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Review

Characteristics of tumor microenvironment and novel immunotherapeutic strategies for non-small cell lung cancer

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ABSTRACT

Immune checkpoint inhibitor-based immunotherapy has revolutionized the treatment approach of non-small cell lung cancer (NSCLC). Monoclonal antibodies against programmed cell death-1 (PD-1) and PD-ligand 1 (PD-L1) are widely used in clinical practice, but other antibodies that can circumvent innate and acquired resistance are bound to undergo preclinical and clinical studies. However, tumor cells can develop and facilitate the tolerogenic nature of the tumor microenvironment (TME), resulting in tumor progression. Therefore, the immune escape mechanisms exploited by growing lung cancer involve a fine interplay between all actors in the TME. A better understanding of the molecular biology of lung cancer and the cellular/molecular mechanisms involved in the crosstalk between lung cancer cells and immune cells in the TME could identify novel therapeutic weapons in the old war against lung cancer. This article discusses the role of TME in the progression of lung cancer and pinpoints possible advances and challenges of immunotherapy for NSCLC.

1. Introduction

Lung cancer is the leading cause of cancer death worldwide[1] and non-small cell lung cancer (NSCLC) is the predominate pathological type. Immunotherapy represented by monoclonal antibodies against programmed cell death-1 (PD-1) and its ligand (PD-L1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) has opened a new era of NSCLC treatment. Nevertheless, non-responsiveness and long-term resistance have been registered.

Tumor cells can develop and facilitate the tolerogenic nature of the tumor microenvironment (TME), resulting in an unexpected immune evasion and tumor progression.[2] A better understanding of the cellular/molecular mechanisms involved in the interplay between all actors in the TME could identify novel therapeutic weapons in the old war against lung cancer. Here, we discuss the characteristics of TME of NSCLC and pinpoint possible advances and challenges of immunotherapy in this area.

2. The intricate immune network in TME of NSCLC

The TME is a dynamic and complex network, in which various immunosuppressive cells, secretory molecules and signal pathways play an active role in immune tolerance and tumor progression (Fig. 1). Chronic inflammatory environments may lead to deviated or altered immune cell differentiation in lung cancer, resulting in a weakened antitumor response and resistance to immune checkpoint inhibitors (ICIs).[3]

2.1. Tumor-infiltrating lymphocytes (TILs)

The density, distribution, and phenotypes of TILs play decisive roles in predicting the clinical outcomes for ICIs treatment in lung cancer. The major TIL populations (CD4, CD8, and CD19/20) comprise a variety of immune cell subsets with effector (anti-tumor) and uppressive (pro-tumor) phenotypes. Their function is affected by the surrounding environment, and the balance between them largely determines the immune status and progress of lung cancer.

2.1.1. Cytotoxic $CD8^+$ T lymphocytes

The density of $CD8^+$ T cells is associated with improved overall survival (OS) in lung cancer.[4] $CD8^+$ T cells are the primary cytotoxic T lymphocytes (CTLs), which mediate antitumor immunity by recognizing the major histocompatibility complex class I (MHC-I) molecules on the surface of tumor cells.[5] However, CTLs-mediated antitumor immu-

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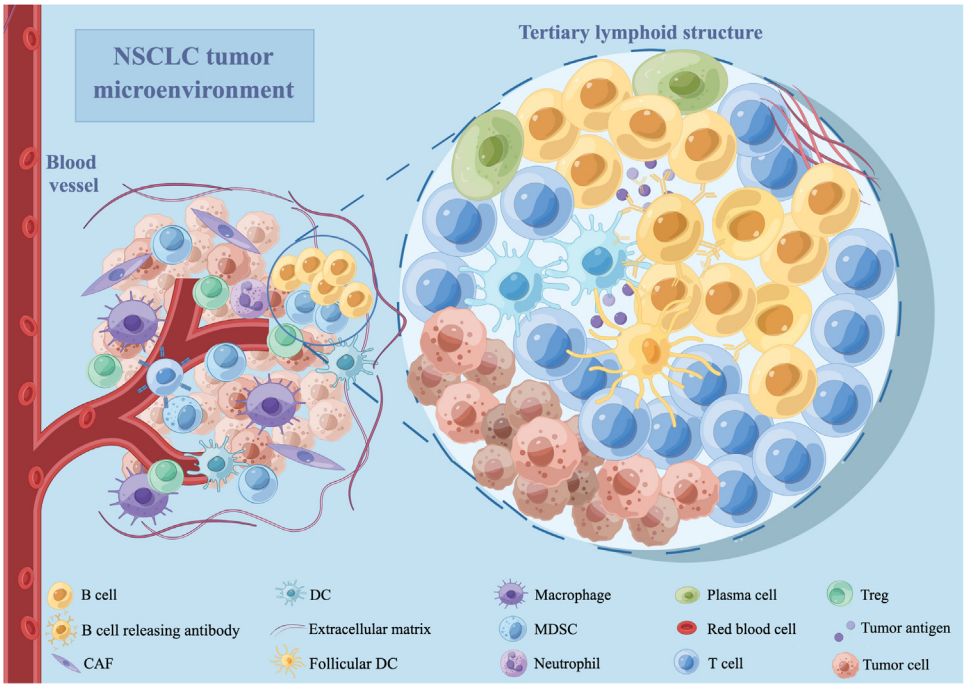

Fig. 1. The landscape of tumor microenvironment of NSCLC. CAF, cancer associated fibroblast; DC, dendritic cell; MDSC, myeloid-derived suppressor cell; NSCLC, non-small cell lung cancer; Treg, regulatory T cell.

nity is functionally limited by multiple mechanisms. The antigen recognition of $CD8^+$ T cells can be directly prevented due to the loss of the expression of MHC-I molecules, achieved by tumor cells via downregulation of the antigen process and peptide antigen presentation on MHC molecules.[6] On the other hand, the effector responses of $CD8^+$ T cells can be attenuated by the interaction with regulatory T cells (Tregs) and other suppressor cells through the secretion of immunoregulatory molecules such as transforming growth factor-beta (TGF-β), IL-10, and IL-4 to TME.[6,7] In addition, tumor cells limit the effector functions of $CD8^+$ T cells by interfering with the metabolism of amino acids and glucose. Tumor cells can up-regulate the indoleamine-2,3-dioxygenase (IDO) by depriving the essential amino acids tryptophan and arginine from TME.[8] It has been shown that the combination of IDO inhibitors with ICIs yielded increased numbers and functions of $CD8^+$ T cells in the TME.[9] Tumor cells with rapid growth also exhibit high glycolytic activity, which results in the limited availability of glucose for intratumoral $CD8^+$ T cells.[10] This process impairs the proliferative capacity and effector functions, such as the production of proinflammatory interferon-gamma (IFN-γ) of $CD8^+$ T cells due to the lack of glucose.[11] Finally, immune checkpoint signaling involving multiple inhibitory costimulatory molecules can be activated by tumor cells and immune cells in the TME, resulting in serious flaws in the proliferation, migration, and cytokine secretion of $CD8^+$ T cells.[12] Among these inhibitory recepors, PD-1, CTLA-4, T cell immunoglobulin and mucin-domain containing 3 (TIM-3), and lymphocyte-activation gene 3 (LAG-3) are best characterized.[13-16] Dysfunctional, "burned-out" $CD8^+$ TILs (Ebo) were identified recently with the presence of high proliferation rate and activation markers but low production of IFNγ. Importantly, these cells with high expression of PD-1, LAG-3 and TIM-3, were associated with resistance to ICIs.[17] A gradual and continuous upregulation of these alternative immune checkpoint receptors on intratumoral $CD8^+$ T cells has been reported during tumor progression in patients with NSCLC.[18] In addition, a recent study showed that CD8 and PD-L1 double-positive T cells were related to greater tumor burden, forming a “hot” but immunosuppressive TME.[19] Therefore, high TILs may impair neoantigen recognization rather than immunosuppression or dysfunction. Patients with these characteristics, however, had a greater likelihood of good response to PD-1 inhibitors.[19] Interestingly, T cells in cancer patients with different responses to immunotherapy exhibited different genetic characteristics. Responders mainly expressed higher memory and effector functions related genes, while non-responders expressed genes related to T cell dysfunction.[20]

2.1.2. Tregs

Treg is an immunosuppressive subtype of $CD4^+$ T cells in the TME. $Foxp3^+$ Treg infiltration indicated poor prognosis in multiple cancer types, supporting their protumoral role.[21,22]

CTLA-4 and CD25 are key molecules expressed on Tregs with immunosuppressive function.[23] CTLA-4 downregulates the expression of CD80/86 on antigen-presenting cells (APCs), resulting in less activation of conventional T cells. CD25 binds to IL-2 high-affinity, resulting in reduced level of IL-2 in the surrounding environment, thus limiting the activation and proliferation of IL-2-dependent T cells.[24] Besides, a series of suppressive cytokines and molecules produced by Tregs, such as TGF-β, IL-10, IL-35, and adenosine, inhibit the expansion and function of effector cells and disrupt cell metabolism.[25] Tregs also up-regulates B7-H4[26] and IDO[27] to suppress the function of APCs in TME and inhibits angiostatic cytokines produced by effector T cells, such as IFNγ, contributing to tumor angiogenesis.[28] Additionaly, the direct cytolysis of Tregs through mediators such as galectin-1[29] and granzyme B[30] induces the apoptosis of effector cells.

Several factors influence the recruitment of Tregs into TME. Tregs expressing CCR4 can be recruited to the tumor site by CCL22 produced by tumor macrophages and tumor cells.[30,31] $CCR10^+$ Tregs can be recruited by tumor cells through the production of CCL28.[32]

Treg depletion represents a promising strategy to reinvigorate antitumor immunity. The use of antibody targeting CD25 to remove Tregs in tumor-bearing mice, especially before tumor inoculation, can significantly increase $CD8^+$ TILs to achieve tumor eradication.[33] An increasing body of evidence suggests that removing $Foxp3^+$ Tregs by different methods is effective in treating tumors and enhancing tumor vaccines *in vivo*.[34,35] Treg removal through local or systemic administration and selecting specific target molecules to hierarchically remove Tregs are two practical approaches for cancer immunotherapy.[21]

2.2. Tertiary lymphoid structure (TLS) and B cells

2.2.1. TLS

TLS in the TME is a favorable prognostic factor for most solid tumors. The presence of its specific subpopulations or respective dynam-

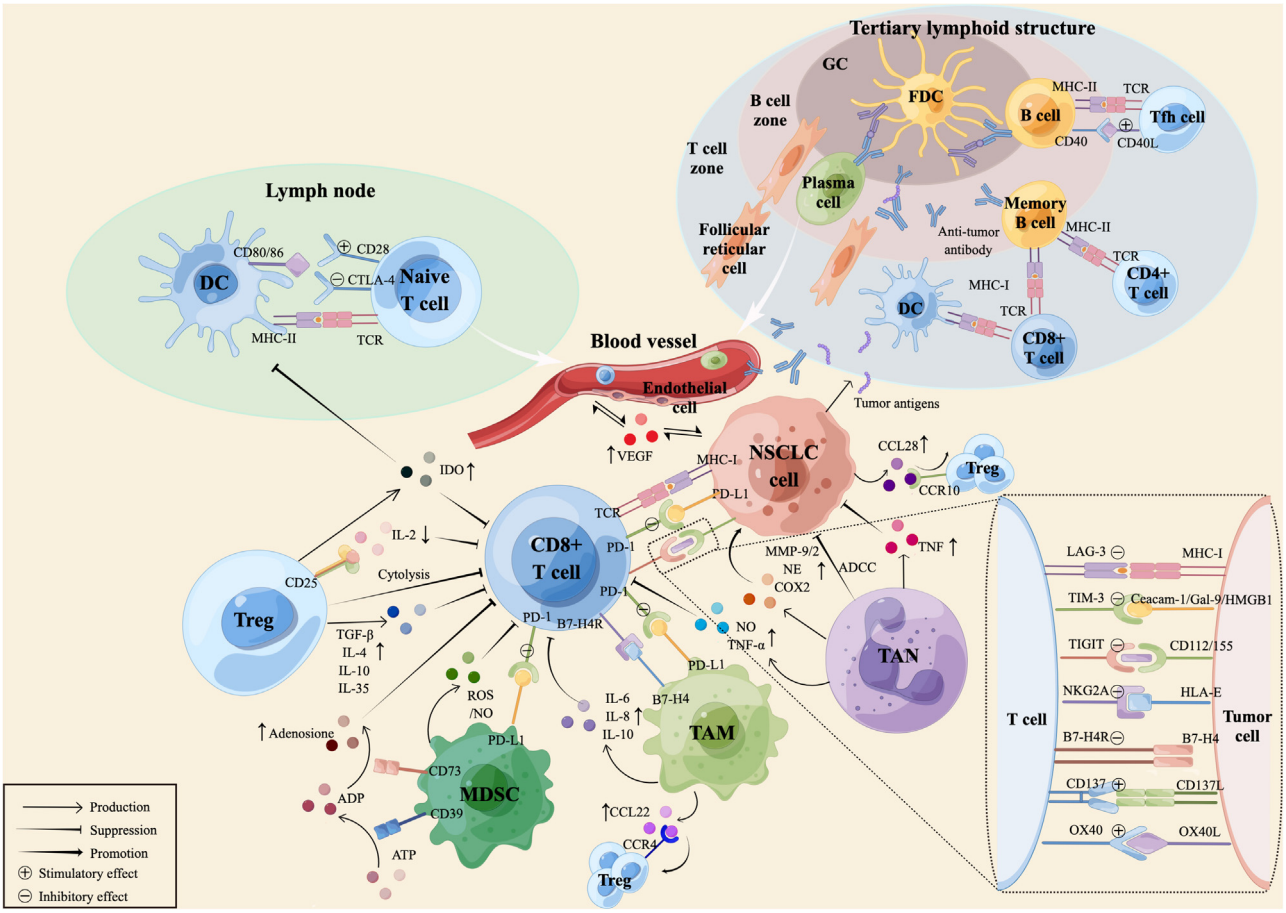

Fig. 2. Modulator role of diverse components of tumor microenvironment in regulating NSCLC immune responses. ADCC, antibody-dependent cellular cytotoxicity; CTLA-4, cytotoxic T lymphocyte antigen 4; DC, dendritic cell; FDC, follicular dendritic cell; GC, germinal center; HLA-E, human leucocyte antigen E; HMGB, high mobility group protein; IDO, indoleamine-2,3-dioxygenase; LAG-3, lymphocyte-activation gene 3; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; NE, neutrophilelastase; NKG2A, NK group 2 member A; NO, nitric oxide; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; TCR, T cell receptor; Tfh, T follicular helper cell; TGF-β, transforming growth factor-beta; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TIM-3, T cell immunoglobulin and mucin-domain containing 3; TNF, tumor necrosis factor; Treg, regulatory T cell; ROS, reactive oxygen species.

ics during therapy can predict response to anti-PD-1 in NSCLC.[36,37] A mature TLS consists primarily of a segregated T cell zone with mature dendritic cells (DCs) adjacent to a B cell follicle containing a germinal center (GC).[38] The presentation of adjoining tumor antigens by DCs, (re-)activation of naïve or memory lymphocytes, and the generation of effector cells can be readily achieved in this structure without the migration of random TILs into the tumor bed (Fig. 2).

CD62L is a specific marker for T cells identification in TLS since its expression favors the homing of lymphocytes into tissue.[39] In lung cancer, $CD4^+$ memory T cells remained the dominant subtype in TLS, while few naive and central memory T cells[40] were present. In advanced NSCLC, $CD8^+$ T cells with high expression of PD-1 ($PD1^{hi}CD8^+$ T cells) were detected in close vicinity to the B cell area in TLS, producing CXC-chemokine ligand 13 (CXCL13), suggesting this population mediates the recruitment of immune cell to TLS.[37] The innate lymphoid cell (ILC)–3 with natural cytotoxicity receptors positive were found to concentrate at the edge of TLS in human NSCLC tissue and exert lymphoid tissue inducer functions of secreting chemotactic factors and pro-inflammatory cytokines.[41] Correspondingly, a set of gene characteristics indicating the recruitment of T cells to intratumoral TLS were identified in lung cancer, supporting that TLS is formed using similar adhesion molecules and chemokines as secondary lymphoid organs.[40]

2.1.2. B cells

Tumor-infiltrating B cells (TIL-Bs) exist in the TME at all stages of differentiation and are generally concentrated at the invasive margin.[42] Although TIL-Bs are present in only a minority of patients with a particular tumor, they positively impact clinical outcomes if abundantly present.[43] An *in vitro* assay showed that TIL-Bs act as local APCs to give secondary stimulation to $CD4^+$ TILs in NSCLC and eventually change their phenotype and function. The effector T cell response was triggered by activated TIL-Bs and antigen-associated B cells, whereas the Treg phenotype was associated with exhausted TIL-Bs.[43] A positive correlation between TLS-Bs density and $CD4^+$ T cell receptor (TCR) clonality was documented in NSCLC,[44] suggesting that the proliferation of selective T cell clones could be induced by active crosstalk between T and B cells in TLS. Moreover, TIL-Bs efficiently produce IgG and IgA against tumor-specific antigens in NSCLC, specifically, LAGE-1, MAGE family, P53, and NY-ESO-1, supporting the existence of humoral immune response in NSCLC.[45]

The function of TIL-Bs is heavily reliant on their major partner T follicular helper cells (Tfh), for the generation and maintenance of antibody-producing and memory B cells in GC. In breast cancer, Tfh have been found to attract TIL-Bs to TME and promote the formation of functional GC in TLS by secreting the B cell chemoattractant CXCL13.[46] In parallel, the stimulation of CXC13 coupled CpG-ODN to $CXCR5^+$ B cells resulted in the elimination of lung metastasis through

$CD8^+$ T cell cytolytic effect in breast cancer-bearing mice.[47] B cells can conversely secrete CXCL13 and lymphotoxin through Toll-like receptor/lymphotoxin receptor 4 (TLR4) signaling in lung cancer, which served as positive feedback to favor the formation of TLS.[48] Moreover, in NSCLC, $PD1^{hi}$ $CD8^+$ T cells and $PD1^{hi}$ $CD4^+$ Tfh cells were observed within the B cell follicles of TLS, while a limited number of DC-$Lamp^+$ DCs was observed,[37] which implies the important synergistic effect between T and B cells in the generation and maintenance of antitumor immunity. Conversely, immunosuppressive TIL-Bs negatively affect the TME and promote tumor progression. It has been reported that regulatory B cells (Bregs), a representative immunosuppressive TIL-Bs, can suppress the immune response by secreting multiple inhibitory cytokines, including IL-10, IL-35 and TGF-β.[49] Increased IL-10-producing Bregs were detected in patients with NSCLC compared with healthy controls[50] and were related to a worse clinical stage.[51] The transcription factors such as IRF4 and BLIMP-1 play a critical role in the immunosuppressive functions of B cells and the differentiation of activated B cells to plasma cells.[52] *In vivo*, B-cell-derived IL-10 is mainly generated by B cells co-expressing IRF4 and BLIMP-1, suggesting plasma cells are an important contributor.[53] In patients with NSCLC, the immunoglobulin kappa C expressing plasma cells in stroma could predict the prognosis, while intratumoral plasma cells could predict outcomes of PD-L1 blockade.[54,55] In addition, IL-10-producing Bregs can be targeted by lipid mediator lipoxin A4 by dephosphorylating signal transducer and activator of transcription 3 (STAT3) and ERK, thus inhibiting tumor growth.[56] Overall, TIL-Bs have both antitumor and pro-tumor functions, and their functional phenotypes change dynamically under the influence of the TME.

2.3. Characteristic immunosuppressive components in TME of NSCLC

2.3.1. Tumor-associated macrophages (TAMs)

TAMs constitute the prevalent cellular component in the TEM of NSCLC, which exert pro- and antitumor effects through their two polarizing phenotypes, M1 (inflammatory) and M2 (anti-inflammatory). M1/M2 polarization dynamically adapts to complex stimuli.[57] Cytokines play a pivotal role in the polarization of macrophages, and the differential expression of TLR on macrophages is also involved.[58,59] TAMs with M2 phenotype are predominant in lung cancer, characterized by several markers including CD163, CD204, and MARCO.

M2 macrophages have been demonstrated to be correlated with poor outcomes in numerous studies in lung cancer.[60] *In vitro*, M2 macrophages were found to upregulate CRYAB expression on lung cancer cells and activated ERK/ SLUG signaling pathway, thus promoting tumor EMT and invasion.[61] Intertumoral high expression of CRYAB was additionally related to lymph node metastasis and late stage in patients with NSCLC. In patients with NSCLC, the density of macrophage infiltration was positively associated with intra-tumor microvessels and predicted worse survival. The up-regulated expression of IL-8 by macrophages may be the involving mechanism.[62]

M2 macrophages also produce immunosuppressive interleukins like IL-6,[63] IL-8,[64] and IL-10[65] to promote tumor growth and metastasis. Through STAT6 signaling, IL-6 polarized macrophages to the IL-4-dependent M2 phenotype by increasing IL-4 receptor expression.[66] Antibodies targeting IL-6 and its receptor inhibited tumor progression in *K-RAS* mutant lung cancer.[67,68] Macrophages provide an immunosuppressive TME by interacting with Tregs by secreting IL-10.[69] IL-10 is also known to induce apoptosis resistance in lung cancer cell lines.[70] Mounting evidence suggests that IL-10 overexpression on TAMs is associated with poor prognosis and advanced stage in NSCLC.[71,72] TAMs accumulation correlated with the expression of integrin $\alpha v\beta 3$ on tumor cells, which drives tumor progression and drug resistance.[73] Macrophage depletion coupled with silenced *CCR2* and *CX3CR1* suppressed tumor development in a mouse model of lung cancer.[74] Importantly, TAMs with negative PD-1 expression can bind to Fcγ receptors expressed on the surface of anti-PD-1 antibodies, allowing them to capture these compounds *in vivo* and thus attenuate their therapeutic efficacy.[75]

2.3.2. Myeloid-derived suppressor cells (MDSCs)

MDSCs facilitate tumor progression by suppressing immunity and promoting angiogenesis.[76] They effectively inhibit T cell function through metabolic reprogramming of TME, including consumption of arginine through arginase (Arg)−1, production of nitric oxide (NO) through inducible nitric oxide synthase (iNOS), and production of reactive oxygen species (ROS).[77] In NSCLC, the MDSCs expressing Arg-1 and iNOS are involved in inhibiting the proliferation of $CD8^+$ T cells and reducing the expression of CD3 ζ.[78,79] MDSCs also release various immunosuppressive molecules and upregulate of inhibitory checkpoints to promote the differentiation or development of Tregs and interfere with the homing and trafficking of tumor-specific T cells.[80] Like Tregs, MDSCs express ectonucleotidases CD39 and CD73, which turn ATP into adenosine thus contributing to immune suppression.[81] The overexpression of CD39 and CD73 on MDSCs can be induced by TGF-β-induced HIF-1α activation, which is dependent on mTOR signaling under normoxic conditions and has been associated with a worse prognosis in patients with NSCLC.[82] MDSCs additionally promote epithelial-mesenchymal transition (EMT) and enhance metastasis through CCL11-mediated ERK and AKT signaling activation in lung cancer cells.[83]

MDSCs are characterized by many biochemical features other than the expression of Arg-1, including the activation of STAT3 signaling pathway and the induction of endoplasmic reticulum (ER) stress.[84] The activation of the STAT3 pathway can inhibit apoptosis and differentiation of myeloid cells by upregulating the expression of anti-apoptosis genes c-myc, cyclin D1 and Bcl-xL,[85] and is considered a key factor in the promotion of the expansion of MDSCs in cancer. In a transgenic mice lung cancer model, continuous activation of the STAT3 pathway and the overexpression of constitutive STAT3C can directly induce carcinogenesis of alveolar epithelial cells type II,[86] possibly mediated by STAT3-stimulated expansion of MDSCs and immunosuppression.[87] In tumor-bearing mice models of lung cancer, increased expression of tumor necrosis factor (TNF)-related apoptosis-induced ligand receptors (TRAIL-Rs) in MDSCs mediated apoptosis compared with neutrophils or monocytes and this event was induced by ER stress in MDSCs, implying that ER stress determines the MDSC pathophysiology.[88] MDSCs can also release exosomes to exert their function,[89] which are faciliated by tumor-derived exosomes,[90] forming an exosomes-mediated communication to further inhibit the anti-tumor immune response. The immunosuppressive function of MDSCs in lung cancer can be affected by many factors, such as the expression of caspase recruitment domain-containing protein 9,[91] tumor-derived tissue factor,[92] and long noncoding RNAs and microRNA networks.[77] Thus MDSCs might be a potential target for resetting immune resistance in lung cancer. In a preclinical study in mice with lung cancer, targeting MDSCs increased the natural killer (NK) cells and APC activity,[93] as well as the memory and effector $CD8^+$ T cell responses. MDSCs have been extensively studied in preclinical studies as a potential therapy for ICI.[94,95]

2.3.3. Tumor-associated neutrophils (TANs)

TANs are neutrophils infiltrating the tumor, originating from peripheral neutrophils attracted by chemokines and relocated to the tumor stroma.[96] Similar to TAMs, TANs have a two-sided anti- or pro-tumoral (N1 or N2) phenotype which can be "alternately activated" when exposed to different TME.[97,98] NSCLC has a neutrophil predominant immune profile.[99] In patients with advanced NSCLC who received anti-PD-1 immunotherapy, the increased neutrophils count was positively correlated with worse clinical outcome response to immunotherapy.[100,101]

By synthesizing and secreting related proteases, such as neutrophile-lastase (NE) and matrix metalloproteinases (MMPs), TANs are closely involved in tumor proliferation, invasion and metastasis. In a mouse model of lung adenocarcinoma, TANs-secreted NE mediated the degradation of insulin receptor substrate-1 and accelerated tumor growth.[102]

TANs also interacted with tumor cells through NE to promote their detachment and metastasis in lung cancer cell lines.[103] A study found that TANs could upregulate the secretion and activity of MMP-9 and MMP-2 under the inhibition of endogenous IFN-β in TME, exhibiting an N2 phenotype to promote the development of tumors.[104] Intriguingly, TANs induce the apoptosis of non-activated $CD8^+$ T cells in a TNF-α and NO-dependent mechanism, promoting a tumor-supportive environment in thoracic malignancy models.[105] Neutrophils can additionally release a variety of inflammatory mediators to promote tumor progression. Furthermore, in lung cancer cell lines, TANs promoted tumor proliferation by releasing COX-2-derived prostaglandin E2.[106]

Contrary to the above-mentioned tumor-promoting effects, the antitumor effects of neutrophils were documented. In addition to the antibody-dependent cell-mediated cytotoxicity effect, TANs directly produce cytotoxic mediators or release TNF-related apoptosis-inducing ligands to inhibit tumor growth.[107] In resected lung cancer tissues, TANs crosstalked with activated T cells, resulting in a significant upregulation of costimulatory molecules on the surface of neutrophils, thus promoting T cell proliferation in a positive feedback cycle.[108] Therefore, the functions of TANs in the TME vary with tumor types, stages and treatment. IFN-β plays a key role in regulating the production, recruitment and longevity of TANs.[109] Accordingly, regulating the phenotype of TANs may be an effective treatment in the future.

2.4. Innate immune players and stromal components

2.4.1. NK cells

NK cells represent the first line of host defense against environmental damage, pathogen, and cancer. NK cells enriched in TME of NSCLC, primarily CD56 bright $CD16^-$ NK cell subset, exhibit immunoregulatory functions.[110] By releasing IL-8/CXCL8, placental growth factor, and VEGF, CD56 bright $CD16^-$ NK cells facilitate protumor neoangiogenesis.[111] A reduction in INF-γ production and peripheral NK cells cytotoxicity was reported in patients with lung cancer, which encouraged tumor growth.[112] A lower number of peripheral NK cells with distinct receptors expression was also observed in patients with NSCLC.[113] Similar dysfunctional peripheral NK cells were found in SCLC, although the NK cell count was equal to healthy individuals.[114] A relatively lower level of granzyme B released by NK cells in lung cancer tissue than in adjacent normal tissues was found,[113] which may be due to cancer-derived soluble factors and the induction of IFN-γ in NK cells.[115] NK cells dysfunction is characterized by altered migratory behavior with reduced CX3C chemotactic receptor 1 and sphingosine-1-phosphate receptor 1 levels.[110] The interaction between the tumor and NK cells, soluble factors, and activated platelets account for intratumoral NK cell dysfunction. The inactivation of NK cells can also be induced by inhibitory signals mediated by the binding of killer cell immunoglobulin-like receptor (KIR) on its surface to the MHC-I ligands on tumor cells.[116] Epigenetic silencing of NK-activating ligands also contributes to defective NK cell activation in SCLC.[117] Additionally, the metabolism and cytotoxic activity of NK cells were found to be impaired by low nutrients and hypoxia in the TME in lung cancer models.[118]

The relationship between tumor NK cell infiltration and the prognosis of lung cancer has been differently addressed.[119,120] Induced-pluripotent stem cells (IPSC)-derived NK cells were reported to increase tumor PD-L1 expression in cell lines,[121] whereas native NK cells in the TME did not affect PD-L1 expression in tumors, suggesting that non-responding tumors could be effectively killed only when expanded NK cells were combined with anti-PD-1 therapy.[122] Consistently, PD-1 inhibitors combined with NK cell therapy demonstrated a synergistic effect in a clinical trial of PD-L1 positive patients with NSCLC.[123]

2.4.2. DCs and DC-based vaccines

DCs prime $CD8^+$ T cells by presenting the tumor-specific antigens to them, which is a key step in initiating anti-tumor immune response.[124] Plasmacytoid DCs (pDCs), as a subset of DCs, are characterized by a high level of IFN-α production[125] and play a crucial role in maintaining self-tolerance rather than antigen presentation.[126] In lung cancer, the complex TME prevents DCs from exhibiting anti-tumor effectiveness in many ways. The functional DCs that activate T cells are dynamically excluded from the tumor area. In the mouse model of lung cancer, the population of $CD103^+$ DCs with antigen-presenting ability was smaller compared with $CD11b^+$ DCs, which promoted the activation of CD4 cells.[127] Accordingly, the proportion of $CD141^+$ DCs (functionally similar to mouse $CD103^+$ DCs[128]) decreased significantly in human lung cancer compared with normal lungs.[129] Moreover, the pDCs immunosuppressive-phenotype are recruited into TME. The IFN-α production is impaired in tumor-associated pDCs, negatively affecting cytotoxic and antitumor immunity.[130] The levels of pDCs in peripheral blood were higher in patients with more advanced NSCLC stages.[131] In addition, more immunosuppressive pDCs with CD33 and PD-L1 overexpression were present in NSCLC tissues than in healthy tissues, which synthesized large amounts of interleukin 1α (IL-1α) to promote cancer cell proliferation.[132] Furthermore, DCs are reprogrammed into regulatory DCs (regDCs) in lung cancer.[133] RegDCs can inhibit the production of IFN-γ from NK cells via many mechanisms[134] and contribute to Treg induction during hepatocyte transplantation.[135] Furthermore, the effector molecules expressed on the surface of DCs are downregulated in lung cancer. In lung cancer TME, the expression of proteins[136] including vesicle associated membrane protein3 (VAMP3), soluble N-ethylmaleimide-sensitive factor accessory protein receptor (SNARE), and costimulatory molecules[137] such as CD80, CD40, CD86, IL-12, and MHC-II were decreased on regDCs, which is necessary for antigen presentation. The ability of DC to secrete cytokines IL-12 and IFN-α was also lost due to inhibition of stimulator of IFN genes (STING) signaling and TLR3 lactic acid in TME. IL-12 secretion in DCs can also be suppressed by the overexpression of miRNA-301.[138] DCs differentiation could be affected by the tumor-derived soluble factors via the suppression of nuclear factor kappa-B (NF-κB) and STAT3 pathways *in vitro* in NSCLC.[139] Finally, DCs express immunosuppressive molecules to facilitate lung cancer development. Inhibitory molecules such as B7-H3, T-cell immunoglobulin and mucin domain 3 (Tim3) were upregulated on DCs in lung cancer tissues compared to normal lung tissues.[140,141]

DCs maturation rate is independently associated with the survival in patients with lung cancer.[142] The immunotherapeutic strategy based on DCs has certain prospects in the fight against lung cancer. DC-based immunotherapy in NSCLC were summarized in Table 1 .

2.5. Typical immune inhibitory factors and modulators

Many cytokines, chemokines and immunosuppressive molecules act as messengers in the vast network of TME, mediating cell-cell communication and facilitating immune evasion in lung cancer. Listed below are the typical players that the current study highlights (Table 2).

2.6. Angiogenesis

Angiogenesis with structurally and functionally aberrant vasculature constitutes an important part of the TME in lung cancer. Vascular endothelial growth factor (VEGF) and its receptor not only increase the vascular permeability by regulating the proliferation, differentiation, and migration of endothelial cells of microvessels but also suppress the functions of effector immune cells, including $CD8^+$ T cells, NKs, and DCs while facilitating the suppressive effect of Tregs, TAMs, and MDSCs.[143] Therefore, it is reasonable to combine antiangiogenic therapy with immunotherapy. Several clinical trials have evaluated this combination in NSCLC in different settings (Table 3).

2.7. Characteristics of TME in NSCLC with oncogenic driver mutations

The TME of NSCLC with oncogenic driver mutations could be unique and dynamic, affected by both the specific mutation itself and the

Table 1
Representative DC-based immunotherapy in NSCLC.

Category	Source	Maturity	Phase	Stage	Number*	ORR (%)	Survival	Immune response (number)	Safety (grade, number)	References
DC	moDCs	Mature	1	I-IIIB	16	N/A	N/A	Tumor-antigen independent response (5) Antigen specific response (6)	No serious AEs; Local reaction at the injection site (1, 10) and fatigue (1, 3)	256,257
DC	moDCs	Mature	1	IV (malignant pleural effusion)	8	12.5	N/A	Minor to moderate increases in T cell responses against tumor antigens (6)	No grade 2 to 4 AEs	258
DC	moDCs	Immature	1	I-IIIB	14	N/A	N/A	Immunologic responses (9)	No treatment related AEs	259
DC	moDCs	Mature	1	IIIB-IV	15	0	N/A	Increase IFN-γ production by $CD8^+$ cells (5)	No grade 3 or 4 AEs; Fever (1, 1)	260
DC	moDCs	Mature	1	IIIB-IV	5	N/A	N/A	Improvement in the specific immune response but was not long lasting (5)	Fatigue and chills (2, 1)	261
DC	moDCs	Mature	Retrospective analysis	Locally advanced or metastatic	62	8.1	MST = 12 months 1-year survival rate = 48% 2-year survival rate = 22%	N/A	No serious AEs; Fever (1–2, 15); Local reaction at the injection site (1, 26)	262
DC	moDCs	Immature	1	IIIB-IV	27	11.1	Median PFS = 4.8 months (95% CI: 4.4, 5.2) Median OS = 10.7 months (95% CI: 10.3, 11.2)	N/A	No grade 4 AEs; Fever (1, 5)	263
DC	moDCs	Mature	Retrospective analysis	Locally advanced or metastatic	260	11.2	MST = 13.8 months (95% CI: 11.4, 16.8) 1-year survival rate = 53.5% 2-year survival rate = 36.1% 5-year survival rate = 8.8%	N/A	N/A	264
DC	moDCs	Mature	1	I-IIIB	16	0	N/A	Positive DTH reaction (6); Significant increase in IFN-γ expression on day 60 vs. day 0 and an increasing trend in the mean CD4:CD8 values of day 30 and day 90	No serious AEs; Fever, chills and fatigue (1, 1); Exanthema (1, 1); Pruritus (1, 3)	265
DC	moDCs	Immature	1	III-IV	16	N/A	MST = 3.9 months	Systemic responses against tumor associated antigens (6); Induced tumor $CD8^+$ T cell infiltration and increased $CD8^+T$ cells positively correlated with increased PD-L1 mRNA expression (7)	Vaccine related AEs (N/A, 3); Flu-like symptoms (1, 1); Hemoptysis (1, 1); Nausea (1, 1); Fatigue (1, 1)	266
DC	moDCs	Mature	Retrospective analysis	IIIB-IV	40	0	MST = 7.4 months (95% CI: 4.2, 10.6) 1-year survival rate = 25%	MUC1-specific cytotoxic immune responses (7 patients who received six vaccinations)	Fever (N/A, 16); Skin reaction at the vaccination site (N/A, 6); Acute lung injury (N/A, 1)	267
DC	moDCs	Mature	1	I-IIIA	15	N/A	N/A	Decreased $CD3^+CD4^+CD25^+Foxp3^+$ Treg number and increased TNF-α and IL-6 (2)	No serious AEs; Fever (1–2, 6); Fatigue (1–2, 5); Myalgia (1–2, 6); Chills (1–2, 1)	268

(*continued on next page*)

Table 1 (*continued*)

Category	Source	Maturity	Phase	Stage	Number*	ORR (%)	Survival	Immune response (number)	Safety (grade, number)	References
DC/CIK	moDCs	Mature	1/2	I-IIIA	42	N/A	No statistical difference in 2-year DFS between immune-CT group (75.6 ± 7.2%) and CT group (65.3 ± 8.0%); The 2-year OS was significantly increased in the immune-CT group (94.7 +/- 3.6%) comparing to the CT group (78.8 +/- 7.0%), $P < 0.05$	Increased production of anti-tumor cytokines, including IFN-γ, TNF-α and TNF-β in patients who had no progression	No grade 3 or 4 AEs	269
DC/CIK	moDCs	Immature	1/2	IIIB-IV (expressing CEA)	14	N/A	The median TTP was significantly increased in the immune-CT group (6.9 months, 95% CI: 5.0, 8.8) comparing to the CT group (5.2 months, 95% CI: 3.3, 6.0), $P = 0.03$; No statistical difference in OS rate between two groups ($P = 0.18$); The 1-, 2-, and 5-year survival rates were 64.3%, 49%, and 21.0%, respectively in immune-CT group.	N/A	Skin toxicity (1–3, 9); Fever (1–4, 10)	270
DC/CIK	moDCs	Mature	RCT	IIIB-IV	30	3.3	The median TTP was significantly increased in the DC/CIK cell group (3.2 months, 95% CI: 2.94, 3.50) comparing to the control group (2.56 months, 95% CI: 2.39, 2.73), $P < 0.05$	Increased proportion of NK-cells, $CD3^+$ and $CD4^+$ T cells, but decreased $CD8^+$ cells in treatment group	Fever (N/A, 4)	271
DC/CIK	moDCs	Immature	Paired cohort study	IIIB-IV	61	18	The 2-year OS was significantly increased in the immune-CT group (57.2% and 27% for 1- and 2-year OS rate) comparing to the CT group (37.3% and 10.1%), $P < 0.05$	Increased secretion of INF-γ and TNF-α, decreased TGF-β, enhanced antitumor activity, and increased $CD3^+CD56^+$ cell ratio in treatment group	No serious AEs	272
DC/CIK	moDCs	Immature	RCT	IIIB-IV NSCLC (EGFR exon 19 and/or 21 mutation)	26	N/A	The median PFS was significantly increased in DC/CIK+erlotinib group (5.02 months, 95% CI: 3.56, 4.40) comparing to the erlotinib group (3.98 months, 95% CI: 4.32, 5.72), $P = 0.002$; No statistical difference in median OS between the DC/CIK+erlotinib group (9.9 months, 95% CI: 9.1, 10.6) and the erlotinib group (10.5 months, 95% CI: 9.6, 11.4), $P = 0.29$	Higher levels of $CD3^+$, $CD4^+$, and $CD8^+$ T cells in DC/CIK+erlotinib group	Fever (N/A, 3); Rash (N/A, 14); Diarrhea (N/A, 9)	273

(*continued on next page*)

Table 1 (*continued*)

Category	Source	Maturity	Phase	Stage	Number*	ORR (%)	Survival	Immune response (number)	Safety (grade, number)	References
DC/CIK	moDCs	Mature	1	Resected stage I-III (arm 1) or metastatic (arm 2)	50	N/A	N/A	Increased INF-γ in patients with resected NSCLC and increased IL-4 and IL-10 in tumor-bearing patients	N/A	274
DC/CIK	moDCs	Mature	RCT	IIIB	30	83.5	The 1-year OS was significantly increased in treatment group (83.3%) compared with control group (60.6%), $P < 0.05$	Increased $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ in treatment group	Fever (1–2, 5)	275
DC/CIK	moDCs	Immature	Retrospective analysis	IIIB-IV	99	N/A	The OS was significantly increased in immunotherapy group compared with non-immunotherapy group ($P = 0.03$)	Positive response to DTH skin test (59)	Fever (1–2, 30; 3, 6); Rash (1–2, 7)	276
DC/CIK	moDCs	Mature	2	III-IV	21	47.6	The median PFS was significantly increased in DC/CIK group (330 days) compared with control group (233 days); HR: 0.51; 95% CI: 0.27, 1.0; $P = 0.0483$; No statistical difference in mOS between treatment group (400 days) and control group (460 days); HR: 0.83; 95% CI: 0.41, 1.69; $P = 0.606$	No differences in the percentage of $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD4^+/CD8^+$ T cell ratio and $CD3^-CD56^+$ NK cells in treatment group, $P > 0.05$; A tendency of a decrease in $CD4^+/CD8^+$ T cell ratio in the control group, $P = 0.08$	Fever (1–2, 5); Anorexia (1–2, 3); Nausea (1–2, 3)	277
DC/CIK	moDCs	Mature	2	Resected IIB-IIIA	169	N/A	N/A	Reduced Tregs frequency and Treg-generated cytokines level in patients received with ≥ 3 cycles of DC/CIK cell treatment compared with those with < 3 cycles of treatment	N/A	278
AKT-DC	TDLNs	Mature	2	Resected III-IV with N2 disease	31	N/A	2-year OS rate = 88.9% 5-year OS rates = 52.9%	N/A	Chills in 83.4% of the courses; Fever in 78.0% of the courses; Fatigue in 23.0% of the courses; Nausea in 17.0% of the courses	279
AKT-DC	TDLNs	Mature	3 RCT	Resected IB-IV	50	N/A	The 2-, 5-, and 7-year RFS rates were significantly increased in immune-CT group (70.0%, 57.9%, and 47.5%) compared with CT group (43.1%, 31.4%, and 28.5%), HR: 0.473; The 2-, 5-, and 7-year OS rates were significantly increased in immune-CT group (96.0%, 69.4%, and 55.1) compared with CT group (64.7%, 45.1% and 38.1%), HR: 0.474	Higher $CD8^+/CD4^+$ T cell ratio in the survivors than in the deceased, $P = 0.0013$	Fever in 6.2% of the courses; Chills in 6.8% of the courses	280,281

* Number of patients receiving DC-based immunotherapy.Abbreviations: AE, adverse event; AKT, activated killer T cells; CEA, carcinoembryonic antigen; CI, confidence interval; CIK, cytokine induced killer; CT, chemotherapy; DC, dendritic cell; DFS, disease free survival; DTH, delayed-type hypersensitivity; EGFR, epidermal growth factor receptor; HR, hazard ratio; IL, interleukin; INF, interferon; moDCs, monocyte derived dendritic cells; mOS, median overall survival; MST, median survival time; MUC1, mucin 1; N/A, not available; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free time; RCT randomized controlled trial; RFS, relapse-free survival; TDLNs, tumor draining lymph nodes; TGF, transforming growth factor; TNF, tumor necrosis factor; Treg, regulatory T cell; TTP, time to progression.

Table 2
Representative cytokines/chemokines' roles in tumor progression and immunoregulation of NSCLC.

Cytokines/chemokines	Category	Interaction with immune cells	Functions
IL-6	Pro-inflammatory cytokine	Produced by T cells, macrophages, adipocytes	Differentiation, cytokine production
IL-8	Pro-inflammatory cytokine	Produced by epithelial cells, macrophages, endothelial cells	Angiogenesis, chemotaxis
IL-10	Anti-inflammatory cytokine	Produced by monocytes, B cells, and T cells	Inhibition of proinflammatory cytokines
IL-17	Pro-inflammatory cytokine	Produced by Th 17 cells	Cytokine and chemokine production, anti-tumor immunity
IL-27	Anti-inflammatory cytokine	Produced by APCs	IL-10 production
IL-35	Anti-inflammatory cytokine	Produced by Tregs	Proliferation of Tregs and suppresses Th17 cells
IL-37	Anti-inflammatory cytokine	Produced by NK cells, monocytes, epithelial cells, and B cells	Antimicrobial, antitumor immunity
TNF-α	Pro-inflammatory cytokine	Produced by macrophages, $CD4^+$ lymphocytes, adipocytes, and NK cells	Cell proliferation, cytokine production, apoptosis
IFN-γ	Pro-inflammatory cytokine	Produced by NK cells, T cells	Antiviral action
TGF-β	Anti-inflammatory cytokine	Produced by T cells, macrophages	Inhibition of proinflammatory cytokine production
GM-CSF	Pro-inflammatory cytokine	Produced by T cells, macrophages, and fibroblasts	Improve neutrophil and monocyte function, macrophage activation
VEGF	Growth factor	Produced by macrophages, endothelial cells, platelets	A growth factor that aids in vasculogenesis, angiogenesis, chemotaxis, migration of endothelial cells
CCL-2	Inflammatory chemokine	Recruits' monocytes, macrophages	Promotes tumor progression, angiogenesis, metastasis
CCL-5	Inflammatory chemokine	Recruits' neutrophils, Tregs	Promotes survival of tumor cells by angiogenesis stimulation
CCL-18	Homeostatic chemokine	Produced by monocytes, macrophages, and immature DCs	Proinflammatory, immune regulation; promotes tumor progression by mediating TME
CXCL-12	Homeostatic chemokine	Recruits' endothelial progenitor cells	Promotes angiogenesis, invasion and metastasis
CX3CL-1	Inflammatory chemokine	Relocates monocytes, mast cells, T cells, and NK cells to the site of inflammation; Aids in M2 macrophage polarization	Regulates the migration, adhesion, and survival of both anti-tumor and pro-tumor immune cells and facilitates cancer growth and metastasis
CXCL-1	Inflammatory chemokine	Recruits' neutrophils and Tregs	Promotes survival and proliferation of tumor cells
CXCL-5	Inflammatory chemokine	Leukocyte placement	Promotes tumor growth, angiogenesis, and metastasis
CXCL-8	Inflammatory chemokine	Produced by macrophages; Recruits' neutrophils	Proinflammatory, promotes survival and proliferation of tumor cells
CXCL-13	Homeostatic chemokine	Produced by follicular DCs and Th cells; Infiltrates B cells into tumor cells	Regulates cancer cell survival, apoptosis, proliferation, differentiation, migration, invasion, and adaptive immunity; dichotomic anti- and pro-tumor functions in the TME

Abbreviations: APC, antigen-presenting cells; DC, dendritic cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; INF-γ, interferon-gamma; NK, natural killer; NSCLC, non-small cell lung cancer; TGF-β, transforming growth factor-beta; Th, T helper cell; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell; TME, tumor microenvironment; VEGF, vascular endothelial growth factor.

targeted therapy, resulting in different anti-tumor immune responses from those of wildtype. For example, epidermal growth factor receptor (*EGFR*) sensitive mutations are characterized by a low tumor mutation burden or neoantigen load, referring decreased tumor immunogenicity and noninflamed TME.[144] *EGFR* mutations can downregulate CXCL10 and CCL5 through interferon regulatory factor–1, resulting in impaired $CD8^+$ T cell infiltration. Instead, they upregulates CCL22 through cJun/cJun N-terminal kinase, which leads to Tregs recruitment.[145] Exosomes containing EGFR induce DCs to produce IDO, which is essential in converting $CD4^+$ T cells into Tregs.[146] In *EGFR*-mutant NSCLC, there is a lack of $CD8^+$ tissue-resident memory (TRM) cells that can secrete CXCL13 and stimulate TLS generation. TAMs and cancer-associated fibroblasts, which recruit, retain, and expand $CD8^+$ TRM cells in the TME, are also absent.[147] *EGFR* mutations may additionally convert ATP into adenosine by upregulating CD73 expression. Abundant adenosine in TME further disturbs macrophages polarization, and inhibits the activity of multiple immune cells (e.g., effector T cells, NK cells and DCs) by activating Tregs and accumulating MDSCs.[148] *EGFR* mutations may further downregulate MHC expression through activating downstream MEK/ERK signal pathways[149] and affecting IFN-γ signal pathway, thus alter antitumor immune responses. Notably, uncommon *EGFR*-mutant tumors (G719X, L861Q, S768I, and exon 20 insertions) are associated with higher levels of TILs and PD-L1 expression compared with common types,[150] which may induce different TMEs. A "colder" TME and reduced NK cells are observed in lung cancer with *EGFR* and *HER2* exon 20 insertions than wildtype tumors.[151]

By contrast, *KRAS*- or *TP53*- mutant tumors display an increased TMB and somatic mutations,[152] indicating enhanced tumor immunogenicity. Consistently, *KRAS* and *TP53* co-mutations show a distinct TME profile including high levels of PD-L1 expression and TILs. However, both mutations can activate the intrinsic inflammatory signal through NF-κB pathway, triggering the production of a variety of inflammatory cytokines (TNF-α, IL-1α/β and CXCL8), which in turn induces a pro-inflammatory TME through polarizing and recruiting immunosuppressive cells.[153,154] It is reported that a pro-tumorigenic TME is observed in *KRAS* mutant tumors, rich in M2 macrophages, Tregs, MDSCs, and T helper (Th) 17 cells.[154]

Targeted therapy, take EGFR-tyrosine kinase inhibitors (TKIs) as an example, causes dynamic changes in TME. Not only the expression of PD-L1 might be suppressed with EGFR-TKIs at first and then increase,[155,156] but also the components of immune cells are inversed during the treatment, resulting in a TME of a pro-inflammatory "hot" phenotype at efficient timepoint to an immunosuppressive phenotype at resistant timepoint.[157] The mechanisms for EGFR-TKIs to reshape TME include: inhibiting Tregs function by Foxp3 degradation and reducing their infiltration; enhancing the cytotoxicity of CTLs; upregulating the secretion of key cytokines including IL-10 and CCL2[158]; increasing the expression of MHC molecules.[159]

3. Novel immunotherapeutic strategies for NSCLC

The inflammatory nature of NSCLC suggests it is a promising target for immunotherapy. Overall, there are five different immunotherapeutic approaches against NSCLC, including immune checkpoint blockade, cellular therapy, therapeutic vaccines, cytokine therapy, and immunotherapeutic agents in combination with conventional treatments (Fig. 3). This report summarizes the representative information on novel immune-based strategies for treatment of NSCLC. The mechanisms, rationales, and applications of these strategies are also discussed.

3.1. Novel immune checkpoint targets beyond PD-1/PD-L1 and CTLA-4

The immune response within the TME is regulated by different checkpoints on the surface of T cells. These molecules bind to their ligands on the APCs or tumor cells, forming axial signals that stimulate or inhibit the effects of cells. Recently, novel immune checkpoint molecules that can be directly blocked or stimulated by specific anti-

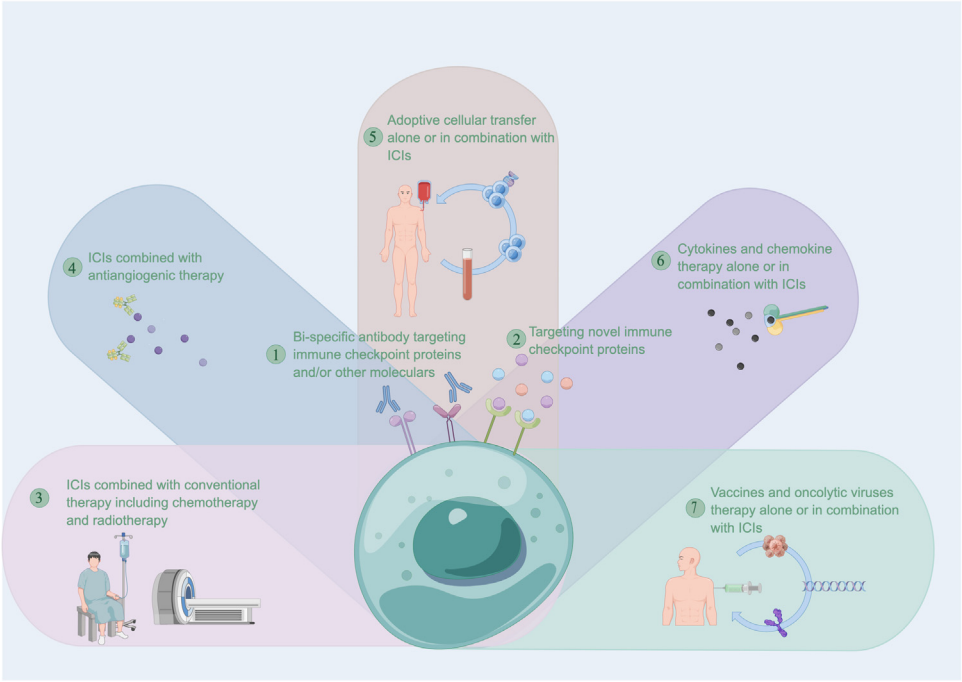

Fig. 3. Overview of novel immunotherapy strategies. ICI, immune checkpoint inhibitor.

bodies and potentially overcome resistance to conventional ICIs have emerged (Fig. 2).

3.1.1. T cell immunoreceptor with Ig and ITIM domains (TIGIT)

TIGIT, an inhibitory receptor that is expressed by lymphocytes and NKs, mainly binds to two ligands, CD155 and CD112, on APCs and tumor cells in TME.[160] It not only directly transmits inhibitory signals to lymphocytes and NKs[161], but also mediates immunosuppression by increasing the secretion of anti-inflammatory factors in DCs and inducing macrophages to polarize to the M2 phenotype.[162] A study found TIGIT overexpression on $CD8^+$ TILs in NSCLC positively correlated with PD-1 expression. An NSCLC mouse model demonstrated that TIGIT and PD-1 act synergistically in promoting tumor immune escape, and it simultaneously blocked TIGIT and PD-1 more effectively than blocking either alone.[163]

Many anti-TIGIT antibodies have been investigated in NSCLC; the most promising is tiragolumab. This agent, combined with atezolizumab, was recently tested in the CITYSCAPE study and presented an improved overall response rate (ORR: 38.8% vs. 20.6%), progression-free survival [PFS: 5.6 months vs. 3.9 months; hazard ratio (HR): 0.62] and OS (23.2 months vs. 14.5; HR: 0.69) compared to placebo in treating naïve patients with advanced NSCLC. In patients with PD-L1 expression ≥ 50%, the advantages of combined immunotherapy were more significant, with a PFS of 16.6 months vs. 4.1 months (HR: 0.29) and the OS of non-evaluable vs. 12.8 months (HR: 0.23).[164] Similar safety profiles were observed. This randomized double-blind study demonstrated for the first time that combined blockade of TIGIT and PD-L1 can further improve the clinical outcomes of this population. Based on this, tiragolumab obtained a breakthrough therapy designation and was approved by the Food and Drug Administration (FDA) for use in combination with atezolizumab for the first-line treatment of advanced NSCLC.

A pilot clinical trial evaluated the efficacy and safety of the combination of vibostolimab, another anti-TIGIT antibody, with pembrolizumab in anti–PD-1/PD-L1-naïve patients with NSCLC. This regimen showed a tolerable safety profile and promising antitumor activity, especially in patients with positive PD-L1 expression. The median PFS was 5.4 months, and the ORR was 29%. The median PFS and ORR were 8.4 months and 46% in patients with PD-L1 expression tumor proportion score (TPS) ≥ 1%, respectively. The median duration of response (DoR) was not reached (range: 4 to 17+ months).[165] Treatment-related adverse events (TRAEs) greater than grade 3 occurred in 15% of patients. Clinical trials on head-to-head comparisons of pembrolizumab/vibostolimab coformulation versus pembrolizumab monotherapy as first-line treatment for patients with metastatic NSCLC whose PD-L1 expression is positive (NCT04738487) and pembrolizumab/vibostolimab coformulation plus docetaxel versus docetaxel alone as second-line treatment for patients with metastatic NSCLC (NCT04725188) are recruiting participants now. An ongoing trial is investigating domvanalimab (anti-TIGIT) and zimberelimab (anti-PD-1) in combination with etrumadenant (adenosine receptor antagonist) in NSCLC (NCT04791839).

3.1.2. LAG-3

LAG-3 is another co-inhibitory molecule expressed on activated T cells, B cells, NK cells, and pDCs.[166,167] By primarily binding to the antigen-MHC-II complex, it negatively regulates T cells[168] and activates Tregs.[169] In patients with NSCLC, LAG-3 has been found to be overexpressed on TILs in TME and correlated with higher PD-1 expression and worse prognosis.[170] Double inhibition of PD-1 and LAG-3 appears to be a valid strategy for immunotherapy, as LAG-3 could synergize with PD-1 to enhance tumor immunoevasion just like TIGIT.

There are several LAG-3 inhibitors under development, and relatlimab as a monoclonal antibody has progressed the farthest in clinical trials. The use of relatlimab and nivolumab combinations resulted in prolonged PFS compared with nivolumab monotherapy in melanoma (10.1 months vs. 4.6 months; HR: 0.75),[171] which offers great hope for the application of this approach in other solid tumors including NSCLC. This combination alone as neoadjuvant therapy in resectable NSCLC (NCT04205552) and plus chemotherapy as a first-line treatment of advanced NSCLC (NCT04623775) are under investigation in clinical trials. Eftilagimod alpha (efti), a soluble LAG-3 protein, can activate DCs and $CD8^+$ T cells by targeting a subset of MHC-II molecules. Unlike monoclonal antibodies, efti does not bind to LAG-3 on T cells, but when combined with PD-1 blockade in preclinical models, it can synergistically enhance antitumor activity (internal data, not yet published). The recommended dose (RP2D) of efti was 30 mg every two weeks in a phase II trial,[172,173] and the treatment of efti plus pembrolizumab yielded en-

Table 3
Representative studies of PD-1/PD-L1 antibodies combined with VEGF inhibitors in NSCLC.

Anti-VEGF	PD-1/PD-L1	Other drugs/Interventions	Phase	Number	Pathology	Treatment line	PFS (95%)	OS (95%)	ORR	References
Bevacizumab	Atezolizumab	Pemetrexed + carboplatin	III	356	Non-squamous	1	8.3 (7.7–9.8)	19.5 (17.0, 22.2)	63.5%	253,282
Lenvatinib	Pembrolizumab	Pemetrexed + platinum	III	13	Non-squamous	1	N/A	N/A	69.2%	283
Bevacizumab	Atezolizumab		II	40	Non-squamous, PD-L1 TPS ≥ 50% (Dako 22C3)	1	15.9; 1-year PFS rate = 54.9%.	1-year OS rate = 70.6%	64.1%	284
Apatinib	Camrelizumab	Albumin paclitaxel	II	63		1	Median PFS = 10.1 months (8.5, NR)		70%	285
Apatinib	Camrelizumab		II	25	Non-squamous	1	9.6 (5.5, NR)	NR	40%	286
Ramucirumab	pembrolizumab		Ia/b	27		2		NR (13.2, NR)	42.3%	287
Apatinib	Camrelizumab		Ib/II	105	Non-squamous	≥ 2 (CT failure, ICI naïve)	5.7 (4.5, 8.8)	15.15 (10.9, 24.5)	30.9%	288
Apatinib	Camrelizumab		Ib/II	25	Squamous	≥ 2 (CT failure, ICI naïve)	6.0 (3.6, 8.3)	12.8 (6.4, NR)	36%	289
Bevacizumab	Atezolizumab		II	24		≥ 2 (ICI and CT failure)	5.6 (4.4, 7.6);	14.0 (10.7, 17.4)	12.5%	290
Cabozantinib	Atezolizumab		Ib	30	Non-squamous	≥ 2 (ICI and CT failure)	4.2 (2.7, 7.0)	N/A	27%	291
Sitravatinib	Nivolumab		II	68	Non-squamous	≥ 2 (prior ICI failure but clinical benefit exceed 12 weeks)	5.7 (4.9, 7.6)	14.9 (9.3, 21.1)	18%	292
Sitravatinib	Tislelizumab		Ib	47		≥ 2 (ICI failure)	5.2 (4.1, 5.9)	N/A	14%	293
Sitravatinib	Tislelizumab		Ib	75		1 or ≥ 2	5.5 (4.1, 7.0)	N/A	17%	294
Camrelizumab	Endostatin	CT	Retrospective	21		1 or ≥ 2	NR	NR	70%	295
Nintedanib	Nivolumab + ipilimumab		II	20		1 or 2 (ICI naïve or failure)	3.0 (1.4, NR)	7.7 (6.0, NR)	22%	296

Abbreviations: CI, confidence interval; CT, chemotherapy; ICI, immune checkpoint inhibitor; N/A, not available; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; ORR, overall response rate; PD-1, programmed cell death-1; PD-L1, PD-1 ligand; PFS, progression free survival; TPS, tumor proportion score; VEGF, vascular endothelial growth factor.

couraging efficacy and tolerable safety. The results were released at the 2022 American Society Clinical Oncology (ASCO) annual meeting.[174] In this phase II TACTI-002 (NCT03625323) study, first-line administration of this combination achieved an ORR of 38.6% and median PFS of 6.9 months in PD-L1 unselected patients with NSCLC. The most common adverse event (AE) greater than grade 3 was dyspnea (11.4%), and less than 10% of patients discontinued therapy due to TRAE.

3.1.3. TIM-3

TIM-3, apart from T cells and macrophages, is constitutively expressed on DCs and NK cells constitutively. By binding to its relevant ligands, including Gal-9, HMGB1, PtdSer, and Ceacam-1, TIM-3 induces T cell apoptosis and negatively regulates T cell responses.[175,176] TIM-3 also favors M2 macrophage polarization[177] and suppresses nucleic acid-mediated innate immune responses of DCs.[140] In NSCLC, TIM-3, along with PD-1 and LAG-3, was expressed on TILs in the TME and associated with a pro-apoptotic phenotype of T cells.[178] TIM-3 blockade demonstrated superior antitumor activity when combined with conventional ICIs over single-agent immunotherapy.[179,180]

The clinical data of anti-TIM-3 agents in NSCLC are still limited. In an early clinical trial, the efficacy and safety of the combination of sabatolimab (anti-TIM-3) and spartalizumab (anti-PD-1) were evaluated in patients with advanced melanoma and NSCLC after the failure of previous anti-PD-1/PD-L1 therapy. The combination showed good tolerance but limited activity in this population.[181] Consistently, the same combination of TIM-3 and PD-1 inhibitors TSR-022 and TSR-042 showed efficacy in NSCLC patients previously treated with anti-PD-1 in another preliminary study.[182] Different combinations of TSR-022D with TSR-042 and TSR-033 (anti-LAG-3) and chemotherapy are being investigated in patients with solid tumors, including NSCLC, in the AMBER trial (NCT02817633).

3.1.4. NK group 2 member A (NKG2A) and CD73

NKG2A is expressed on NK cells and T cells, especially $CD8^+$ T cells, and exerts an immunosuppressive effect by binding to its ligand HLA-E.[183,184] CD73 is an ecto-5′-nucleotidase, but acts as an inhibitory immune checkpoint by releasing adenosine.[185] Both overexpression of HLA-E and CD73 in tumors are associated with poor prognosis.[186,187]

Combining PD-L1 and NKG2A or CD73 inhibition reportedly yields a promising clinical approach since it has demonstrated synergistic antitumor activity in preclinical studies.[188] In the COAST study, a randomized phase trial, durvalumab showed superior clinical outcomes when combined with monalizumab (anti-NKG2A) or oleclumab (anti-CD73) over durvalumab monotherapy in patients with stage III, unresectable NSCLC as maintenance after chemo-radiation.[189]

3.1.5. Stimulatory immune checkpoints OX40 and CD137

OX40 and CD137 are co-stimulatory immune checkpoint molecules of great interest in NSCLC, encoded by the TNF receptor superfamily genes. OX40 is expressed on T cells, neutrophils, NKT cells, and NK cells,[190] and by binding to ligand OX40L on APCs and activated T cells, perform the following series of functions: promote T cell survival, expansion, and function; inhibit immunosuppression mediated by Tregs; enhance T cell immune response and maintain their phenotype.[191-194] In NSCLC, OX40 and OX40L were found on the TILs and tumor cells, suggesting that the OX40/OX40L axis plays an immunological role in NSCLC.[195] Agonistic OX40-targeted agent 9B12 has shown enhanced T cell effect and a certain degree of tumor regression in a phase I study,[196] and its combination with PD-L1 inhibitors could be more effective since two checkpoints with opposite effects are targeted (stepping on the gas pedal and unlocking the brake) simultaneously.[197-199] Based on this hypothesis, a combination of MOXR0916, an OX40 agonist, with atezolizumab is being evaluated in patients with late-stage malignancies.[200]

CD137 is expressed on several immune cells, including T lymphocytes, DCs, NK cells, neutrophils, eosinophils and monocytes.[201] By

binding to ligand CD137L mostly on APCs,[202] CD137 promotes the survival, proliferation and activation of $CD8^+$ T cell, thus enhancing the cytotoxic response.[203] Importantly, it can promote NK cell proliferation and IFN-γ production, leading to $CD4^+$ T cell priming and subsequent apoptosis.[204] Interestingly, this CD137/CD137L axis can also reversely transmit the signal to APCs to enhance their activity and induce their differentiation, thereby enhancing the immune response.[205] CD137L is expressed on multiple cancer cell lines, including lung cancer. Preclinical studies have demonstrated that CD173 activation alone[206] or with TIM-3 blockade[207] exerts antitumor activity. Urelumab, an agonist antibody to CD137, showed certain immunological activity with dose-dependent transaminitis in patients with advanced cancers.[208] Another agonist agent, utomilumab showed promising anti-tumor activity either as monotherapy[209] or in combination with pembrolizumab in patients with solid tumors but with less liver toxicities.[210]

Other immune checkpoint molecules, such as IDO-1, V-domain immunoglobulin suppressor of T cell activation (VISTA), glucocorticoid-induced TNFR-related receptor (GITR), CD47, and B7-H3 (CD276), are under investigation either alone or in combination with PD-1/PD-L1 inhibitors in ongoing studies.

3.1.6. Bispecific antibodies

Bispecific antibodies are a class of novel immunotherapeutic agents characterized by the dual affinity of a single compound to different targets. Bispecific antibodies can achieve localized synergistic or directed activation through dual effects on the immune pathway, thus enhancing the local effect and reducing systemic toxicity.[211] The most studied immunomodulator bispecific antibodies in lung cancer are different combinations based on the PD-1/PD-L1 axis, given their great achievements in this field.

Bintrafusp alfa, known as M7824, is a novel bifunctional fusion protein composed of an antibody against PD-L1 fused to a TGF-β "trap".[212] As a pleiotropic cytokine, TGF-β not only induces EMT and exerts immunosuppressive function in TME,[213] but also upregulates PD-L1 expression in NSCLC cell line and thus enhances the tumor susceptibility to PD-L1-targeting agents.[214] With this dual targeting of two negative immune regulators, bintrafusp alfa enhanced antitumor activity compared with anti-PD-1 monotherapy in murine models and demonstrated manageable toxicity and encouraging efficacy in solid tumors in a phase I study.[212] With the RP2D of 1200 mg dose, bintrafusp alfa achieved an ORR of 25.0% in all patients, 36.0% in patients with PD-L1 positive expression, and 85.7% in patients with PD-L1 high expression, respectively. The median PFS in three populations was 4.0 months, 5.5 months, and 15.2 months, respectively. TRAEs $\geq$ 3 and treatment discontinuation due to TRAEs occurred in 29% and 10% of the patients, respectively.[215] A head-to-head comparison of bintrafusp alfa with pembrolizumab in treatment-naïve advanced NSCLC patients with PD-L1 expression is ongoing.[216] Bintrafusp alfa combined with chemotherapy as first- or second-line treatment for advanced NSCLC is also under investigation (NCT03840915, NCT04396535).

KN046 is a recombinant PD-L1/CTLA-4 bispecific antibody, which can target and enrich the TME with high PD-L1 expression and eliminate immunosuppressive Tregs.[217] In the KN046–021 study, promising outcomes were noted with KN046 as monotherapy as a second-line treatment for NSCLC: the median PFS was 3.68 months, and OS at 6 and 12 months were 85.6% and 69.7%, respectively.[218] KN046 with chemotherapy as first-line treatment in patients with advanced NSCLC confirmed its encouraging antitumor activity. The ORR and the disease control rate (DCR) were 50.6% and 87.7%, respectively. The OS rates at 12 months and 15 months were both 74.9%. Similar survival rates were observed in patients with PD-L1 $\geq$ 1% and PD-L1 < 1%, and the median PFS was 10.8 months in patients with squamous cell carcinoma with PD-L1 $\geq$ 1%.[219]

AK104 is a novel bispecific antibody targeting PD-1 and CTLA-4. A preliminary report of a study of AK104 in combination with anlotinib in patients with advanced NSCLC showed good tolerability and efficacy, as TRAEs greater than grade 3 occurred in 6% of the patients, the ORR was 62.5% and the DCR was 100%, respectively.[220]

Other approaches of bispecific antibodies targeting PD-1/LAG-3 (NCT04140500, NCT03219268), PD-1/TIM-3 (NCT03708328, NCT 04931654), PD-1/PD-L1 (NCT04777084), PD-1/VEGF (NCT04900363, NCT05184712, NCT04736823), PD-L1/CD27 (NCT04440943) are being explored in advanced NSCLC.

3.2. Adoptive cellular transfer (ACT)

Adoptive cellular therapies have been widely explored and developed for treating solid tumors based on their robust and durable antitumor immunity effect. There are currently two general types of ACT in lung cancer: TIL and chimeric antigen receptor-T cell (CAR-T).

TIL therapy is an individualized immunotherapeutic approach in which a mixture of T lymphocytes is isolated from resected tumor tissue from the patient, amplified *ex vivo* in the presence of cytokines and then infused back into the patient after host lymphodepletion.[221] Polyfunctional TILs can be effectively isolated and expanded from NSCLC samples, exhibiting reactivity against primary tumors in a preclinical study.[222] A phase I clinical study showed that TIL therapy is generally safe and clinically active, resulting in objective response rates of 23% (3/13) and a median best tumor change of 35% in patients with metastatic NSCLC who failed initial nivolumab monotherapy.[223] Many ongoing trials are testing TIL therapy alone or combined with ICIs in NSCLC.

Despite some clinical successes, TIL therapy still needs to be optimized to further improve the efficiency in solid tumors. On one hand, MHC restrictions limit the applicability of T cells among different individuals; on the other hand, the expansion scheme of TIL is lengthy and laborious to produce a sufficient number of cells to combat tumor growth. The introduction of a large amount of T cells from donors further challenges the availability of host homeostatic cytokines.[224,225] In addition, lymphodepletion for removing competitive host T cells leads to collateral damage to the recipient. The selective expansion of TILs without exhaustion phenotypes and tumor-specific T cells could overcome the challenges of TIL therapy.[221]

CAR-T is an alternative promising immunotherapeutic approach for NSCLC. Through genetic engineering, patients-derived T cells are chimeric with antibodies against tumor-associated antigens (TAAs) to achieve the purpose of targeted killing of tumor cells.[226] In NSCLC, only a small number of TAAs can be designed as targets with heterogeneous expression, limiting CAR-T's application in this area. The most promising target antigens for CAR-T therapy in clinical trials of NSCLC include EGFR, carcinoembryonic antigen (CEA), mesothelin, prostate stem cell antigen (PSCA), human epidermal growth factor receptor 2 (HER2), etc.[227] CAR-T therapy for lung cancer is still in its early stages, showing mixed results with slow progression.[228]

The major concern of CAR-T cell therapy in lung cancer is the lack of specificity for TAAs. During CAR-T therapy, on-target/off-tumor toxicity may trigger serious adverse reactions such as immune-related neurotoxicity and cytokine release syndrome. The heterogeneity of TAAs and complex immunosuppressive TME also restrict the efficacy of clinical applicability of CAR-T in the treatment of lung cancer. Indeed, more specific target antigens and optimization of the structure of CAR-T cells represent a future research direction.

3.3. Cytokines, chemokine and other cellular signaling pathways

Cytokines in the TME mediate the communication between immune cells and play a role in cancer progression in hematologic and solid tumors.[229] IL-2 and INF-α are the only two cytokines approved for monotherapy in melanoma and renal cell carcinoma (RCC) based on their mild clinical benefit.[230] The synergistic combinations of several cytokines with immunotherapeutic approaches, mainly in conjunction

with PD-1/PD-L1 inhibitors, are being investigated in many types of solid tumors, but little research has been conducted on NSCLC.

IL-15 is a vital cytokine for the ontogeny, proliferation, and effector function of NK cells and T lymphocytes, and its antitumor activity has been supported by preclinical studies.[230] An early clinical trial initially evaluated the safety of IL-15 in advanced solid tumors, including NSCLC. A tolerable safety profile and mild efficacy were observed with subcutaneous administration of IL-15 at a dose of 2 mcg/kg/day.[231] ALT-803, an IL-15 superagonist, combined with nivolumab was tested in previously treated patients with stage IIIB or IV NSCLC in a phase I study. The results showed that the combination was safe. In all enrolled patients, the ORR was 29%, and the median PFS and OS were 9.4 months and 17.4 months, respectively. 91% of patients who failed prior PD-1 inhibitor treatment achieved disease control.[232] The promising clinical efficacy of adding ALT-803 to ICIs as a salvage treatment was confirmed in a phase II multicohort study that enrolled 60% of patients with NSCLC. More than half of the patients (59%) exhibited disease control and a median OS beyond one year of 13.8 months after the progression on an ICIs-containing regimen.[233] An early clinical trial is currently being conducted on another recombinant protein of IL-15 and PD-1, PF-07,209,960, in NSCLC (NCT04628780).

NKTR-214 is a recombinant IL-2 compound with the potential synergistic effect in combination with PD-1/PD-L1 inhibitors since it stimulates the proliferation of TILs and increases the expression of PD-1 and PD-L1. It is being evaluated in combination with multiple ICIs in clinical trials. In the PIVOT study, NKTR-214 plus nivolumab was well-tolerated in patients with solid tumors, including melanoma, RCC or NSCLC, with no TRAE-associated discontinuations. Preliminary results showed encouraging ORR and DCR in immunotherapy-naïve patients.[234]

Colony-stimulating factor-1 receptor (CSF1R) is a promising therapeutic target. Inhibiting CSF1R may lead to TAMs depletion and reverse the immunosuppressive TME. A phase I study evaluating sotigalimab (CD40 agonist) and cabiralizumab (CSF1R inhibitor) with or without nivolumab in patients with anti-PD-1/PD-L1-resistant tumors found that the combination demonstrated safety and pharmacodynamic activity.[235]

CCR4 is another immunosuppressive molecule due to its promotion of Tregs recruitment. In 2 phase I trials, mogamulizumab, an anti-CCR4 monoclonal antibody, was tested in conjunction with conventional ICIs. Adding mogamulizumab to nivolumab showed safety and moderate efficacy in patients with solid tumors. Three of 15 patients with NSCLC achieved a partial response and disease control.[236] Similar results in terms of safety and efficacy were observed for the combination of mogamulizumab with durvalumab or tremelimumab.[237]

Camidanlumab tesirine is an anti-CD25 antibody-drug conjugate, which can efficiently deplete Tregs and increase activated TILs in TME.[238] Recruitment is currently underway for a phase I study combining it with pembrolizumab in different cancer types, including NSCLC (NCT03621982).

Notably, not all preclinical observations can be confirmed in clinical settings. The combination of IDO-1 inhibitor epacadostat (NCT03322540) or IL-1β inhibitor (NCT03631199) with anti-PD-1 antibodies failed to show improved outcomes as first-line therapy in patients with advanced NSCLC. ASA404, an agonist of the STING, also exhibited negative results when combined with chemotherapy in initial investigations of NSCLC.[239] Combining TAK-676 (a novel STING agonist) with other immunotherapy awaits further study.[240]

3.4. Vaccines and oncolytic viruses

In light of the discovery of TAAs, there has been renewed interest in therapeutic vaccines against TAAs. Belagenpumatucel-L is a whole-cell vaccine produced from four allogeneic NSCLC cell lines modified with the TGF-β-antisense gene. An earlier study of belagenpumatucel-L for maintenance after initial chemotherapy did not meet its survival endpoint in advanced NSLCL, although the vaccine exhibited antisense inhibition of the expression of TGF-β and enhanced antitumor immunity in a preclinical study.[241]

An alternative important vaccination strategy for NSCLC treatment is antigen-specific vaccines. However, it should be borne in mind that vaccines targeting single antigens such as MUC-1,[242] MAGE-A3,[242] and PRAME[243] showed minimal clinical activity in previous studies on NSCLC. TG4010 is a combination of recombinant modified poxvirus encoding MUC-1 and IL-2, which was highly anticipated since the combination of TG4010 with chemotherapy improved the prognosis of advanced NSCLC in early clinical studies. However, in subsequent studies, it did not significantly increase the ORR when combined with chemoimmunotherapy in treatment-naïve NSCLC patients with PD-L1 < 50% (NCT03353675). Given the overexpression of EGFR in NSCLC, this protein has become a promising target for vaccination. CIMAvax-EGF vaccine contains a chemical conjugate of human-recombinant EGF with *Neisseria meningitides*-derived P64 and acts as an "EGF-trap" through the generation of neutralizing antibody.[244] In the context of chemotherapy, the CIMAvax-EGF vaccine as a maintenance therapy significantly prolonged the survival of patients with advanced NSCLC, especially those with high EGF concentrations in serum at baseline.[245] Increasing evidence suggests that EGFR and PD-L1 expression are related in NSCLC; CIMAvax-EGF reportedly has the greatest potential for use in conjunction with anti-PD-1/PD-l1 therapies. Indeed, this combination is currently being tested for its efficacy and safety in the multi-line treatment of NSCLC.[244] The preliminary results showed that the serum EGF concentration decreased rapidly after administering CIMAvax-EGF combined with second-line nivolumab, and the clinical efficacy was encouraging. 30% of patients with negative PD-L1 expression had a partial response, and patients with wild-type KRAS had a median OS of 22.4 months, which was remarkable compared with historical data.[246] Tedopi (OSE-2101) is an anti-cancer vaccine with modified epitopes restricted to HLA-A2$^+$ derived from five TAAs. A phase III trial showed that Tedopi was more effective than chemotherapy in HLA-A2$^+$ patients with advanced NSCLC who progressed from prior immunotherapy, as it prolonged median OS from 7.5 months to 11.1 months.[247] There are plans to investigate Tedopi in combination with docetaxel or nivolumab for further study (NCT04884282). Individualized neoantigen specific immunotherapy (INeST) is a novel and attractive tumor vaccine strategy. RO7198457 is an mRNA-based vaccine targeting up to 20 unique neoantigens derived from tumor tissue and peripheral blood of an individual patient. RO7198457, combined with atezolizumab in solid tumors including NSCLC, demonstrated an enhanced neoantigen-specific immune response with a manageable safety profile in a phase I study.[248] Numerous studies are underway in order to develop a personalized cancer vaccine.

The oncolytic virus is a native or genetically modified virus that selectively replicates in tumor cells, capable of infecting and lysing them.[249] Direct intra-tumoral injection of oncolytic virus can prevent the virus from being recognized and cleared by the host's immune system, but has little effect on disseminated metastatic diseases like NSCLC. At present, three oncolytic viruses have been approved for different indications in different countries, namely Rigvir (modified RNA virus) and T-VEC (modified herpes simplex virus type 1) for melanoma in Latvia and the US respectively, H101 (modified adenovirus) for nasopharyngeal carcinoma in China. Clinical trials of oncolytic viruses involving lung cancer are relatively limited. The oncolytic virus can regulate TME, which provides a reasonable strategy in combination with ICIs. For instance, the combination of coxsackievirus A21 and pembrolizumab has shown preliminary activity in early-phase studies, including in NSCLC, with further results pending.[250] Recombinant *Listeria monocytogenes* as a live vaccine vehicle has aroused scientific interest, but early investigations of these approaches, including CRS-207 and JNJ-64,041,757, only demonstrated minimal clinical activity in pleural mesothelioma. ADXS-503 is an attenuated *Listeria monocytogenes* that expresses a fusion protein targeting 22 common TAAs found in NSCLC. In cases of disease progression, when added to pembrolizumab, ADXS-503 showed

preliminary activity as the DCR was 44% in early trials of advanced NSCLC,[251] and more studies are under way (NCT03847519).

3.5. Immunotherapeutic strategies for NSCLC with oncogenic driver mutations

NSCLC with driver mutations is not an absolute contraindication of immunotherapy represented by PD-1/PD-L1. Anti-PD1/PD-L1 therapy for *KRAS*- and *BRAF*-mutated NSCLC appears to be as effective as unselected NSCLC. For other common driver mutations such as *EGFR*, the combination of immunotherapy can still bring survival benefits beyond traditional chemotherapy after the failure of targeted therapy.[252,253] Considering the characteristic TME of *EGFR* mutant tumors, new immunotherapeutic drugs may be the future direction. *EGFR* mutations is associated with overactivated Tregs. Targeting CD36, a metabolic modulator of Tregs, may have a synergistic effect with immunotherapy.[254] CD 73 could be another target in *EGFR*-mutant NSCLC and an anti-CD73 drug is being tested in combination with atezolizumab (NCT03835949). *EGFR* mutations also induce T cell depletion, thus anti-LAG3 antibody may revive depleted T cells to exert anti-tumor effect.

4. Conclusions

TME is a vital participant in the progression and development of lung cancer. Various immune components in TME interact with tumor cells in a very complicated and multifaceted manner, ultimately determining the fate of the tumor. Importantly, as highly heterogeneous tumors, transcriptional and epigenetic alterations in lung cancer cells contribute to TIL depletion phenotypes. ICIs-based immunotherapy has proved to be successful in lung cancer treatment. but only targets a specific phase of anti-cancer immunity and often ends up in failure against a “cold” TME phenotype characterized by the lack of tumor-specific T cell priming and the absence of TILs.[255] Therefore, more combination strategies are needed to mobilize all components involving in all steps of anti-tumor immunity in this war against lung cancer.

Immunotherapy for lung cancer is becoming diversified, innovative and individualized, which benefits from sustained basic and transformational research. The rational combinations of ICIs and conventional therapy have achieved better results. Inhibitors targeting alternative immune checkpoint molecules are also emerging. The components in the TME will be interesting targets for immunotherapy of lung cancer to overcome the resistance of ICIs since they play a key role in many steps of tumor immunity cycles and may serve as a complement of immune checkpoint molecules. In the foreseeable future, lung cancer will gradually evolve into a chronic disease under the emerging immunotherapy strategies.

Declaration of competing interest

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Author contributions

F.W. and Q.Z. conducted the conceptualization. F.W. drafted the original manuscript. M.Y. and W.L. revised and edited the manuscript. Q.Z. provided the funding. All authors have read and agreed to the published version of the manuscript.

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