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REVIEW ARTICLE

Application of natural killer cell-based immunotherapy in lung cancer treatment

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Abstract

Lung cancer is a malignant tumor originating in the bronchi, trachea, or other lung tissues. Despite significant advances in treatment, clinical outcomes remain unsatisfactory due to factors such as chemotherapy and heterogeneity. Natural killer (NK) cells are a key component of the innate immune system. A reduction in NK cell number or dysfunction can lead to immune evasion by tumor cells, contributing to malignant progression. In lung cancer, NK cell imbalance is closely associated with tumor immune escape mechanisms, making the modulation of NK cell activity a promising therapeutic strategy. This review examines the role of NK cell dysfunction in lung cancer immune escape and highlights recent advances in NK cell-based immunotherapy. Therapeutic approaches include cell-based NK therapies, cytokine stimulation, immune checkpoint inhibitors, monoclonal antibodies mediating antibody-dependent cell-mediated cytotoxicity, signal pathway-targeted agents, and bioactive compounds derived from medicinal and edible plants. Furthermore, emerging clinical evidence demonstrates the effectiveness of NK cell immunotherapy in improving treatment outcomes in lung cancer patients. This article aims to provide a comprehensive overview of current strategies to enhance NK cell function and presents novel therapeutic avenues to support future lung cancer interventions.

Keywords: Natural killer cells; Immunotherapy; Lung cancer

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1. Introduction

Lung cancer remains one of the most prevalent malignant tumors. According to the latest cancer statistics, lung cancer ranks first in deaths caused by cancer, accounting for nearly 20%[1] while small cell lung cancer (SCLC) has a relatively poor prognosis.[2] Pathologically, lung cancer is categorized into two main types: SCLC and non-SCLC (NSCLC). NSCLC comprises several histological subtypes, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Among these, adenocarcinoma accounts for 40% of NSCLC cases. It is more commonly observed in females and is often asymptomatic in its early stages. Squamous cell carcinoma accounts for 25% of cases and is relatively sensitive to radiotherapy and chemotherapy, with a relatively high survival rate. Large cell carcinoma accounts for 15% of NSCLC, arises from epithelial cells, exhibits a high propensity for metastasis, and is associated with a poor

prognosis. Genetic factors and molecular alterations play a critical role in the occurrence, recurrence, and prognosis of lung cancer.[3] Common genetic mutations implicated in lung cancer include alterations in the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), reactive oxygen species (ROS) fusion, and mesenchymal epithelial transition amplification. Several signal pathways are essential in both the onset and progression of lung cancer,[4] including PI3K/AKT/mTOR, RAS-MAPK, and NTRK/ROS1 pathways. While conventional treatments – such as surgical resection, radiotherapy, and chemotherapy, – alongside emerging modalities such as targeted therapy and immunotherapy have enhanced the patient outcomes to some extent, the overall 5-year survival rate remains below 7%. This is attributed to factors such as tumor cell heterogeneity, immune evasion, and resistance to radiotherapy and chemotherapy.[5,6] Therefore, there is a pressing need for innovative treatment strategies and the development of novel drugs for lung cancer management.

The immune system plays a key role in tumor development and progression. Dysregulation of immune homeostasis within the immune microenvironment (TME) can induce tumor cell proliferation. Various cytokines within the TME further regulate and mediate tumor progression.[7] The tumor ecosystem is highly complex, and interactions between cancer cells and host immune cells influence disease progression. Among non-cancerous cell types, immune cells are the most prevalent and functionally diverse within solid tumors, exhibiting both anti-tumor and pro-tumor activities. During tumor progression, cancer cells adopt multiple strategies to evade immune attacks, such as modulating antigen presentation mechanisms and activating inhibitory immune checkpoint molecules. In the process of cancer development and metastasis, immune pressure also drives clonal evolution. Simultaneously, cancer cells manipulate immune cells – such as neutrophils, macrophages, and regulatory T cells (Treg cells) – to create an immunosuppressive and pro-inflammatory TME. This manipulation subsequently facilitates immune evasion and encourages the restructuring of blood vessels and extracellular matrix, ultimately resulting in cancer progression and treatment resistance.[8] Natural killer (NK) cells, a critical component of the innate immune system, possess the intrinsic ability to recognize and directly eliminate tumor cells. As such, they play a significant role in lung cancer surveillance and therapy.[9] This review explores the regulatory mechanisms governing NK cell function in lung cancer and summarizes recent advancements in NK cell-based immunotherapeutic strategies, with the aim of informing future clinical applications.

2. Biological activity and mechanism of NK cells

NK cells, similar to B and T lymphocytes, play a crucial role in the innate immune system, serving as the initial defense against infections caused by viruses and bacteria. They contribute to the activation of T cells and the polarization of helper T cells through cytokine release, which in turn stimulates the maturation of dendritic cells (DC) and B cells. This positions NK cells as crucial mediators that bridge both innate and adaptive immune responses.[10] NK cells are primarily found in lymph nodes, peripheral blood, spleen, and bone marrow, comprising approximately 15% of the lymphocytes in peripheral blood. They are often characterized as $CD3^{-}CD56^{+}$ cells and can be divided into two main subgroups with different functions and mature states: $CD56^{+}CD16^{-}$ and $CD56^{+}CD16^{+}$.[11] Most NK cells have low CD56 and high CD16 expression levels, latter of which plays a key role in stimulating DC maturation.[12] NK cells play an important role in immune surveillance in the body and constitute essential effectors of anti-cancer immune responses. They monitor and kill malignant cells by regulating the release of cytokines and chemokines.[13] Activated NK cells exert their cytotoxicity effects through multiple mechanisms, as illustrated in Figures 1 and 2. These mechanisms include:

- Perforin and granzyme release: NK cells induce target cell apoptosis through the secretion of cytotoxic molecules containing granzymes and perforin.[14] Perforin forms transmembrane pores in target cells, allowing granzymes – particularly granzyme B – to enter and initiate apoptosis. Granzyme B also promotes the upregulation of inflammatory mediators and enhances immune cell infiltration, further contributing to the inflammatory response and tumor clearance.[15,16]
- Secretion of cytokines and chemokines: NK cells release a range of effector molecules, such as cytokines, chemokines, and growth factors that engage with DCs, macrophages, T cells, and endothelial cells to curb tumor angiogenesis and trigger adaptive immune responses.[17] Key cytokines include interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α).[18] IFN-γ is an important immune regulator that binds to target cell receptors, generating activation signals and further activating effector genes involved in immune regulation.[19] TNF-α is a multifunctional pro-inflammatory cytokine that regulates various physiological and pathological signaling pathways, including cell differentiation, proliferation, apoptosis, and inflammatory responses. It accelerates cancer progression by promoting cancer cell proliferation, migration, adhesion, and the generation of new tumor blood vessels.[20]

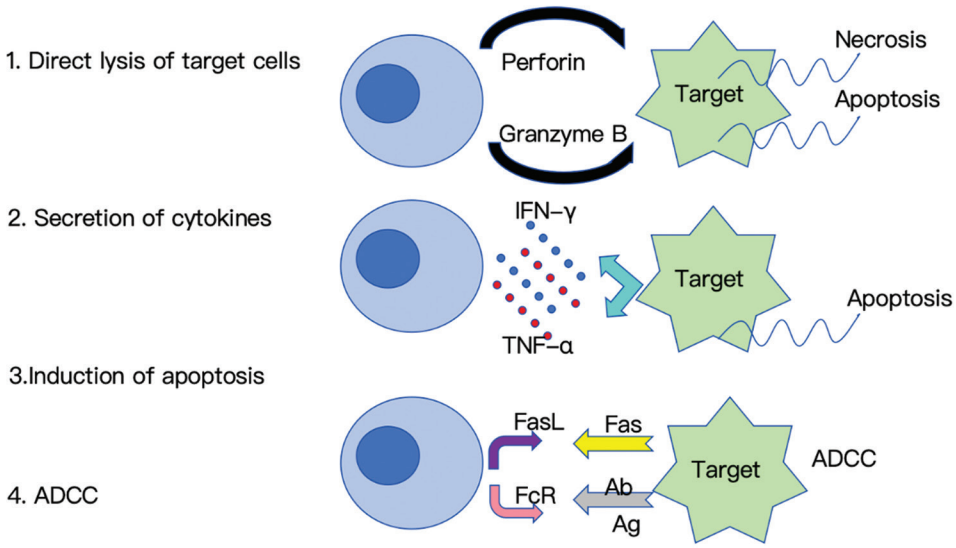

Figure 1. Mechanisms of NK cell-mediated cytotoxicity. Image created by the authors.
Abbreviations: Ab: Antibody; ADCC: Antibody-dependent cell-mediated cytotoxicity; Ag: Antigen; CRTAM: class-I MHC restricted T cell associated molecule; DNAM-1:DNAX accessory molecule 1; FcR: Fc receptor; IFN-γ: Interferon-γ; MICA/B: MHC class I chain-related A/B; MULT1:Murine ULBP-Like Transcript 1; TIGIT: T cell immune receptor with immunoglobulin and ITIIM domain; TNF-α: Tumor necrosis factor-α; ULBP1-6:UL16-binding protein 1-6.

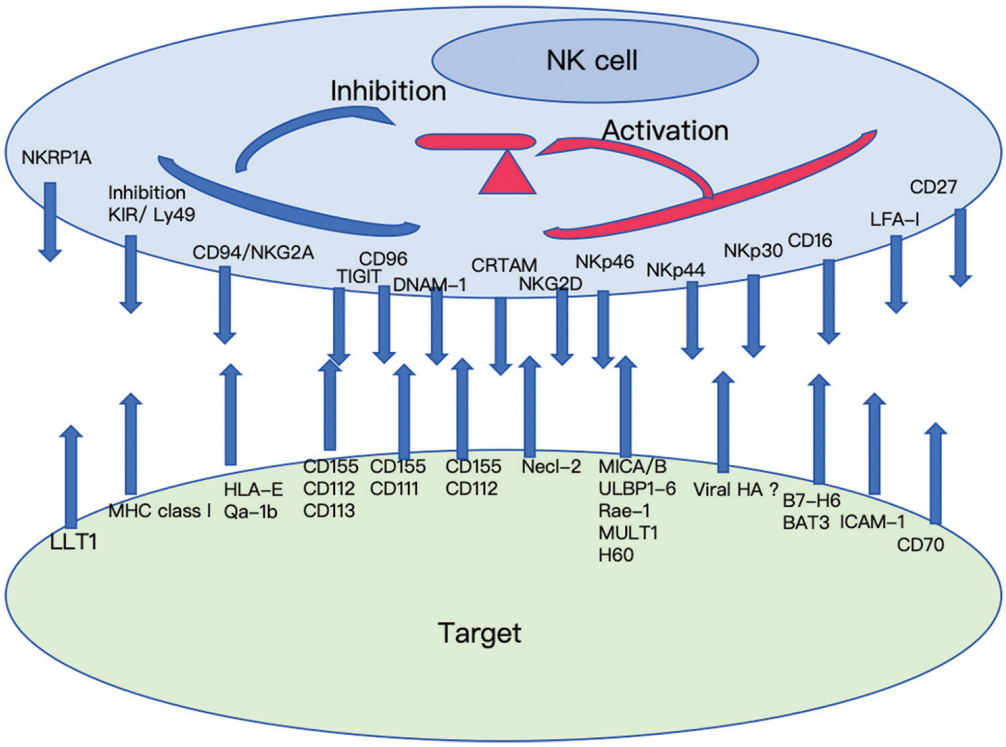

Figure 2. Interactions of NK cell surface receptors and ligands on the target cells. Image created by the authors.
Abbreviations: BAT3: HLA-B-associated transcript 3; CD: Cluster of differentiation; CRTAM: Class-I MHC restricted T cell associated molecule; DNAM-1: DNAX accessory molecule 1; HA: Hemagglutinin; HLA-E: Human leukocyte antigen E; ICAM-1: Intercellular adhesion molecule 1; IgG: Immunoglobulin G; KIR: Killer-cell immunoglobulin-like receptor; LFA-1: Lymphocyte function-associated antigen 1; LLT1: Lectin-like transcript 1; MHC: Major histocompatibility complex; MICA/B: MHC class I chain-related A/B; MULT1: Murine ULBP-Like Transcript 1; NCRs: Natural cytotoxicity receptors; NK: Natural killer; TIGIT: T cell immune receptor with immunoglobulin and ITIIM domain; ULBP1-6: UL16-binding protein 1-6.

- Activating cell apoptosis pathways through death receptors: NK cell activity is governed by a balance between the activation and inhibition signals transmitted by cell surface receptors. Inhibitory receptors such as killer immunoglobulin-like receptors (KIR), CD94/NKG2A, and ILT2/CD85 prevent cytotoxic activity by recognizing self-MHC molecules. In contrast, activating receptors – including the natural cytotoxicity receptors (NKp46, NKp30, NKp44), NKG2D, and DNAM-1 – recognize stress-induced ligands on tumor cells, triggering cytotoxic responses. NK cells can also induce apoptosis in tumor cells through death receptor-ligand interactions, such as FasL on NK cells binding to Fas on tumor cells, thereby activating the apoptotic cascade.[21]
- Antibody-dependent cell-mediated cytotoxicity (ADCC): ADCC is an important mechanism underlying the clinical efficacy of many therapeutic antibodies. NK cells express CD16 molecules, which bind to the Fc region of antibodies attached to tumor antigens. This interaction activates NK cells to kill antibody-coated tumor cells through cytotoxic mechanisms.[22]

3. NK cells' impairment and lung cancer immune evasion

During tumor development, tumor cells achieve immune escape by inhibiting NK cell function, thereby promoting disease progression.[23]

Flow cytometry analysis revealed that in lung cancer patients, T cells, NKT cells, and NK cells secrete TNF-α, IFN-γ. The ratio of granzyme B to perforin decreases, and cancer cells release soluble factors that inhibit granzyme B, perforin, and IFN-γ. One proposed mechanism involves the prostaglandin E2/cyclooxygenase-2 (COX-2) pathway, where increased COX-2 expression contributes to immune suppression and may underlie tumor immune escape.[24] In lung cancer mouse models, NK cells within the TME exhibit immature phenotypes and diminished function, with significantly decreased expression of granzyme B, perforin, and IFN-γ.[25] Furthermore, NK cell cytotoxicity is modulated by NKG2D, an activating receptor that recognizes its ligands on the surface of tumor cells and activates NK cell-mediated cytotoxic effects. TGF is secreted by tumor cells in advanced lung cancer patients. Inhibiting NK cell lysis or damaging NK cell function can downregulate NKG2D expression.[26]

Different subsets of NK cells play different roles in tumor immunotherapy.[27] Xu *et al.*[28] found that high expression of T cell immunoglobulin and mucin domain-containing protein 3 (Tim-3) in $CD3^-CD56^+$ and $CD3^-CD56^-$ NK cells was associated with decreased NK cell cytotoxicity and poor prognosis in patients with lung adenocarcinoma. According to the report by Niu *et al.*[29], found elevated level of programmed cell death receptor-1 (PD-1) in lung cancer patients. Although these $PD\text{-}1^+$ NK cells can secrete IFN-γ, their granzyme B and perforin activity are compromised, and CD107a expression is low. PD-1 expression was positively correlated with plasma interleukin-2 (IL-2) levels, and IL-2 itself was found to induce PD-1 expression on NK cells. Compared with PD-1-negative NK cells, PD-1-positive NK cells showed weaker anti-tumor effects. Blocking the interaction between PD-1 and programmed cell death ligand 1 (PD-L1) can restore the normal function of NK cells, offering therapeutic potential in advanced cancer.

In terms of metabolic function, lack of nutrients and oxygen in the TME, as well as high concentrations of tumor-derived metabolic end products such as lactate, result in damage to NK cells, thereby limiting their effector function.[30] Donnelly *et al.*[31] found that directly inhibiting glycolysis weakens the effector function of NK cells. During the lung cancer development, abnormal expression of fructose-1,6-diphosphatase in NK cells inhibits their glycolysis, weakens their cytotoxicity, and causes NK cell dysfunction.[32] Therefore, improving NK cell metabolic fitness may represent a novel strategy to improve antitumor responses in lung cancer.

The TME can locally suppress NK cell infiltration and cytotoxicity, thus facilitating tumorigenesis. Platonova *et al.*[33] showed that the immunosuppressive nature of the TME reduces both the number and function of infiltrating NK cells. Similarly, Zhang *et al.*[34] studied immune microenvironmental changes in patients with ground-glass opacity-type early lung adenocarcinoma and found reduced proportions of tumor-infiltrating NK cells using flow cytometry.

In summary, the imbalance of NK cells can contribute to the occurrence and development of lung cancer. Frese-Chaper *et al.*[35] confirmed in mouse experiments that tumors are more prone to metastasis when NK cell function is abnormal, and mice lacking NK cells have a higher incidence of tumors. Therefore, regulating NK cell activity and enhancing their cytotoxic capacity may serve as an effective strategy for immunotherapies of lung cancer.

4. Regulating NK cell-based immunotherapy for lung cancer

4.1. Adoptive NK cell therapy

Adoptive NK cell therapy involves the *in vitro* activation and induction of cultured NK cells, followed by their

reinfusion into cancer patients to exert direct or indirect tumor-killing effects.[36] This therapeutic strategy includes two primary approaches: chimeric antigen receptor (CAR)-NK cell treatment and NK cell infusion.

4.1.1. Car-NK cell therapy

CAR-NK cell therapy is an anti-cancer therapy that involves molecular modification of the patient's NK cells *in vitro* and the subsequent reinfusion of these enhanced cells back into the patient's body, as illustrated in Figure 2.

CAR-NK cells offer several advantages over CAR-T cells. NK cells can be derived from diverse sources, including umbilical cord blood, human embryonic stem cells, induced pluripotent stem cells, and established cell lines such as NK-92. Importantly, NK-92 cells are capable of producing cytokines such as IFN-γ and GM-CSF without triggering cytokine release syndrome, a common complication in CAR-T therapies.

CAR-modified NK cells can effectively target and eliminate heterogeneous tumors. The body's immune system plays a key role in how tumors develop and progress, and the imbalance of homeostasis within TME can induce the proliferation of tumor cells.[6] This therapy showcases the innovative application of CAR technology in immunotherapy.[37] R-NK therapy has gained significant attention in recent years due to its notable advantages.[38] NK cells can be obtained from various sources, including umbilical cord blood, human embryonic stem cells, and induced pluripotent stem cells.[39] These cells demonstrated significant cytotoxicity against B7-H3-positive tumor cells and effectively suppressed tumor growth in NSCLC mice.[40]

Although CAR-modified NK-92 is a promising adoptive immunotherapy for lung cancer, it faces several limitations, such as loss of targeted antigens, tumor heterogeneity, and rejection by TME. The clinical efficacy remains modest, and overcoming these challenges requires further optimization of the CAR-NK cell manufacturing process to achieve safer and more effective cellular immunotherapy (Figure 3).

4.1.2. NK cell infusion therapy

NK cell infusion therapy involves infusing unmodified autologous or allogeneic NK cells into tumor-bearing patients. Clinical studies have demonstrated that the mismatch between KIRs on donor NK cells and human leukocyte antigen molecules on autologous tumor cells can prevent the transmission of inhibitory signals. As a result, allogeneic NK cells – free from KIR-mediated inhibition – remain in an activated state and exhibit enhanced cytotoxicity against tumor cells.[41] Evidence shows that the combined infusion of pembrolizumab and allogeneic NK cells into advanced NSCLC patients can significantly improve patient survival, with median survival reaching up to 18.5 months.[42] Repeated infusions of allogeneic NK cells as a standardized treatment of NSCLC patients have been proven to be safe, with significant clinical efficacy in phase I clinical trials.[43]

4.2. Drugs that regulate NK cells to treat lung cancer

The drugs used for regulating NK cell therapy in lung cancer has been summarized as follows, in order to provide a more intuitive understanding of the types and their functions (Table 1).

4.2.1. Cytokine factor

Cytokine-induced killer (CIK) cell therapy is an emerging immunotherapeutic strategy that harnesses the anti-tumor properties of pro-inflammatory cytokines, such as ILs, to activate NK cells and other anti-tumor effector cells.[44] At present, new therapies based on NK cells have shown good anti-tumor effects in clinical trials. For example, Bates *et al.*[45] treated Lewis lung cancer mice with the IL-2 pathway agonist – BEMPEG (NKTR-214) – significantly increasing the proportion of infiltrating NK cells and improving the treatment outcome. Desbois *et al.*[46] demonstrated that IL-15 super agonist (RLI-15) reduces lung cancer metastasis in tumor-bearing mice by increasing NK cell infiltration, maturation, and proliferation, while reducing the number of infiltrating neutrophils.

4.2.2. Immune checkpoint inhibitors (ICIs)

Immune checkpoint molecules, such as cytotoxic T lymphocyte-associated molecule-4, PD-1, and PD-L1, play essential roles in regulating immune responses.[47] ICIs targeting PD-1/PD-L1, including pembrolizumab and durvalumab, have shown substantial efficacy in reactivating anti-tumor immunity in a subset of NSCLC patients.[48] Recent studies suggest that ICIs not only reinvigorate CD8-positive T cells but also enhance the cytotoxic function of PD-1-positive NK cells in NSCLC.[49] The therapeutic effect is further amplified when combined with radiotherapy, which has been shown to augment immune-mediated tumor control in advanced NSCLC.[50] In addition, Li *et al.*[51] developed an LLC mouse model by subcutaneous injection of tumor cells and found that mice lacking the immune checkpoint receptor PVRIG exhibited reduced tumor burden and prolonged survival. Both genetic ablation and therapeutic blockade of PVRIG enhanced anti-tumor immunity by promoting the function of CD8-positive T cells and activating NK cells, identifying PVRIG as a compelling therapeutic target in lung cancer immunotherapy.

At present, ICI has been established as a standardized treatment for locally advanced or metastatic NSCLC

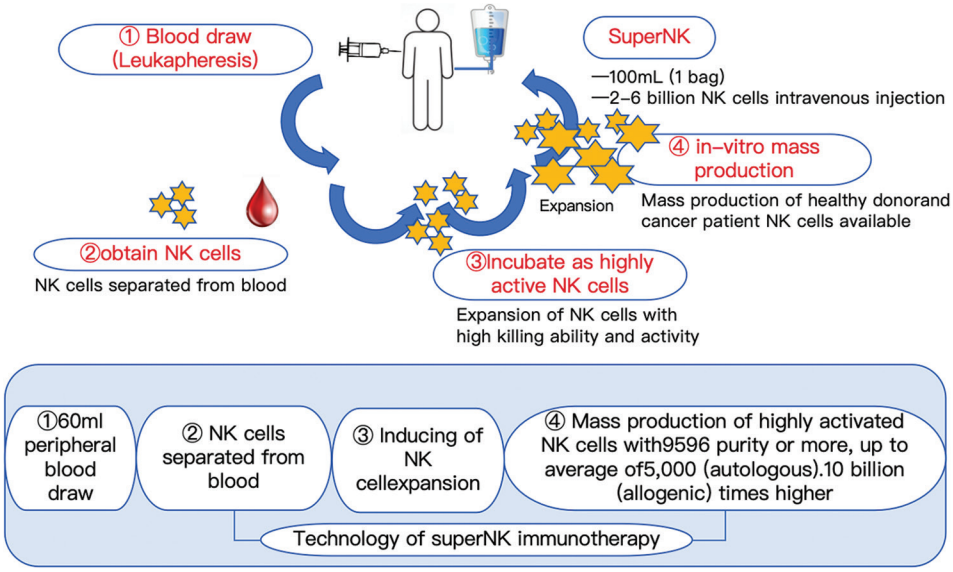

Figure 3. Schematic diagram for CAR-NK cell-based therapy
Abbreviations: CAR: Chimeric antigen receptor; NK: Natural killer.

patients. However, due to the widespread use of ICI, the emergence of drug resistance presents a huge challenge. A deep understanding of the potential biological mechanisms of acquired ICI resistance remains a critical area of ongoing research to optimize the efficacy of the therapy.

4.2.3. Monoclonal antibody drugs and ADCC

With the widespread use of monoclonal antibodies in the treatment of clinical diseases, the anti-tumor effects mediated through ADCC have garnered increasing attention. NK cells, phagocytes, T cells, and granulocytes can all exhibit the anti-tumor activity through ADCC, among which NK cells play a crucial role.[52] Cetuximab is an antibody targeting EGFR, which is often overexpressed in lung cancer. It exerts ADCC activity against EGFR-expressing lung cancer cell lines by activating NK cells.[53] HER2 is a member of the human EGFR family, which is highly expressed in cisplatin-resistant SCLC cells. Trastuzumab, a monoclonal antibody against HER2, can enhance the local infiltration of NK cells and inhibit the development of SCLC.[54]

4.2.4. Inhibitors of the enzyme-linked receptor signaling pathway

Signal transduction through enzyme-linked receptor pathways is critical in lung cancer development. Key targets such as KRAS, BRAF, and ALK are frequently mutated or rearranged in lung cancer, and therapeutic inhibitors directed at these molecules offer novel treatment opportunities.[55] For instance, tyrosine kinase inhibitors (TKIs) such as erlotinib, pemetrexed, and abemaciclib, which target KRAS mutations, not only suppress tumor cell growth but also enhance NK cell proliferation and tumor infiltration.[56] BRAF mutations occur in 3% of lung adenocarcinoma patients.[57] Targeted clinical therapeutic drugs such as vemurafenib, dabrafenib, and trametinib can activate NK cells and produce high levels of IFN-γ, TNF-α, and granular enzyme B.[58] Furthermore, about 7% of NSCLC patients have ALK rearrangement,[59] and therapeutic agents such as crizotinib have been shown to stimulate granzyme B release and demonstrate good efficacy in clinical trials.[60] Although the use of targeted drugs such as monoclonal antibodies, TKIs, and cytokines enhances the anti-tumor activity of NK cells, bringing dawn to the treatment of lung cancer, the molecular complexity and heterogeneity of lung cancer demand continuous efforts to discover and develop more effective, personalized treatments.

4.2.5. Bioactive compounds from edible fungi or plants: Single-based compound

Active ingredients derived from edible and medicinal fungi and plants have always been recognized for their therapeutic potential, particularly in traditional Chinese medicine. Many traditional Chinese medicines can inhibit tumor growth and prolong the survival rate of cancer patients.[61]

Small-molecule nitrogen-containing compounds extracted from natural plants can effectively inhibit the occurrence and development of tumor cells.[62] Among them, Rocaglamide (RocA) is a class of compounds isolated

Table 1. Drugs that regulate NK cells for lung cancer treatment

Agent type	Effect
Cyanobacteria-derived factor	Exhibit significant anti-tumor effect
ICIs	Strong anti-tumor immune response
Monoclonal antibody drugs	Enhance the local infiltration of NK cells and inhibit the development of SCLC
Inhibitors targeting of enzyme-linked receptor pathway	Enhance the proliferation and infiltration of NK cells
Bioactive compounds from edible fungi or plants	Inhibit the growth of tumors and prolong the survival rate of cancer patients

Abbreviations: Ab: Antibody; ADCC: Antibody-dependent cell-mediated cytotoxicity; ICIs: Immune checkpoint inhibitors; NK: Natural killer; SCLC: Small cell lung cancer.

from the genus Aglaia. Experiments have confirmed that RocA can enhance the NK cell-mediated NSCLC cell lysis. RocA does not act directly on NK cells or influence their binding to target cells. Instead, it enhances the expression of death receptors in tumor cells and restores granzyme B production by NK cells, which had been suppressed due to impaired autophagy initiation in NSCLC. This dual action strengthens NK cell cytolytic activity, making RocA a promising therapeutic agent for NK cell-based immunotherapy.[63]

Terpenoids are a large class of natural products, known for diverse pharmacological activities, including anti-inflammatory, anti-tumor, and antibacterial effects.[64] Lian *et al.*[65] demonstrated that combining triterpenoids from *Centella asiatica* with naringin, a natural flavanone from citrus fruits, enhances NK cell infiltration and suppresses lung tumor growth in murine models through modulation of Smad3/Smad7 signaling. Another terpenoid, ingenol-3,20-dibenzoate (IDB), a diterpenoid diester from *Euphorbia officinalis*, acts as an activator of the protein kinase C pathway. IDB significantly improves NK cell-mediated lysis of NSCLC cells by stimulating IFN-γ secretion and promoting NK cell degranulation.[66] In addition, the combination of paclitaxel (PTX) – a well-known diterpenoid – and cisplatin (CDDP) is the main treatment for lung cancer.[67,68] While standard chemotherapy often results in low survival rates among advanced NSCLC patients,[69] Yue *et al.*[70] demonstrated that combining interleukin-12 (IL-12) with PTX and CDDP chemotherapy in mouse models induces rapid NK cell activation, increases IFN-γ production, inhibits tumor angiogenesis, and leads to potent anti-tumor effects. These findings support the therapeutic potential of integrating terpenoid compounds with immune-stimulating strategies.

Flavonoids are a class of polyphenolic compounds with a wide range of biological activities, such as antibacterial, antioxidant, anti-tumor, neuroprotective, and cardioprotective properties.[71] Sun *et al.*[72] showed that isolated tanshinone IIA from traditional Chinese medicine, Danshen, enhanced the killing effect of NK cells on NSCLC. Chen *et al.*[73] found that the combination therapy of isovitexin and CDDP can also enhance the activity of cytotoxic T lymphocytes and NK cells, promoting apoptosis of NSCLC cells.

4.2.6. Bioactive compounds from edible fungi or plants: Polysaccharides

Polysaccharides have a variety of biological functions, such as anti-tumor, antioxidant, anti-diabetes, anti-virus, lipid-lowering, and immunomodulatory effects.[74] For example, polysaccharides extracted from edible fungi stimulate T cells, B cells, NK cells, and macrophages to mediate tumor suppression, thereby extending the patient's survival.[75] Wang *et al.*[76] demonstrated that intranasal administration of complement factor properdin effectively activated NK cells and inhibited the infiltration of LLC cells into the lungs.

The GFP1 polysaccharide isolated from ginseng fruit can also improve the activity of NK cells and increase serum levels of IL-2 and IFN-γ. The GFP1 significantly inhibits tumor growth and lung metastasis in LLC tumor-bearing mice and improves their immune organ status.[77]

CC2a polysaccharide isolated from chicken oil fungus promotes the proliferation of NK92 cells, enhances their vitality, regulates the expression of p38 and Erk, and boosts NK cells' effectiveness against lung cancer.[78] In addition, the type I polysaccharide of rhamnoglucuronic acid polysaccharide (BCE-I), extracted from broccoli, has been shown to induce NK cell activation, inhibit lung cancer cell metastasis, and exert anti-tumor effects.[79]

4.2.7. Bioactive compounds from edible fungi or plants: Others

For example, compound matrine injection, composed of matrine and oxymatrine, has been found to inhibit the proliferation of acute myeloid leukemia cells.[80] In addition, selenium nanoparticles (SeNPs) embedded in β-(1,3)-D-glucan extracted from the edible fungus *Auricularia auricula* form BFP-Se nanotubes, which induce AML cell apoptosis.[81]

Monomeric compounds, polysaccharide polymers, and complex mixtures derived from these natural sources have

demonstrated the ability to enhance NK cell activity. By stimulating NK cells, these compounds can contribute to anti-tumor immune responses, offering promising avenues for immunotherapy of lung cancer based on natural bioactive substances.

Some studies have also investigated formulations combining multiple edible and medicinal plants to regulate NK cell activity and exert anti-cancer effects. For example, Luo *et al.*[82] found that the traditional Chinese medicine Yupingfeng, composed of Fangfeng, Huangqi, and Baizhu, can promote NK cell infiltration, increase the proportion of NK cells in the spleen, and enhance NK cell cytotoxic activity, thereby inhibiting tumor cell growth in the LLC mice model.

5. Clinical effects of NK cell-combined chemotherapy

Immunotherapy has become the fourth major cancer treatment method following surgery, radiotherapy, and chemotherapy, and is the most cutting-edge research field in both applied research and clinical medicine. In recent years, NK cell therapy has been widely used in practice. With the constant advancement in elucidating its mechanism of action, NK cell-based immunotherapy has emerged as a promising approach in the clinical management of cancer.[83] In the treatment of solid tumors such as lung cancer, the combined application of NK cell-based immunotherapy and traditional chemotherapy effectively improves the disease control rate (DCR) and reduces the side effects of chemotherapy (Table 2). It also improves patients' quality of life and enhances their immune function.[84]

A meta-analysis by Ren,[85] involving 594 patients treated with adoptive immunotherapy and 602 patients receiving chemotherapy alone, demonstrated that the experimental group had significantly higher short-term response rates. Subgroup analysis confirmed these findings across different strata. Importantly, adoptive NK cell therapy significantly improved 1-, 2-, and 3-year survival rates, reduced mortality risk, enhanced immune function, and alleviated leukopenia when combined with chemotherapy – without increasing adverse reactions.

In a study by Wang *et al.*,[86] 37 patients with stage IV adenocarcinoma were enrolled, Group A (n = 17) received monoclonal targeted drugs combined with chemotherapy drugs and *in vitro*-cultured NK cells, while Group B (n = 20) received chemotherapy combined with monoclonal targeted drugs (Group B). The results showed that the number and activity of NK cells in Group A increased significantly compared to Group B, while the granulocyte/lymphocyte ratios decreased significantly. The DCR of Group A improved significantly compared to Group B, while the functional status score improved in both groups, with Group A showing significantly more improvement compared to Group B. Moreover, time to disease progression was significantly longer, and the incidence of severe bone marrow suppression (grades 3 – 4) was markedly lower in Group A, with no significant difference in the incidence of adverse reactions, fever, and discomfort during infusion between the two groups.

Lu[87] retrospectively analyzed treatment outcomes in patients with advanced NSCLC, comparing a combined therapy group (n = 27) receiving cellular immunotherapy with chemotherapy and a control group (n = 26) receiving chemotherapy alone. The DCR was significantly higher in the combined group (88.9% vs. 65.4%). The incidence of moderate-to-severe myelosuppression (grades II – IV) was lower in the combined group (25.9% vs. 53.8%). Moreover, the Karnofsky score improved in 89.3% of the combined group compared to 65.4% in the control. Immunologically, the combined therapy led to significant increases in CD4+ T cells, the CD4+/CD8+ ratio, and both B and T lymphocytes, suggesting restored immune competence.

In a separate study, Cao[88] conducted in-depth observation and analysis of 58 SCLC patients and divided them into experimental (n = 29) and control (chemotherapy-only group; n = 29) groups. The results showed that the overall survival (OS) in the experimental group was significantly higher than that in the control group (23.0 months vs. 14.5 months) which indicates advanced stage of SCLC. Experimental results showed that the OS of patients in the treatment group was better than that of the control group (29.5 months vs. 14.8 months) which indicates localized stage of SCLC. The progression-free survival and OS of patients in the extensive stage were both longer than those of the control group (8.0 months vs. 5.7 months, 17.5 months vs. 12 months, respectively). It has been proven that cell immunotherapy, as a treatment method for SCLC, has significant effects in prolonging survival and is safe and reliable.

In addition to lung cancer, NK cell-based immunotherapy has shown potential in the treatment of various other cancers. Yin[89] enrolled 1st-time recurrent ovarian cancer patients as the research subjects and divided them into a simple chemotherapy group (n = 33) and a combination therapy group (n = 72 cases; NK cells, CIK, and γδ T cells administered during the chemotherapy interval). With a median follow-up of 16 months, the combination therapy group exhibited significantly elevated levels of $CD3^-CD56^+$ NK cells and $CD19^+$ B cells in peripheral blood compared to the chemotherapy-only group. While the total effective rate was comparable

Table 2. Experimental research related to NK cells

Reference	Key findings
Ren[85]	The experimental group showed higher overall efficacy (in survival rate and immune function) than the control group, with no increase in adverse reactions.
Wang[86]	DCR of the treatment group was significantly improved compared to the control group. No significant difference in adverse reactions such as fever and discomfort.
Lu[87]	T cell counts significantly increased after treatment in the combined therapy group compared to before the treatment.
Cao[88]	Cytokine immunotherapy combined with chemotherapy helped prolong the survival in lung cancer patients.
Yin[89]	The combined therapy group showed significant advantages in peripheral blood immune cell levels, DCR, PFS, and OS. No statistically significant difference in adverse reactions.
Xie[90]	Cellular immunotherapy combined with chemotherapy enhanced the therapeutic effect, reduced the tumor recurrence rate, and prolonged survival in patients with colorectal cancer.
Sun[91]	Allogeneic NK cells facilitated donor cell engraftment in haploidentical non-myeloablative bone marrow transplantation without significant GVHD, promoting immune tolerance.
Li[92]	NKTm cells demonstrated a significant inhibitory effect on tumor cell growth.

Abbreviations: DCR: Disease control rate; NK: Natural killer; NKTm: Memory-like NK T cells; GVHD: Graft-versus-host disease; OS: Overall survival; PFS: Progression-free survival.

between groups (33.3% vs. 34.7%), the DCR was slightly higher in the combination group (78.8% vs. 73.6%). Improvements in fatigue symptoms were noted in the combination group, and adverse reactions were minimal, with only one case of mild immunotherapy-related fever, suggesting a favorable safety profile.

Xie[90] retrospectively analyzed 377 patients with colorectal adenocarcinoma, of whom 97 cases received chemotherapy-induced thrombocytopenia (CIT) combined with chemotherapy and 280 cases received chemotherapy alone. The CIT group received reinfusions of CIK cells, NK cells, and γδ T cells, cultured from autologous peripheral blood mononuclear cells. The results showed that the combination group achieved significantly better clinical outcomes, including improved therapeutic efficacy, lower tumor recurrence rates, and longer survival, with cellular immunotherapy identified as an independent prognostic factor. The therapy also maintained a high safety standard across the cohort.

Sun[91] conducted a preclinical study using a murine bone marrow transplantation model, dividing mice into four groups: Group A received chemotherapy as a pre-treatment; Group B received chemotherapy regimen and infusion of donor NK cells as pretreatment without bone marrow transplantation; Group C underwent chemotherapy pretreatment before undergoing bone marrow transplantation; and Group D underwent chemotherapy pretreatment, infusion of donor NK cells, followed by bone marrow transplantation. The results showed that allogenic reactive NK cells can clear the donor's hematopoietic cells, promote graft implantation in haploid non-myeloablative bone marrow transplantation, without significant GVHD expression, and induce immune tolerance of donor lymphocytes in the receptor.

In another *in vitro* study, Li *et al.*[92] explored the synergistic effect of combining NKTm cells (modified NK T-like memory cells) and cisplatin (DDP) against PLA-801D human lung cancer cells. The sequential application of NKTm cells followed by DDP demonstrated a significantly higher tumor inhibition rate than either agent alone. The combination yielded Q values more than 1.15, indicating strong synergism. Notably, the regimen with 4-h NKTm pre-treatment before DDP administration achieved the highest synergistic effect, suggesting that timing and sequencing are critical factors in optimizing combination immunotherapy.

6. Conclusion

Lung cancer remains a major threat to global health, with a persistently low 5-year survival rate despite advancements in conventional treatments such as surgery, radiation, and chemotherapy. Tumor development depends on the characteristics of cancer cells and their interaction with the TME and the immune system. In this context, immunotherapy has emerged as a transformative treatment strategy by boosting the body's immune response to inhibit tumor growth and promote cancer cell death, offering new hope for lung cancer patients. NK cells are part of the innate immune system, and they help kill tumor cells, fight viral infections, and regulate the immune response. NK cells recognize and target various cell types, including tumor cells, virus-infected cells, and other harmful cells. They form the basis of several immunotherapies, including those that use antibodies. These cells are readily available and can be derived from both autologous and allogeneic

sources, making them a promising tool for enhancing the effectiveness of cancer treatments while reducing their side effects.

The discovery and characterization of immunomodulatory components from edible and medicinal fungi/plants offer a promising direction for the development of novel, less-toxic anti-lung cancer agents. These natural compounds have demonstrated the ability to activate NK cells and modulate immune responses, contributing to anti-tumor effects through various mechanisms. Continued exploration of such bioactives and clarification of their mechanisms of action may pave the way for safer, plant-derived immunotherapies.

Numerous clinical trials have shown that NK cell therapy has a definite therapeutic effect in lung cancer. However, to fully establish the clinical utility of NK cell immunotherapy, larger sample sizes and multicenter clinical trials are necessary to validate and standardize treatment protocols for lung cancer.

With the increasing number of studies on CAR-NK cell therapy, the landscape of NK cell-based immunotherapy is rapidly evolving. Nevertheless, the current studies are largely pre-clinical, due to the significant individual differences among cancer patients. Further comprehensive, multi-center studies are needed to confirm efficacy, optimize treatment strategies, and explore long-term safety.

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Conflict of interest

Xianbin Kong is an Editorial Board Member of this journal and Guest Editor of this special issue. The authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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