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Review

Tumor Microenvironment as a Key Target for Immunotherapy in Lung Cancer Patients

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Abstract: Lung cancer with a five-year survival rate of less than 20% is currently one of the most common malignancies worldwide. Cell-based immunotherapy showed promising results over the past two decades, but some patients still experience disease progression. Numerous studies identified the critical role of the tumor microenvironment in tumor progression, immune evasion, and treatment response. The dynamic interplay between the tumor and its surrounding microenvironment significantly influences both tumor behavior and the immune response. One of the critical components of this interplay is how essential nutrients and structural support are involved in tumor growth per se and cancer pathophysiology in general. A comprehensive understanding of the underlying mechanisms and molecular players critical to the tumor microenvironment is crucial to optimize immunotherapy strategies. This review examines key therapeutic targets in lung cancer, uncovering the complex interactions within the tumor microenvironment to enhance the efficacy of immunotherapy.

Keywords: tumor microenvironment, lung cancer, immunosuppression, cytokine-induced killer cells, immunotherapy.

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Tumor microenvironment

The tumor microenvironment (TME) consists of various cell types, including immune cells and cancer-associated fibroblasts (CAFs). The former encompasses T cells, macrophages, myeloid-derived suppressor cells (MDSCs), and endothelial cells. In addition, the extracellular matrix (ECM) maintains tumor architecture and influences cell behavior. Signaling molecules (cytokines, chemokines, and growth factors) in the TME facilitate communication between different cell types.

The TME plays a key role in tumor initiation, progression, and immune evasion [9]. In epidermal growth factor receptor (EGFR)-dependent lung adenocarcinoma, malignant cells manipulate a specialized population of lung-resident immune cells, particularly macrophages, which are essential for pulmonary homeostasis and immune surveillance by maintaining a delicate balance of protective lipids (fats) around the lung alveoli [10]. Tumor-associated macrophages (TAMs) and tissue memory T cells (TMCs) are two key immune cell subtypes that play an important role in tumor immunology. TAMs are derived from circulating monocytes that are recruited to the tumor site by various chemokines and cytokines such as CCL2, CSF-1, and vascular endothelial growth factor (VEGF) [11]. Dendritic cells (DCs), CD8+, and CD4+ T lymphocytes (mainly Th1 subtype) are other immune cells are found in the lung tissue [12].

Non-small cell lung cancer (NSCLC) has distinctive cellular and molecular properties as well as unique mutational heterogeneity [11]. This heterogeneity extends to both tumors and the surrounding TME. Immune cell infiltration into the TME in NSCLC patients is tumor stage dependent implying that the TME plays a role in carcinogenesis as well as treatment response or resistance [9].

Cell types in the tumor microenvironment

CD4+ T cells

T cells expressing the transcription factor Foxp3, known as regulatory T cells (Tregs), are a specialized subset of CD+ T cells and play an important role in tissue homeostasis and regeneration [13]. In particular, they play a critical role in establishing and maintaining immune homeostasis and self-tolerance by suppressing the activity of autoreactive and inflammatory T cells (*Table 1*). Tregs are identified by the presence of surface markers (CD4 and CD25), which suppress the activation and proliferation of CD4+ T helper cells, CD8+ cytotoxic T cells, and prevent B cell activation [14].

T cell effector function can be inhibited by cytotoxic T lymphocyte antigen-4 (CTLA-4) after initial activation by costimulatory signals. Systemic binding of antibodies to cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) limits their antitumor activity. In contrast, a recently developed double-chain molecule

targeting CTLA-4 and CD47 expressed on the surface of Tregs effectively targets tumors and enhances antitumor immunity [15]. Monoclonal antibodies targeting CTLA-4 were shown to enhance T cell activity and antitumor response in patients with advanced metastatic melanoma [16]. The use of various methods, including specific therapy, radiotherapy, chemotherapy, or other immune modulators, can improve the efficacy of CTLA-4 blockade [17].

Tregs suppress the inflammatory response by controlling innate and adaptive immunity through the secretion of IL-10 and TGF-β [18]; however, their excess in the TME is associated with impaired antitumor immune response and poor prognosis [19]. In particular, the forkhead box P3 (Foxp3+) transcription factor of Tregs enhances cytokine production, which stimulates effector CD4+ and CD8+ tumor-infiltrating lymphocytes (TILs), as well as checkpoint inhibition [20, 21]. Tregs stimulate tumor angiogenesis by inhibiting tumor-reactive T cells, but recent studies demonstrated that they can also synthesize and secrete proangiogenic factors such as neuropilin-1 (NRP-1) and VEGF to directly regulate tumor angiogenesis. NRP-1 is a type III semaphorin receptor involved in axon guidance, angiogenesis, and T cell activation. NRP-1 is continuously expressed on the surface of Foxp3+ Treg cells and can be used as a cell surface marker molecule to identify Tregs. Effector Th1 T cells can synthesize and secrete a large number of antiangiogenic factors including TNF-α, interferon-γ (IFN-γ) and interferon-inducing chemokines such as CXCL9, CXCL10, CXCL11, thereby suppressing the formation of new blood vessels [22]. In patients with NSCLC and pancreatic ductal adenocarcinoma, increased enrichment of tumor-infiltrating Treg cells was associated with worse outcome and survival [14, 21].

Similar to tissue-resident memory (TRM) T cells, CD4+ T cells exhibit functionally heterogeneous subtypes, such as one of the TRM-like phenotypes [23]. Interestingly, CD103-expressing pulmonary CD4+ T cells most actively produce cytokines such as TNF-α and IFN-γ compared to other CD4+ T cell phenotypes in NSCLC samples [23].

Table 1. The role of the tumor microenvironment (TME) in facilitating immune evasion by cancer cells

Tumor suppression of immune responses	*Pathway*	*Mechanism of action*	*References*
Immune Checkpoint Pathways	Programmed cell death protein 1 (PD-1) / Programmed death-ligand 1 (PD-L1)	• PD-1 acts as an inhibitory receptor located on T cells, while its ligand PD-L1 is frequently found on tumor cells and within the TME • The interaction between PD-1 on T cells and PD-L1 on tumor cells leads to reduced T cell activation and diminished effector functions, ultimately weakening anti-tumor immune responses • Tumors often increase PD-L1 expression to take advantage of this pathway, allowing them to escape immune scrutiny	[106-108]
	Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)	• CTLA-4 present on T cells competes with the costimulatory receptor CD28 on antigen-presenting cells (APCs) for binding to B7 molecules (CD80/CD86) • When CTLA-4 is engaged instead of CD28, it suppresses T cell activation and proliferation, which impairs the ability of an immune system to perform an effective attack against tumors	[108, 109]
Metabolic Alterations	Nutrient deprivation	• Tumor cells heavily consume essential nutrients, such as glucose and amino acids (e.g., glutamine), which are vital for T cell activation and functionality • The resulting depletion of these nutrients creates an energy-deficient environment for T cells, thereby adversely affecting their proliferation and cytotoxic capabilities	[100, 110]
	Lactic acid accumulation	• Tumors often rely on aerobic glycolysis (the Warburg effect), producing significant amounts of lactic acid within the TME • The buildup of lactic acid lowers the pH in the microenvironment, inhibiting T cell function and promoting a more immunosuppressive milieu	[111]
	Adenosine production	• Tumor and stromal cells within the TME express CD39 and CD73, which are enzymes responsible for converting ATP into adenosine, a molecule known for its immunosuppressive properties • Adenosine binds to A2A receptors on various immune cells, including T cells and natural killer (NK) cells, leading to decreased cytokine production and impaired anti-tumor immunity	[110]
Immunosuppressive Cell Populations	Regulatory T cells (Tregs)	• Tregs are specialized CD4+ T cells that inhibit the activity of effector T cells and APCs either through direct interactions or by releasing immunosuppressive cytokines such as IL-10 and TGF-β • In the TME, Tregs are often expanded and recruited, thereby creating barriers to effective immune responses	[100, 108]
	Tumor-associated macrophages (TAMs)	• TAMs are macrophages that often exhibit an M2-like phenotype within the TME, which is associated with tissue repair, angiogenesis, and immune suppression • M2-like TAMs produce anti-inflammatory cytokines (such as IL-10) and facilitate tumor progression by inhibiting T cell functions and enhancing tumor growth	[87, 95, 112]
	Cancer-associated fibroblasts (CAFs)	• CAfs carry out multiple intercellular communications in tissues and participates in (patho)physiological processes • Stimulation of autophagy of healthy cells, stimulation of proliferation of cancer cells, activation of epithelial-mesenchymal transition, enhancement of stem cells and migration of cancer cells	[67, 74-76]
	Myeloid-derived suppressor cells (MDSCs)	• MDSCs are immature myeloid cells that accumulate in the TME and are known to suppress T cell activation and proliferation. • They achieve this through the secretion of reactive oxygen species (ROS), nitric oxide (NO), and immunosuppressive cytokines, such as IL-10 and TGF-β	[100, 101]

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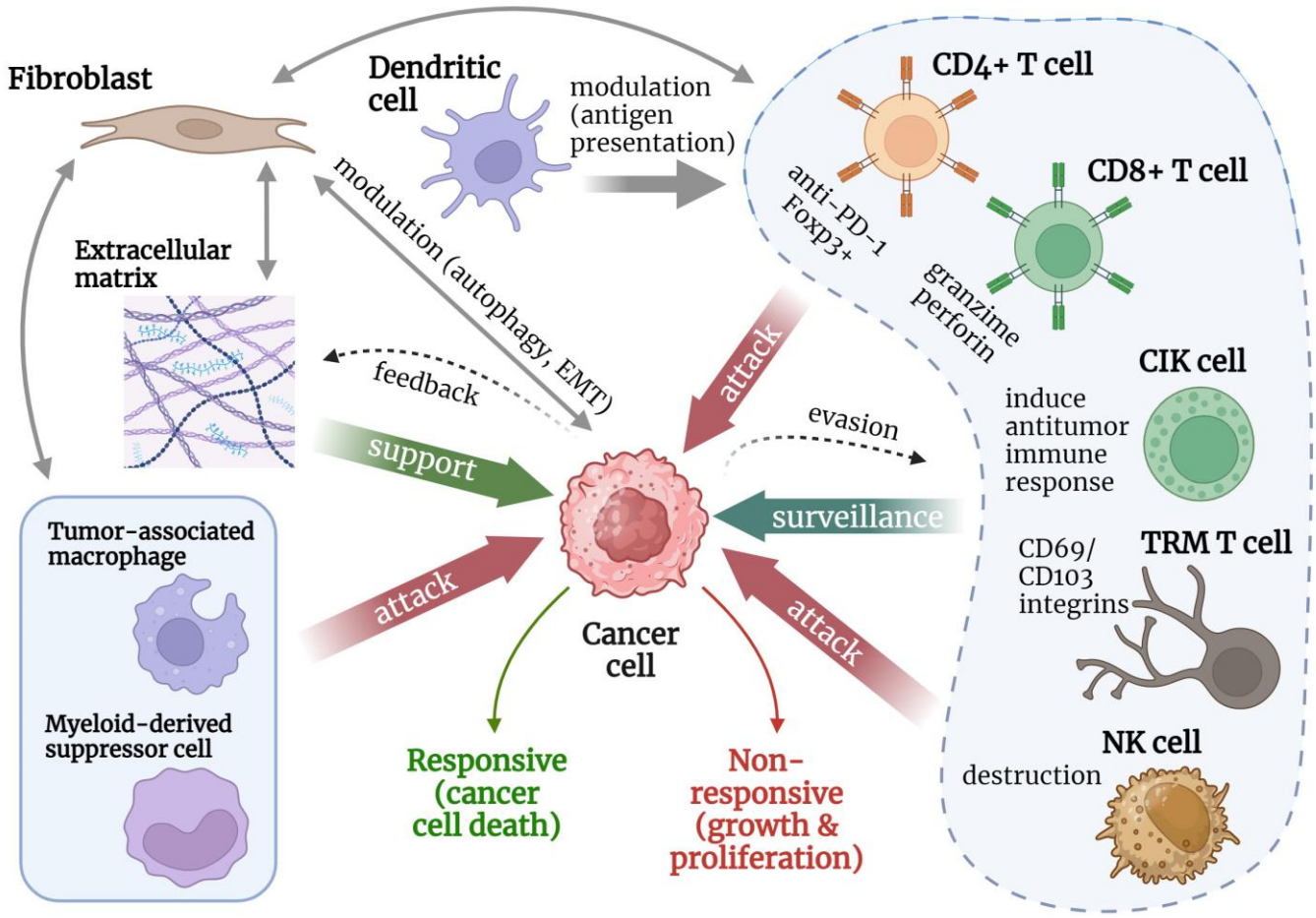

Figure 1. Schematic diagram showing that the tumor microenvironment interface is occupied by different cell types as well as extracellular matrix. EMT, epithelial-mesenchymal transition; PD-1, programmed cell death protein; Foxp3, forkhead box P3 transcription factor; CIK, cytokine-induced killer; TRM, tissue-resident memory; NK, natural killer.

Dendritic cells

DCs are innate immune cells that absorb and process tumor antigens in their microenvironment [24]. Molecular structures grouped with defects affect the formation of these cells. They increase the ability of DCs to present antigens to lymphocytes [25]. Antigen-presenting cells (APCs) that have passed the formation stage are transported to the lymph nodes, where they enhance the activity of CD8+ and CD4+ T lymphocytes. It is important to note that mature DCs produce protein-peptide structures and costimulatory molecules: B7 and TNF proteins. Their main function is to excite T cell activity [26]. In addition, the described cells secrete interleukin-12 (IL-12), stimulating innate immune lymphocytes.

The discovery of the inductive effect of some cytokines, such as IL-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF), on the differentiation of monocytes and CD34 progenitor cells into DCs in vitro has opened up prospects for the use of DCs for therapeutic purposes [27].

Conventional DCs enhance the antitumor immune response [28]. DCs produce interferon lambda (IFN-III), which affects the secretion of IL-12p70 leading to the differentiation of Th1 cells and effector CD8+ T cells. This finding correlates with improved clinical outcomes in patients with cancer. The classification of DCs according to [29, 30] is as follows:

1) Conventional type 1 dendritic cells (cDC1), which function as APCs for CD8+ T cells;

2) Conventional type 2 dendritic cells (cDC2) stimulating CD4+ T cell responses.

The goal of immunocompetent dendritic cells in a vaccine is to stimulate a specific and long-lasting immune response to dangerous signals by introducing activated antigen-presenting dendritic cells ex vivo [27]. These include danger-associated molecular patterns (DAMPs), a type of inflammatory stimulus that initiates DC maturation, which increases the expression of effective chemokine receptors, predominantly CCR7, thereby allowing DCs to migrate to lymph nodes followed by licensing (DC maturation) [27].

According to recent clinical experiments, in NSCLC, the differential gene profile and expression of TLR3 and TOP2A genes are closely associated with DC infiltration in tumors [31, 32]. These specialized cells are present in the dura mater of patients due to their high survival rate [33].

The efficacy of DC-based vaccines has been studied since 2010, when the first personalized DC-based vaccine for the treatment of prostate cancer was presented [27]. According to the study protocol, APCs were isolated from the patient and incubated with recombinant fusion protein antigens consisting of prostate cancer

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cells and GM-CSF [27]. Studies are ongoing in resistant solid malignancies such as ovarian and colorectal cancer [34].

CD8+ T cells

Cytotoxic T lymphocyte (CTL) infiltration into the TME is stimulated by specific chemokines including CXCL9, CXCL10, CXCL11, and CXCL16, as well as CCL3, CCL4, CCL5, and CCL20 [35]. CCL5 release by tumor cells and CXCL9 release by APCs in response to IFN-γ are key factors, as CCL5hi CXCL9hi tumors have high levels of TIL infiltration and respond well to immune checkpoint inhibitors [36]. CTLs target and kill tumor cells through T cell receptor interaction with major histocompatibility complex (MHC) class I and induction of apoptosis, respectively. Apoptosis can be induced by the secretion of granzyme B and perforin, and ligation of death receptors, TRAIL and FasL [37]. Since MHC-I antigen presentation by cancer cells is an important way for immune cells to recognize cancer cells, there are many studies focusing on the regulation of MHC-I in cancer cells. However, most studies focused on some key proteins involved in the process of MHC-I antigen presentation. These studies showed that mutations or deletions in some key protein-coding genes can lead to decreased MHC-I levels or impaired antigen processing/presentation [38]. The presence and abundance of TILs in the TME may have prognostic significance, especially in the early stages of lung cancer [39]. TILs in lung cancer patients downregulate perforin and granzyme B expression, indicating a dysfunctional state of CD8+ T cells [40]. However, patients with fewer exhausted T cells, as indicated by a low programmed cell death protein 1 (PD-1) to CD8 ratio, may have a more favorable tumor immune microenvironment and benefit more from immunotherapy in advanced NSCLC [39].

Tumor CD8+ T cell abundance is an independent prognostic factor for progression-free survival in NSCLC patients and can therefore be used to assess the efficacy of immunotherapy [41]. Furthermore, radiomics combined with machine learning can differentiate NSCLC patients as low- or high-responsive to immunotherapy based on tumor CD8+ expression [42, 43]. Indeed, radiomics studies in various malignancies suggest that CD8B gene expression, which indicates the presence of tumor-infiltrating CD8+ cells in tissue, may be a useful predictor of the success of anti-PD-1/programmed death-ligand 1 (PD-L1) immunotherapy [44]. Recent data support the use of radiomics models to predict immunotherapy outcomes, especially based on immune checkpoint inhibitors used in NSCLC, allowing personalization of immunotherapy to achieve better outcomes [45-47]. Moreover, the development of radiomics models led to a very important finding that tumor profiling is site-specific in NSCLC patients [48]. In other words, there is spatial heterogeneity in biomarker expression within the tumor, and the molecular profile in one site may differ from that in another, an important finding for assessing the efficacy of immunotherapy.

Tissue-resident memory T cells

TRM T cells are a subset of CD8+ TILs found in peripheral tissues [49], making them key players in immunodiagnostics and tumor biology. In animal studies, increased levels or pre-activation of TRM cells suppressed tumor growth in mouse models of cancer [50]. Their increased numbers are known to correspond to increased cancer survival [49, 51]. For example, increased TRM cell infiltration into tumors correlated with increased overall survival in melanoma patients; moreover, their increased presence in tumors additionally positively influences the abundance of other immune cells, such as macrophages, T cells, and NK cells [52]. Similarly, in NSCLC samples, increased TRM cell numbers were associated with more abundant CD4+ T helper 1 cells, M1 macrophages, and resting DCs found in tumors [53]. TRM cells coordinate their function through a set of signaling proteins. For example, the integrins CD69 and CD103 are phenotypic markers of TRM cells and have recently been recognized as potential molecular targets for immunotherapy modulation [54–56].

Moreover, genetic screening of TRM cell signatures in NSCLC samples revealed that the signatures vary among patients, allowing stratification of NSCLC patients into low- and high-risk groups [53]. Another important finding is that CD8+-expressing TRM cells demonstrated the highest predictive power for immunotherapy response in NSCLC patients treated with immune checkpoint inhibitors [41]. Furthermore, the TRM cell family may contain subtypes and their distribution in tissue may be uneven. A recent study strongly supports this by identifying at least two populations of TRM cells (progenitor and already differentiated) in the small intestine, distributed in different tissue locations [57]. Therefore, not only do different TRM cell phenotypes contribute differently to the TME and antitumor immunity, but also their subtypes and spatial distribution within the tumor may influence the tumor-directed immune response.

NK cells

Natural killer (NK) cells are CD3−/CD56+ cells that destroy any potentially dangerous cells [58]. These cells constitute approximately 15% of all circulating human lymphocytes [58]. NK cells act against tumor cells by producing granzyme B and perforin or by stimulating apoptosis mediated by TNF-related apoptosis-inducing ligand (TRAIL) and FasL [59]. NK cells also regulate T cell proliferation by killing activated T cells and stimulating Th1 polarization through the release of IFN-γ [60]. Through the release of chemotactic cytokines such as XCL1 and CCL5, NK cells attract myeloid cells and effector lymphocytes to inflamed tissues [61]. In cancer, NK cells play an important role in stimulating antitumor immunity and are associated with better clinical outcomes in cancer patients [61]. These cells secrete proinflammatory cytokines and chemokines such as TNF-a, IFN, and GM-CSF to activate T cells, macrophages, DCs, and neutrophils, thereby stimulating antitumor immunity [62]. The success of cytokine-induced killer (CIK) cells in NSCLC patients are associated with the activation status of peripheral NK cells as well as NK cell infiltration into the TME [63–65]. It was demonstrated that NSCLC patients with higher NK cell gene expression responded better to CIK cells and had longer survival [66].

Cancer-associated fibroblasts

Fibroblasts mediate multiple intercellular communications in tissues and are involved in many pathophysiological pathways of diseases. In particular, in cancer, there is a distinct population of fibroblasts called CAFs that promote tumor growth and progression [67]. Interestingly, CAFs exhibit dynamic changes in secreted factors driven by epigenetic modifications as the tumor progresses, thereby promoting further cancer evolution [68]. Accordingly, CAF-associated genes are closely associated with an increased risk of tumor resistance to chemotherapy, and their utility as a prognostic tool has recently been proposed for NSCLC [69, 70], as well as breast cancer [71], colorectal cancer [72], and

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gastric cancer [73]. The actual mechanisms by which this occurs include stimulation of autophagy in healthy cells [74], promotion of cancer cell proliferation [75], and activation of epithelial-mesenchymal transition, which allows for increased stemness and migration of cancer cells [76], as demonstrated in various cancers such as breast cancer, renal cancer, pancreatic cancer, colorectal cancer, etc. Furthermore, through certain pathways, CAFs make cancer cells more resistant to chemotherapy, thereby reducing its therapeutic efficacy [77, 78]. One of the pathways by which CAFs regulate tumor fate is the secretion of exosomes containing important signaling molecules (e.g., microRNAs) that protect cancer cells from elimination [79]. Therefore, exosome-targeted therapies are promising in anticancer therapy. It was also established that poor prognosis in NSCLC patients is associated with increased expression of several structural proteins in CAFs, including integrin α11, collagen type XI α1, and the major ligand of collagen type I α1 ITGA11 [80]. These proteins are involved in CAF migration and their ability to interact with other cell types.

Another important aspect of CAF-TME interactions is their contribution to the ECM assembly and growth [81]. Since CAFs are a type of stromal cell, CAF-mediated signaling pathways that promote ECM development serve as a substrate for further cancer cell settling and proliferation. For example, this is one of the regulatory mechanisms that promote renal cell carcinoma development and chemoresistance [82]. NSCLC-derived CAFs also express mediators that can increase ECM stiffness, which further structurally supports and stimulates cancer cell proliferation [83].

It is important to emphasize that the interaction between cancer cells and fibroblasts is a bidirectional process: not only fibroblasts influence the function of cancer cells, but cancer cells also modulate CAF activity. As a result, cancer-induced changes in CAF activity negatively affect immune cells, suppressing their anti-tumor behavior [84]. For example, changes in CAF activity induce remodeling of leukocyte behavior through multiple signaling pathways and, therefore, can make them either deficient in the expression of specific anti-tumor molecules or even inactive against tumor cells [85]. Therefore, one of the anticancer strategies involves the so-called retraining of CAFs to produce those signaling molecules that trigger normalization of neighboring cells, rather than converting them to a cancer-like phenotype [81]. Moreover, this retraining may require preliminary sorting of CAFs into subtypes to select those that are most susceptible to a particular treatment. Indeed, CAFs exhibit both phenotypic and functional heterogeneity [86], and this determines the expected efficacy of specific treatments targeting CAFs.

Tumor-associated macrophages

The population TAM is markedly heterogeneous and includes several macrophage subtypes such as SPP1+, APOC1+ and MARCO1+, each of which exhibits specific expression of molecular markers and, consequently, different functional activities [87–89]. Although some of the markers are expressed in normal tissues, it was recently discovered that the above-mentioned macrophage subtypes are frequently associated with pathological conditions and have therefore become the focus of oncology research. Notably, they exert their activity both directly and indirectly.

As mentioned above, CAFs can modulate the activity of other surrounding cells, including resident macrophages. It was shown that advanced NSCLC tumor status corresponds to an increased content of a specific myofibroblastic CAF phenotype, and that this is accompanied by an increase in the number of colocalized profibrotic macrophages of the SPP1+ subtype [69]. In turn, increased levels in both cell types resulted in decreased activity of resident T cells, i.e., both their cytokine secretion and infiltrating capacity. Similar pattern was confirmed in a large set of colorectal cancer samples (2550 samples with >54000 gene-profiled single cells), where increased levels of CAFs (FAP+ phenotype) positively correlated with increased levels of SPP1+ macrophages [90]. Similarly, increased numbers of the SPP1+ macrophage subtype are a contributing factor to a higher risk of precancerous ECM remodeling and increased metastatic activity in gastric cancer [91]. Moreover, another recent study showed that the reciprocal increase in CAFs and SPP1+ macrophages increases the risk of tumor progression [92]. Increased SPP1+ was also associated with an increased capacity for intravascular penetration and, consequently, an increased rate of metastasis [93]. At least in part, this may be due to the reciprocal effect of TAMs on CAFs and the formation of a TAM-CAF feedback loop, which causes the ineffectiveness of immune cells against the tumor [94]. In other words, the two sets of cells (TAMs and CAFs) are spatially and functionally close to each other and demonstrate pronounced interactivity. In addition, TAMs (in particular, the SPP1+ phenotype) can affect cancer cells directly, i.e., without the participation of CAFs, through the secretion of key cytokines and cellular factors such as TNF-α and IL-1β [95]. SPP1+ was proposed for use as an independent marker for assessing tumor progression in lung cancer, since its elevated levels are associated with a worse prognosis and higher chemoresistance in lung adenocarcinoma [96].

It is important to highlight that the SPP1+ resident macrophage subtype can also trigger macrophage polarization from the proinflammatory M1 state to the anti-inflammatory M2 state via altering PD-L1 expression, which is a direct effector of macrophage polarization [97]. Furthermore, the SPP1+ resident macrophage subtype plays a key role in pro-fibrotic activity following various pathological conditions [98].

Myeloid-derived suppressor cells

MDSCs are a type of immature myeloid cells that accumulate in the TME. Like many other cell types, they exist in several subpopulations that differ in their properties and functional outcomes. Some MDSC subpopulations have decreased activities of specific metabolic enzymes, which correlates with poor clinical outcome in lung cancer [99]. In patients with NSCLC, this is accompanied by increased activities of glucose- and glutamine-related metabolic enzymes, which presumably positively affects the growth rate of tumor cells [99]. They inhibit T cell activation and proliferation by secreting reactive oxygen species (ROS), nitric oxide (NO), and cytokines such as IL-10 and transforming growth factor beta (TGF-β) [100, 101]. This occurs because the cells are pathologically activated through various signaling cascades occurring in the TME, making them a subpopulation of cells with immunosuppressive properties [102]. MSCs promote lung cancer metastasis as they activate signaling pathways involved in the mechanisms of epithelial-mesenchymal transition in tumor cells [103]. Their functional properties, heterogeneous nature and potential make them a target for ongoing research in the field of cancer immunotherapy [99, 104].

These cells of different types and functions, as well as extracellular components and tissue vasculature, form a dynamic

interface in the TME. As a result, the TME has a complex effect on the immune response, leading to immunoresistance or immunoreactivity of tumor cells and, accordingly, to cancer progression or a stabilized state when the cancer stops progressing (*Figure 1*).

The role of the tumor microenvironment in immune response

The TME plays a key role in mediating immune evasion by cancer cells, allowing them to avoid detection and destruction by the immune system. This suppression of the immune response is mediated by several mechanisms, including immune checkpoint pathways, metabolic changes, and infiltration of immunosuppressive cell populations (*Table 1*).

Immune checkpoints serve as regulatory systems of the immune response, helping to promote self-tolerance and prevent autoimmune reactions. Cancer cells often manipulate these checkpoints to suppress immune activity. Two major checkpoint pathways involved in this process include the PD-1/PD-L1 and CTLA-4 pathways [105]. PD-1 acts as an inhibitory receptor located on T cells, while its ligand (PD-L1) is frequently found on tumor cells and in the TME. The interaction between them results in decreased T cell activation and decreased effector functions, which ultimately weakens the antitumor immune response [106, 107]. CTLA-4 is another inhibitory receptor present on T cells that competes with the costimulatory receptor CD28 for binding to B7 molecules (CD80/CD86) on APCs. CTLA-4 suppresses T cell activation and proliferation, which reduces the ability of the immune system to effectively attack tumors [108, 109].

The TME often presents a complex metabolic landscape for immune cells, primarily due to competition for nutrients between tumor and immune cells. Several metabolic changes contribute to this immune suppression, such as nutrient deficiencies, lactic acid accumulation, and adenosine production. Tumor cells actively consume essential nutrients such as glucose and amino acids, which are critical for T cell activation and function. Depletion of these essential nutrients creates an energy-deficient environment for T cells, impairing their proliferation and cytotoxic activity [100, 110].

Tumors often rely on aerobic glycolysis (Warburg effect), producing large amounts of lactic acid in the TME. The accumulation of lactic acid decreases the pH of the microenvironment, impairing T cell function and promoting an immunosuppressive environment [111]. Furthermore, the TME is characterized by the presence of a complex network of cells, including both tumor and stromal elements, that express enzymes such as CD39 and CD73. These enzymes are responsible for the conversion of ATP to adenosine, a molecule with well-known immunosuppressive properties. Adenosine, in turn, binds to A2A receptors on various types of immune cells, such as T cells and NK cells. This interaction leads to decreased cytokine production and weakening of antitumor immunity [110].

As shown above, the TME is populated by various types of immunosuppressive cells that contribute to the suppression of the antitumor immune response. These cells include Tregs (CD4+ T cells), which specialize in inhibiting the activity of both effector T cells and APCs. Tregs carry out this inhibition either through direct cell-cell interactions or by secreting immunosuppressive cytokines such as IL-10 and TGF-β. In the context of the TME, expansion and recruitment of Tregs is often observed, which creates a barrier to effective immune responses [101, 108]. TAMs are another type of immune cell found in the TME. They often exhibit an M2-like phenotype, which is associated with tissue repair, angiogenesis, and immune suppression. M2-like TAMs produce anti-inflammatory cytokines such as IL-10, and they promote tumor progression by suppressing T cell function and stimulating tumor growth [112, 113].

Cellular targets for immunotherapy

The goal of immunotherapy is to enhance the immune response to cancer cells, which can be achieved via several mechanisms. The mechanisms underlying immunotherapy in lung cancer are complex and interrelated, and are significantly influenced by the TME. A comprehensive understanding of these mechanisms is vital to the development of more effective therapeutic strategies and improved patient outcomes.

The TME plays a key role in facilitating cancer cell immune evasion, allowing them to avoid detection and destruction by the immune system. This suppression of the immune response is mediated by several mechanisms, including immune checkpoint pathways, metabolic changes, and infiltration of immunosuppressive cell populations.

The primary mechanism of action of immunotherapy involves immune checkpoint inhibitors. Cancer cells often manipulate these checkpoints, such as PD-1/PD-L1 and CTLA-4, to evade immune detection. In lung cancer, monoclonal antibody therapy targeting these checkpoints can activate T cell responses, allowing the immune system to recognize and attack cancer cells. The interaction between PD-1 and PD-L1 plays a key role in modulating the immune response. PD-L1 expression is significantly increased in many lung tumors, resulting in suppression of T cell activation. By disrupting this interaction, therapies such as pembrolizumab and nivolumab exhibited high efficacy, significantly improving survival outcomes in patients with NSCLC [114, 115]. CTLA-4 is another important checkpoint that inhibits T cell activation. Ipilimumab, an antibody to CTLA-4, is used in various cancers including lung cancer and is often combined with PD-1 inhibitors to optimize the therapeutic effect [116].

The TME plays an important role in the success of the applied immunotherapy. It includes a complex consisting of immune cells, stromal components and ECM elements. This complex can both stimulate and suppress the immune response against the tumor. Lung cancer is usually characterized by a high content of immunosuppressive cells, such as Tregs and MDSCs. These cells secrete immunosuppressive factors that suppress T cell function, creating an environment favorable for tumor growth (*Table 1*). Current therapeutic approaches are aimed at targeting or reprogramming these suppressor cells to improve the effectiveness of immunotherapy [117].

In addition, it should be noted that the recruitment and activation of immune cells are highly dependent on cytokines and chemokines. E.g., TAMs can switch between proinflammatory and anti-inflammatory states depending on the surrounding cytokine environment [118]. In addition, vaccines used for cancer treatment were widely discussed in the past few decades. They are designed to induce an immune response against specific tumor antigens. In the field of lung oncology, vaccines targeting mutated proteins such as KRAS or EGFR are actively studied. By presenting these antigens to the immune system, vaccines can induce a stronger and more sustainable antitumor response.

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Given the complex nature of lung cancer, a comprehensive approach to immunotherapy is needed, including a combination of immune checkpoint inhibitors with other treatments such as chemotherapy, targeted therapy, or radiation therapy, which can undoubtedly increase the overall efficacy of therapy. For example, chemotherapy can induce immunogenic cell death by releasing tumor antigens and potentially increasing the effectiveness of subsequent immunotherapy [119, 120].

It was recently proposed to distinguish two subtypes of cancer immunotherapy based on the molecular target they employ: the so-called 'don't eat me' and 'eat me' signaling pathways [121]. If the molecular target is known to promote cell survival/proliferation, its increased expression provides a "don't eat me" signal to immune cells. For example, based on this concept, PD-L1 is an example of a 'don't eat me' signal. Accordingly, immunotherapy targeting PD-L1 is an example of a 'don't eat me' signal-based immunotherapy. Moreover, combination therapies can combine focusing on specific 'don't eat me' signals with other 'eat me' signals, involving the use of different signals; such a balanced treatment enhances the antitumor activity of immune cells [122]. Ongoing research in the field of respiratory cancer offers opportunities for such innovative therapies. By targeting key elements of the TME, including different immune cell subtypes, TAMs, CAFs, and other cell types, researchers can optimize the therapeutic potential of immunotherapy for cancer patients.

Finally, malignant tumors are now considered 'cold' or 'hot' depending on the reactivity of immune cells against tumors [123]. Importantly, the efficacy of immune checkpoint inhibitor therapy in cancer patients (in terms of outcomes such as progression-free survival and overall survival) demonstrated some direct correlation with the activity of the patient's immune system: with an immunoreactive and more inflammatory process in a 'hot' tumor, anticancer success is higher. 'Cold' tumors suppress immune cell activity, thereby preventing anticancer efficacy. Recent developments in chimeric antigen receptor (CAR) T cell therapy showed that the antitumor efficacy of immune cells is enhanced if they are armored with certain cytokines, such as IL-15 and IL-21, prior to infusion [124]. Armored immune effector cells may be more effective against cancer cells, and further research in this field is needed to improve the efficacy of immunotherapy.

New approaches to immunotherapy in the context of the tumor microenvironment

Cytokine-induced killer cells as an option for cancer immunotherapy

CIK cells were first described in the 1990s and are now known as a class of immune cells with potent antitumor properties [125, 126]. The heterogeneity of this population of cells carrying positive markers (CD3+CD8+, CD3+CD56+ and CD3+CD56-) is determined primarily by their ability to function independently of the MHC [127]. CIK cells exhibit antitumor activity in both solid and non-solid tumors [125, 126].

CIK cell therapy is currently widely used in medicine due to the simplicity of the preparation methods. The main advantages of this therapy include prevention of disease relapse after complete recovery, improved quality of life, increased progression-free survival, safety and tolerability throughout treatment, and cytotoxicity against many tumor types. In 2021, over 80 clinical trials involving CIK cells were registered [128]. The most compelling rationale for using CIK cells is the possibility of obtaining them also from peripheral blood mononuclear cells of healthy donors, mainly from elderly or immunocompromised patients. Undoubtedly, the parameters of the TME affect the methods of immunotherapy, specifically CIK cells [11]. Thus, the development of a reliable method that is more effective in the fight against oncology is an important achievement in medicine. Currently, it has been proven that the combination of CIK with other immunotherapy methods enhances the effects of both [129].

Current clinical trials confirm that CIK therapy is a promising and safe method for fighting cancer. Additional large-scale studies are needed to analyze in detail the effectiveness of this measure taking into account these treatment protocols. It is important to continue developing this therapy, increasing the selectivity of CIK cells using immunological and genetic engineering technologies, as well as to determine the reliability of biomarkers that allow more accurate selection of patient groups. Moreover, it is expected that the combination of CIK with chemotherapy, radiotherapy or other immunotherapies can significantly enhance tumor targeting and improve patient survival. However, further research should focus on understanding the complex processes occurring and developing in the TME.

Gene editing and CAR T-cell therapy

One of the most promising advances in immunotherapy is CAR T-cell therapy, which has demonstrated success in treating a number of malignancies, especially of hematological nature. However, lung cancer remains a major challenge due to the TME, which often suppresses the immune response. CAR T cells are designed to target specific tumor cell antigens, but their effectiveness is reduced by the immunosuppressive effects of the TME in cancer. Current research in CAR T-cell therapy aims to improve T cell entry into the TME and overcome these inhibitory factors. Promising strategies include targeting novel antigens such as EGFR and ganglioside GD2, and combining CAR T therapy with checkpoint inhibitors or immunomodulators [130, 131].

Combination with conventional therapies

Combination of immunotherapy with conservative therapies such as chemotherapy and radiotherapy is a promising approach to improve its efficacy in solid tumors. Conventional therapies block the immunosuppressive barriers of the TME, making it more permeable to immune cells, including CAR T cells and TILs. For example, chemotherapy reduces stromal cell density, improves immune cell infiltration into the tumor, and then provides antigen presentation and activates the immune response in the TME [130]. These combination strategies are currently actively studied in clinical trials and are showing encouraging results.

Oncolytic viruses

Oncolytic viruses, genetically modified to damage and destroy malignant cells, are created using innovative methodologies and are a promising method of immunotherapy. In addition to directly affecting tumors, they stimulate the immune system by releasing antigens and enhancing its ability to detect and attack cancer cells. Currently, studies are underway to combine oncolytic viruses with other immunological approaches to enhance their effectiveness, especially against hard-to-detect tumors [130].

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Existing challenges and future directions of research

While targeting the TME offers significant prospects for the development of immunotherapy for lung cancer, several key issues need to be addressed to improve treatment outcomes, one of which is the heterogeneity of the TME. The TME is characterized by significant cellular and molecular diversity, which complicates the development of effective treatment strategies. Different lung tumors may have different TME compositions characterized by different immune cell populations, ECM components, and signaling pathways [132]. This diversity may result in different responses to immunotherapy. To address this issue, there are ongoing efforts to identify specific immune factors and incorporate these factors into prognostic models for the assessment of the efficacy of monotherapy or combination therapy [123]. Future studies should be aimed at identifying specific TME characteristics associated with different lung cancer subtypes to allow the development of tailored immunotherapy approaches that account for this variability [132, 133].

Many patients with lung cancer exhibit resistance to immunotherapy, often due to immune evasion strategies embedded in the TME. These include activation of immune checkpoint pathways, metabolic alterations, and the presence of immunosuppressive cell types such as Tregs and MDSCs [134]. Understanding and targeting these resistance mechanisms is essential to improve the efficacy of existing therapies. The development of combination strategies that include immunotherapy with drugs targeting these resistance pathways may provide noteworthy benefits [135].

The search for reliable biomarkers that can predict response to immunotherapy is ongoing and represents a significant challenge. Although PD-L1 expression is frequently used, it does not fully reflect the complexity of immune responses in the TME. Future studies should focus on identifying new biomarkers, including genetic, epigenetic, and metabolic indicators, that can elucidate TME characteristics and aid in patient selection for immunotherapy [136, 137].

Current therapeutic strategies predominantly involve monotherapies targeting either immune checkpoints or specific elements of the TME. However, combination therapies that simultaneously target multiple pathways, such as immune checkpoints, TAMs, and metabolic pathways, need to be explored. Clinical trials investigating these combination approaches are critical to determine their safety and efficacy in patients with lung cancer [138, 139]. Developing optimal treatment protocols, including dosing, timing, and sequencing of therapy, is vital to maximize therapeutic efficacy. Given the dynamic nature of the TME, adaptive treatment strategies may be required to tailor therapy to individual patient responses. Future studies should examine the temporal effects of different immunotherapies on the TME and their subsequent impact on treatment efficacy [140, 141]. As immunotherapy becomes more mainstream, understanding long-term outcomes and managing potential side effects is critical. The immunomodulatory effects of therapy may result in unexpected autoimmune reactions or prolonged activation of the immune system. Future studies should focus on monitoring long-term safety and efficacy, along with developing strategies to mitigate side effects [142].

Conclusion

The TME promotes a highly immunosuppressive environment through a combination of immune checkpoint activation, metabolic competition, and recruitment of immunosuppressive cell populations. These mechanisms collectively reduce the effectiveness of the antitumor immune response, allowing malignancies to thrive without immune resistance. The TME represents a challenging target for improving immunotherapy outcomes in patients with lung cancer. Addressing these challenges through innovative research and collaborative efforts are vital to improving treatment strategies and ultimately improving survival in this patient population. Further elucidation of the interplay between the TME and the immune response will pave the way for more effective, personalized therapeutic approaches in lung cancer immunotherapy.

Author contributions

A. Ganina and M. Doskali conceived the study. L. Zaripova, L. Kozina, and M. Karimova wrote part of the manuscript. P. Mukhamedzhanova and A. Brimova provided critical discussion during the preparation of the manuscript. A. Baigenzhin, E. Chuvakova, and M. Askarov edited the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare no conflicts of interest.

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