial transcriptomics with scRNA-seq addresses the limitations of each approach—mixed-cell signals in spatial transcriptomics and loss of spatial context in scRNA-seq—enabling precise mapping of subcellular populations and their spatial organization within the TME [273]. Notable applications include the discovery of keratin 8-positive (KRT8+) alveolar intermediate cells (KACs) as intermediate states in the transformation of alveolar type II cells into tumor cells during early-stage lung adenocarcinoma [274]. Spatial transcriptomics has also revealed the cooperative roles of angiogenesis and matrix-associated CAFs in promoting early LUAD invasion [275].

10.3 Proteomics

Proteomics bridges the gap between gene expression and functional output by mapping signaling networks, post-translational modifications, and druggable targets [276]. Advanced mass spectrometry techniques have identified post-translational modifications of HIF-1α that regulate its stability and activity, providing insights into hypoxia-driven TME remodeling [277]. Proteogenomic characterization has revealed that transcriptomic diversity via allele-specific expression and RNA editing is a major driver of intratumoral heterogeneity, improving metastasis potential combined with genomic features [278]. Integration of proteomics with genomics and transcriptomics enables comprehensive characterization of TME biology and identification of novel therapeutic targets [279].

10.4 Metabolomics

Metabolomics has exposed rewired metabolic pathways that drive immune suppression and therapy resistance in lung cancer [280]. Studies employing RNA-seq combined with metabolomics have linked overexpression of key glycolytic enzymes aldolase C and enolase 2 to increased lactate production and metabolic adaptation in lung adenocarcinoma [281]. Metabolomics sheds light on metabolic reprogramming induced by HIF-1α, such as the shift to glycolysis and lactate production, with elevated levels of lactate and other hypoxia-associated metabolites linked to immune suppression and therapeutic resistance [282]. These approaches offer potential targets for metabolic interventions that could reprogram the TME to enhance immunotherapy efficacy [283].

10.5 Multi-Omics Integration

Multi-omics integration combines data from genomics, transcriptomics, proteomics, metabolomics, and epigenomics to provide a comprehensive understanding of TME biology [284]. Horizontal integration of different technologies within the transcriptomic layer—such as the combination of spatial transcriptomics and scRNA-seq—has enabled precise mapping of subcellular populations, revealing both their molecular states and spatial organization within the TME [285]. Integrative analyses of RNA-seq, DNA methylation sequencing, and mass spectrometry have revealed that STAT5A hypermethylation is associated with immune cell depletion in lung squamous cell carcinoma [286]. These multi-layered approaches provide biomarkers that reveal cell subpopulations correlated with metabolic reprogramming and therapeutic response [287].

10.6 Systems Biology Approaches

Systems biology approaches utilize computational modeling and network analysis to integrate multi-omics data and predict emergent properties of the lung cancer TME [288]. Graph-based models of cell-cell communication networks have identified key signaling hubs that regulate TME composition and function [289]. Dynamic modeling of TME evolution under therapeutic pressure has provided insights into resistance mechanisms and optimal treatment scheduling [290]. These computational approaches complement experimental studies by generating testable hypotheses and identifying potential therapeutic targets that might not be apparent from individual datasets [291].

10.7 AI and Machine Learning Applications

Artificial intelligence and machine learning are transforming lung cancer TME research through enhanced data analysis, biomarker discovery, and therapeutic prediction [292]. Deep learning models have achieved exceptional performance in analyzing histopathology images to predict TME composition, immune cell infiltration, and response to immunotherapy [293]. Machine learning-based immune phenotyping, which analyzes the spatial distribution of T cells in resected NSCLC, can identify patients at greater risk of disease recurrence after surgical resection [294]. Multimodal machine learning models integrating radiology (CT scans), pathology (digitized PD-L1 slides), and genomics have been developed to predict response to PD-(L)1 blockade immunotherapy in advanced NSCLC patients [295]. The integration of AI with multi-omics data holds promise for developing predictive models that can guide personalized TME-targeted therapeutic strategies [296].

11. Clinical Translation and Biomarkers

11.1 Predictive Biomarkers

Predictive biomarkers for TME-targeted therapies in lung cancer have become essential tools for patient selection and treatment optimization [297]. PD-L1 tumor proportion score (TPS), assessed by immunohistochemistry using standardized assays (Dako 22C3, Ventana SP142, Ventana SP263), remains the most widely used predictive biomarker for PD-1/PD-L1 inhibitor therapy [298]. Tumor mutational burden (TMB), measured by next-generation sequencing of tumor tissue or circulating tumor DNA (blood TMB), has emerged as a complementary biomarker, with high TMB associated with increased neoantigen load and improved response to immunotherapy [299]. Recent studies have identified additional predictive biomarkers, including STK11 and KEAP1 mutational status, which are associated with distinct TME phenotypes and differential responses to combination immunotherapy approaches [300].

11.2 Prognostic Biomarkers

Prognostic biomarkers in lung cancer provide information about patient outcomes independent of treatment and are valuable for risk stratification and clinical decision-making [301]. The immune cell composition of the TME serves as a powerful prognostic indicator, with high CD8+ T-cell infiltration generally associated with improved survival across NSCLC subtypes [302]. Recently, BTG2 methylation and expression have been identified as reliable prognostic biomarkers for early-stage NSCLC, with higher BTG2 expression associated with better survival outcomes [303]. ECM-based "matreotypes" and a 28-gene matrix-risk signature have been defined to predict progression of squamous carcinoma in situ, with ECM-High subtypes correlated with poorer prognosis [304].

11.3 Liquid Biopsy Approaches

Liquid biopsy, the analysis of circulating biomarkers in blood or other body fluids, offers a non-invasive approach to monitor TME dynamics and therapeutic response [305]. Circulating tumor DNA (ctDNA) analysis enables real-time monitoring of tumor genomic alterations, treatment response, and emergence of resistance mutations [306]. The absence of ctDNA at baseline and changes in ctDNA abundance in the early post-treatment period have been associated with radiographic responses, progression-free survival, and overall survival [307]. Novel machine learning-enhanced platforms, such as MRD-EDGE, have improved ctDNA detection sensitivity by approximately 300-fold, enabling ultrasensitive monitoring of minimal residual disease and immunotherapy response [308].

11.4 Circulating Tumor DNA

Circulating tumor DNA has emerged as a versatile biomarker for lung cancer management, with applications spanning diagnosis, treatment selection, response monitoring, and recurrence detection [309]. In immunotherapy, blood tumor mutational burden (bTMB) calculated from ctDNA profiles has been evaluated as a predictive biomarker for ICI response [310]. Recent bibliometric analyses of ctDNA in lung cancer research from 2001 to 2024 have identified residual disease detection, adjuvant chemotherapy guidance, outcome prediction, and immunotherapy monitoring as current research frontiers [311]. The standardization of ctDNA detection and analysis methods remains a critical priority for clinical implementation [312].

11.5 Immune Biomarkers

Immune biomarkers that reflect the composition and functional state of the lung cancer TME are increasingly recognized for their clinical utility [313]. Multiparameter immune profiling, including assessment of tumor-infiltrating lymphocytes (TILs), PD-L1 expression, and immune gene expression signatures, provides comprehensive information about TME immune status [314]. AI-powered spatial analyzers of TILs in H&E images have been developed, correlating with tumor response and progression-free survival in patients with advanced NSCLC undergoing ICI therapy [315]. Immune-related gene expression signatures, such as the interferon-gamma signature, have shown predictive value for immunotherapy response and are being incorporated into clinical trial designs [316].

11.6 Precision Oncology Applications

The integration of TME biomarkers into precision oncology frameworks is advancing personalized treatment selection for lung cancer patients [317]. Multi-omics approaches combining genomics, transcriptomics, and proteomics enable comprehensive characterization of tumor and TME features that inform treatment decisions [318]. ScRNA-seq combined with spatial transcriptomics has identified COL11A1+ CAFs and SPP1+ macrophages as key contributors to immune evasion, suggesting COL11A1+ CAF as a potential biomarker to predict patient response to immuno-chemotherapy [319]. Radiomics features extracted from CT scans, combined with genomic and transcriptomic data, have demonstrated potential for non-invasive prediction of TME characteristics and treatment response [320].

12. Current Challenges and Limitations

12.1 Tumor Heterogeneity

Tumor heterogeneity remains one of the most significant challenges in lung cancer treatment, as the diverse cellular and molecular landscapes within and between tumors limit the efficacy of targeted therapies [321]. Intratumoral heterogeneity encompasses genetic diversity, phenotypic plasticity, and spatial variation in TME composition, creating a moving target for therapeutic intervention [322]. The clonal evolution of tumor cells under therapeutic pressure leads to the emergence of resistant subclones, while TME remodeling further complicates treatment responses [323]. Addressing heterogeneity requires combination therapies that target multiple tumor and TME components simultaneously [324].

12.2 Dynamic TME Evolution

The lung cancer TME is not static but undergoes continuous evolution in response to intrinsic tumor progression and extrinsic therapeutic pressure [325]. Temporal changes in TME composition during treatment can lead to acquired resistance, as demonstrated by the shift from immune-infiltrated to immune-excluded phenotypes following immunotherapy [326]. Real-time monitoring of TME dynamics remains challenging due to the limitations of current biopsy-based approaches and the need for repeated tissue sampling [327]. Developing non-invasive methods to track TME evolution is a critical priority for adaptive treatment strategies [328].

12.3 Biomarker Limitations

Despite significant advances, current TME biomarkers have important limitations that restrict their clinical utility [329]. PD-L1 expression as a predictive biomarker has demonstrated variable performance across different assays and clinical contexts, with substantial inter-tumor and intra-tumor heterogeneity [330]. Tumor mutational burden lacks standardized measurement and reporting methodologies, complicating cross-trial comparisons and clinical implementation [331]. The dynamic nature of TME biomarkers necessitates serial monitoring, which is not feasible with current tissue biopsy approaches for many patients [332].

12.4 Resistance Mechanisms

Primary and acquired resistance to TME-targeted therapies remain major obstacles in lung cancer treatment [333]. Over 70% of NSCLC patients ultimately exhibit primary or acquired resistance to immune checkpoint inhibitors, underscoring the need for deeper understanding of resistance mechanisms [334]. The complexity and redundancy of immunosuppressive pathways in the TME create multiple escape routes that limit the efficacy of single-agent therapies [335]. Combating resistance will require rational combination strategies that address both tumor-intrinsic and TME-mediated resistance mechanisms [336].

12.5 Clinical Trial Challenges

Clinical trial design for TME-targeted therapies faces unique challenges related to patient selection, endpoint selection, and combination testing [337]. The dynamic and heterogeneous nature of the TME complicates biomarker development and patient stratification [338]. Determining optimal combination partners and sequencing strategies for TME-modulating agents requires extensive preclinical and clinical investigation [339]. Translational endpoints that capture TME modulation, such as immune cell infiltration and activation markers, need to be incorporated into early-phase clinical trials to accelerate development [340].

12.6 Translational Barriers

Translating TME research findings from preclinical models to clinical applications remains a significant challenge in lung cancer [341]. Preclinical models, including cell lines, patient-derived xenografts, and genetically engineered mouse models, do not fully recapitulate the complexity and heterogeneity of the human TME [342]. The lung-on-a-chip technology and organoid models offer improved physiological relevance but require further validation and standardization [343]. Bridging the gap between preclinical findings and clinical outcomes necessitates rigorous biomarker development and innovative clinical trial designs [344].

12.7 Data Integration Issues

The integration of multi-dimensional TME data from diverse sources presents significant analytical and interpretive challenges [345]. Large-scale multi-omics datasets require sophisticated computational approaches for integration, including machine learning and network analysis methods [346]. Standardization of data collection, processing, and analysis pipelines is essential for enabling cross-study comparisons and meta-analyses [347]. The development of user-friendly databases and visualization tools will facilitate data sharing and accelerate discovery [348].

13. Future Perspectives

13.1 Next-Generation Immunotherapy

The next generation of immunotherapy for lung cancer will likely involve increasingly sophisticated approaches to overcome TME-mediated resistance [349]. Novel immune checkpoint targets, including LAG-3, TIM-3, TIGIT, CD73, and NKG2A, are being evaluated in combination with PD-1/PD-L1 blockade in multiple clinical trials [350]. Bispecific and trispecific antibodies that simultaneously engage multiple immune targets offer the potential for enhanced efficacy with simplified dosing compared to combination regimens [351]. Cell therapy approaches, including CAR-T cells, T-cell receptor (TCR)-engineered T cells, and tumor-infiltrating lymphocyte (TIL) therapy, are being adapted for solid tumor application through innovative strategies to overcome the immunosuppressive TME [352].

13.2 Precision Immuno-Oncology

Precision immuno-oncology aims to match patients with the most appropriate immunotherapy based on comprehensive characterization of their tumor and TME [353]. Multi-omics profiling, including genomics, transcriptomics, proteomics, and metabolomics, will enable detailed characterization of TME features that guide treatment selection [354]. Artificial intelligence and machine learning models that integrate multi-modal clinical, imaging, and molecular data will facilitate personalized treatment recommendations [355]. The development of companion diagnostics that capture TME complexity will be essential for implementing precision immuno-oncology in clinical practice [356].

13.3 AI-Assisted Cancer Therapy

Artificial intelligence is poised to transform lung cancer therapy through enhanced diagnosis, treatment selection, and response monitoring [357]. AI algorithms for analysis of radiology, pathology, and genomics data have demonstrated performance matching or exceeding human experts in specific tasks [358]. Multimodal AI frameworks that integrate CT radiomics, PD-L1 immunohistochemistry, and genomics have shown promise for predicting immunotherapy response with high accuracy (AUC = 0.80) [359]. Real-time clinical deployment of AI tools is becoming increasingly achievable, with potential applications in treatment planning, adverse event prediction, and adaptive therapy [360].

13.4 Spatial Biology

Spatial biology technologies, including spatial transcriptomics, spatial proteomics, and spatial metabolomics, are transforming our understanding of TME organization and function [361]. These approaches enable the mapping of cell types, molecular states, and cell-cell interactions within intact tissue sections, preserving the positional context that is lost in dissociated single-cell analyses [362]. Spatial biology has already revealed critical insights into immune cell exclusion, TLS formation, and regional heterogeneity in lung cancer [363]. Future applications will include spatial biomarker development and the identification of novel therapeutic targets based on spatial TME features [364].

13.5 Digital Pathology

Digital pathology, the digitization of histopathology slides for computational analysis, is enabling objective, quantitative assessment of TME features in lung cancer [365]. AI-powered analysis of H&E-stained slides can predict genomic alterations, immune cell infiltration, and treatment response with high accuracy [366]. Deep learning models trained on whole-slide images can classify NSCLC subtypes and predict mutation status of key driver genes directly from histology [367]. The integration of digital pathology with multi-omics data and clinical information will support comprehensive biomarker development and precision treatment selection [368].

13.6 Multi-Omics Integration

The integration of multi-omics data is essential for capturing the full complexity of the lung cancer TME [369]. Horizontal integration of complementary technologies, such as the combination of spatial transcriptomics and scRNA-seq, addresses individual limitations while preserving the strengths of each approach [370]. Vertical integration across molecular layers—from genomics to transcriptomics, proteomics, and metabolomics—provides a comprehensive view of TME biology [371]. Computational frameworks for multi-omics integration, including machine learning and deep learning approaches, are rapidly evolving to handle the increasing scale and complexity of TME datasets [372].

13.7 Personalized Medicine

The ultimate goal of TME research is to enable truly personalized medicine for lung cancer patients [373]. Dynamic monitoring of TME features through liquid biopsy and advanced imaging will enable adaptive treatment strategies that respond to evolving tumor biology [374]. Patient-derived models, including organoids and patient-derived xenografts, will facilitate preclinical testing of personalized treatment combinations [375]. The convergence of multi-omics profiling, artificial intelligence, and targeted therapeutics holds the promise of delivering the right treatment to the right patient at the right time [376].

13.8 Future Clinical Trials

Future clinical trials for TME-targeted therapies will require innovative designs that account for TME heterogeneity and dynamics [377]. Basket and umbrella trials that classify patients based on TME biomarkers rather than histology alone may accelerate the development of personalized treatment strategies [378]. Adaptive trial designs that incorporate real-time biomarker monitoring will enable treatment modification based on evolving TME features [379]. The incorporation of novel endpoints that capture TME modulation, in addition to traditional clinical outcomes, will provide mechanistic insights and accelerate clinical development [380].

14. Conclusion

The tumor microenvironment in lung cancer represents a complex and dynamic ecosystem that profoundly influences tumor progression, immune evasion, and therapeutic response. This comprehensive review has highlighted the cellular diversity of the lung cancer TME, including the critical roles of cancer-associated fibroblasts, tumor-associated macrophages, regulatory T cells, myeloid-derived suppressor cells, and other stromal components in creating an immunosuppressive milieu that supports tumor growth. We have discussed the molecular mechanisms driving TME remodeling, including NF-κB, TGF-β, PI3K/AKT/mTOR, and HIF-mediated signaling pathways, as well as the metabolic adaptations—particularly aerobic glycolysis and lactate-mediated immunosuppression—that further reinforce the protumorigenic environment.

The review has critically evaluated emerging therapeutic strategies targeting the TME, from immune checkpoint inhibitors and combination immunotherapies to novel approaches such as CAR-T cell therapy, cancer vaccines, anti-angiogenic agents, CAF targeting, TAM reprogramming, and nanomedicine-based interventions. While significant progress has been made, with several TME-targeted therapies now approved for clinical use, substantial challenges remain. Primary and acquired resistance to immunotherapy, intratumoral heterogeneity, and the dynamic evolution of the TME under therapeutic pressure continue to limit treatment efficacy for many patients.

Looking forward, the integration of single-cell and spatial transcriptomics, multi-omics profiling, artificial intelligence, and liquid biopsy approaches is transforming our understanding of TME biology and accelerating clinical translation. Precision immuno-oncology strategies that match patients to optimal therapies based on comprehensive TME characterization hold particular promise for improving outcomes. Future research priorities should include the development of non-invasive TME monitoring tools, rational combination therapies that address multiple immunosuppressive mechanisms, and innovative clinical trial designs that account for TME heterogeneity and dynamics. By continuing to unravel the complexities of the lung cancer TME and translate these insights into effective therapeutic strategies, we can advance toward the goal of personalized, TME-centred care that improves survival and quality of life for patients with lung cancer.

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