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Research Progress on CAR-T in Treating NSCLC

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Abstract: As a subtype, non-small cell lung cancer (NSCLC) represents about 85% of all cases. This rate is largely due to the disease often being diagnosed at an advanced stage, the tendency for metastasis, and the development of resistance to treatments. While advancements in targeted therapies and immunotherapies have improved outcomes, challenges such as toxicity and tumor heterogeneity still persist. Chimeric antigen receptor T-cell (CAR-T) therapy, which has a breakthrough in the Leukemia, shows emerging potential in NSCLC despite limitations in solid tumor applications. This review summarizes recent progress in the CAR-T therapy for NSCLC, focusing on target selection, combination strategies, challenges, and future directions. Key targets under investigation include EGFR, MSLN, MUC1, PSCA, $CD133^{+}$, EphA2, and B7-H3, which demonstrate varied efficacy in preclinical and early clinical studies. For instance, EGFR-targeted CAR-T cells reduced metastatic lesions and improved survival in murine models, while MSLN-directed therapy achieved partial remission in patients. Combination regimens with chemotherapy and radiotherapy, could enhance the constructed cell infiltration and improve the therapeutic efficacy. Despite these advances, challenges such as cytokine release syndrome (CRS), antigen heterogeneity, immunosuppressive microenvironments, and high costs hinder clinical translation. Innovative solutions like dual-target CAR-T cells, gene-edited constructs and personalized approaches leveraging liquid biopsy are under exploration. While this therapy for NSCLC is still under research, ongoing preclinical optimization and clinical trials highlight its transformative potential. Future efforts must prioritize multi-target strategies, synergistic combination therapies, and cost-effective manufacturing to treat NSCLC patients.

Keywords: Chimeric antigen receptor T-cell, Non-small cell lung cancer, Target

1. Introduction

As a member of the malignant tumors, lung cancer poses a significant threat to the health of people, while patients with NSCLC accounted for 85% all over the world. NSCLC disrupts multiple organ functions through invasive growth and distant metastasis, leading to severe respiratory disorders, systemic failure, and fatal complications, ultimately resulting in high mortality rates and posing a serious threat to life and health. Histopathologically, it is classified into three principal subtypes. Current treatments depend on tumor stage and molecular characteristics. Surgery, chemotherapy, and radiation remain standards for early-stage disease, while advanced NSCLC is managed with targeted therapies (CAR-T) and immunotherapies [1]. Recent years have witnessed remarkable progress in the creation of diagnostic methods and treatment approaches for NSCLC, driven by innovations in

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molecular profiling and targeted therapies, but challenges remain in clinical treatment due to drug resistance and some other reasons. CAR-T therapy, as an emerging immunotherapy method, has demonstrated remarkable efficacy in the Leukemia, but its translational potential in NSCLC remains constrained by tumor microenvironment complexities and antigen heterogeneity. Nevertheless, with ongoing improvements in this technology and progress in clinical trials, its prospective role in treating NSCLC is gradually emerging.

This article aims to list the latest research progress of this therapy in treating NSCLC, analyzing its mechanism of action, target selection, combination therapy options, challenges faced, and future development directions, with the hope of offering new insights and approaches for treating NSCLC.

2. Basic mechanism

This therapy is a breakthrough medical technology, utilizes genetic engineering to modify patients' own T cells, endowing them with the ability to express chimeric antigen receptors (CARs), enabling them to precisely identify and eliminate tumor cells. The CAR typically has three core components: the antigen recognition domain, which is commonly referred to as the single-chain variable fragment (scFv), the transmembrane segment and the intracellular signaling region. After being inserted into T cells through viral or non-viral vector gene transfer systems, the CAR structure becomes CAR-T cells. After amplification, these cells are injected into the patient's body for systemic or local treatment. This makes it possible to treat NSCLC with this therapy [2].

3. Research progress

Target selection is crucial for this therapy in NSCLC. Currently, the primary targets for NSCLC encompass traditional targets that have undergone extensive experimentation, such as EGFR and MSLN, as well as emerging and promising targets, such as $CD133^{+}$ and EphA2.

3.1. Traditional targets

3.1.1. Epidermal Growth Factor Receptor (EGFR)

It is a receptor tyrosine kinase (RTK). Besides, it also belongs to the ErbB receptor family. In patients who have NSCLC, it often exhibits high expression, which can promote tumor cell proliferation, inhibit cell apoptosis, enhance its invasive ability, and accelerate angiogenesis by activating multiple downstream signaling pathways. A study has used CAR-T cells targeting EGFRvIII to treat the mice. It shows significantly reduced lung metastatic lesions and the survival rate has increased to 62.5%. Moreover, these constructed cells persisted in the body of mice for up to 11 weeks, indicating their potential long-term anti-tumor effect [3]. Research has confirmed that the constructed cells exhibit positive therapeutic effects in treating NSCLC, particularly in inhibiting NSCLC metastasis and prolonging survival.

3.1.2. Mesothelin (MSLN)

Mesothelin (MSLN) is a glycosylphosphatidylinositol (GPI)-anchored cell surface glycoprotein that expresses highly in NSCLC and closely associated with tumor aggressiveness and metastatic characteristics. Research has found that the second-generation of the constructed cells targeting MSLN exhibit inhibitory effects on solid tumors, including NSCLC, but they cannot completely eliminate cancer cells. A research team from China has developed MSLN CAR-T cells (aPD1-MSLN-CART) that secrete autologous PD-1 nanobodies. According to statistics, among five NSCLC patients, one patient has achieved response partially. No severe side effects were observed. Experiments have demonstrated that MSLN may exhibit therapeutic effects through the therapy [4].

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3.1.3. Mucin 1(MUC1)

As a transmembrane glycoprotein, it often exhibits abnormal expression NSCLC. A research team has successfully constructed cells targeting MUC1 and verified the specificity and potent killing effect of these cells against their target in vitro experiments. The experiments showed that the constructed cells could specifically recognize and eliminate NSCLC cell lines expressing MUC1, while releasing various cytokines (IL-2). In the studies within living systems, researchers have discovered that the constructed cells can effectively inhibit the growth of tumors that are positive for MUC1. These research findings confirm that MUC1 can be a potential target for treating NSCLC [5].

3.1.4. Prostate Stem Cell Antigen (PSCA)

It is a GPI-anchored cell surface antigen. What's more, it is always overexpressed in NSCLC. Employing the same experimental method as for the MUC1 target, the research team found that the constructed cells exhibited a similar therapeutic effect to CAR-MUC1 T cells against PSCA-positive tumors. Overall, it is a promising target for the therapy, especially when combined with MUC1, showing synergistic effects and resulting in superior anti-tumor effects [5].

3.2. Emerging targets

In addition to the aforementioned targets that have undergone extensive trials, there are also some targets that are currently undergoing preliminary research and are promising as effective treatments for NSCLC.

3.2.1. $CD133^+$

$CD133^+$ cells refer to the cell population expressing CD133, a five-transmembrane glycoprotein which is a member of the important markers of tumor stem cells. In NSCLC, these cells are tumor-initiating cells, possessing strong tumorigenic potential and chemoresistance. Targeted treatment of these cells may enhance the efficacy of chemotherapy. By targeting $CD133^+$ cells with CAR-T cells, these normally quiescent cells can be activated, increasing their sensitivity to chemotherapy and subsequently improving the overall treatment outcome [6].

3.2.2. Erythropoietin-producing hepatocellular A2(EphA2)

It is the RTK which belongs to Eph family. The research team discovered that EphA2-specific constructed cells can target and eliminate EphA2-expressing lung cancer cells in vitro, while producing interferon-γ (IFN-γ), demonstrating specific cytotoxic effects. In vivo experiments, although NSCLC-bearing mice have not yet been cured, mice treated with the constructed cells showed lower tumor growth signals at the fourth week compared to those treated with normal T cells. These research results suggest that the constructed cell immunotherapy could become a promising strategy for treating NSCLC [7].

3.2.3. B7-H3(CD276)

It belongs to the type I transmembrane glycoprotein. What's more, as a part of B7 family, its role extends beyond immune regulation, also contributing to the migration and invasion of tumor. Preliminary research results indicate that B7-H3 inhibitors exhibit significant antitumor activity in NSCLC patients. In phase I/II trials, some patients achieved partial response, particularly prominent in squamous NSCLC patients. Furthermore, the ORR is 35.7% in cases who had not received

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immunotherapy using combination therapy [8]. Research has demonstrated that the B7-H3 target has great potential in treating NSCLC.

In summary, the functions of various targets, the cytokines induced to be released, and the therapeutic effects of targeting these targets are summarized in Table 1. These targets all have continued research value in the treatment of NSCLC due to their characteristics. However, the use of this therapy targeting a single target alone cannot currently cure NSCLC. It still needs to be combined with other treatment methods (such as chemotherapy) to achieve maximum therapeutic effect.

Table 1: Summary of various targets

Target name	Target function	Induced-release cytokines	Treatment effect
EGFR	Promote tumor cell proliferation, inhibit apoptosis, enhance invasion and angiogenesis	IFN-γ, TNF-α, perforin, granzyme B	Inhibited lung metastasis of tumor cells and prolonged survival time in mice, with a survival rate of 62.5%
MSLN	Interacts with MUC16/CA125, promoting tumor cell adhesion, migration, and invasion.	IFN-γ, TNF-α, perforin, granzyme B	The treatment demonstrated certain efficacy in patients with chemotherapy-refractory metastatic lung cancer, with 1 patient achieving partial remission, 2 patients experiencing stable disease, and 1 patient experiencing disease progression. No severe side effects such as CRS or neurotoxicity were observed.
MUC1	It is closely related to the occurrence, development, invasion, and metastasis of tumors	IL-2, IFN-γ	It has shown growth inhibitory effects on MUC1-positive tumors in the PDX mouse model
PSCA	It is associated with the proliferation, migration, and invasion of tumor cells, as well as poor prognosis	IL-2, IFN-γ	Similar to CAR-MUC1 T cells
CD133+	Possessing strong tumorigenic potential and chemoresistance, it is a significant source of chemoresistance in non-small cell lung cancer (NSCLC).	HIF-2α, MMP-9, and TGF-β1	Targeting CD133+ cells can increase their sensitivity to chemotherapy and enhance the overall treatment effect.
Eph2	It is significantly correlated with the aggressiveness and metastatic ability of tumors, as well as the poor prognosis of patients	IFN-γ	The tumor growth signal in mice treated with EphA2-specific T cells was significantly lower than that in the control group
B7-H3	Participate in immune regulation, promote tumor migration, invasion, metastasis, drug resistance, metabolism, and poor prognosis.	IL-6, IL-10, and TNF-α	In NSCLC patients who had not received immunotherapy, the objective response rate (ORR) reached 35.7% with the use of combination therapy

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3.3. Combined treatment regimen of CAR-T

3.3.1. Combined with chemotherapy

Chemotherapy is a widely used for treating NSCLC. It with Oxaliplatin + Cyclophosphamide (Ox/Cy) can induce immunogenic cell death (ICD) in tumor cells and activate tumor-associated macrophages (TAMs) to express T-cell recruitment chemokines (such as CXCL9, CXCL10, CXCL16, CCL5). Unlike in hematological malignancies, issues like poor infiltration are the problems which the constructed cells often face while treating NSCLC. However, when combined with chemotherapy (Ox/Cy), Ox/Cy pretreatment significantly enhances the infiltration and significantly improves the microenvironment. This combined treatment strategy provides new insights for this therapy in NSCLC, especially in terms of improving the constructed cells infiltration and overcoming tumor microenvironment inhibition [9].

3.3.2. Combined with radiotherapy

Radiotherapy is a traditional treatment for NSCLC. However, CAR-T therapy may encounter issues such as poor infiltration and reduced chemotaxis when applied to solid tumors (NSCLC). Studies have shown that local radiotherapy can induce mice to secrete IFN-γ, which fosters the tumor microenvironment that facilitates T-cell infiltration. Furthermore, it could also enhance tumor cell recognition. Finally, to increase the production and transport of anti-tumor immune effector cells to the tumor site [10]. This combined treatment approach maximizes therapeutic efficacy in treating NSCLC.

Currently, research on this therapy for NSCLC is still in its early stages, particularly regarding the combined application of this therapy with radiotherapy and chemotherapy. At this stage, it is not yet possible to determine the specific sequence, dosage, and other issues related to the combined treatment of chemotherapy and radiotherapy with the constructed cells. More clinical experiments are needed to accumulate relevant experience.

4. Challenges and solutions

4.1. Adverse reactions

For safety, this therapy may cause several severe adverse reactions. A relatively common one is CRS, which results in releasing substantial inflammatory cytokines (such as IL-6, etc.). It manifests as persistent high fever, general fatigue, etc. If not treated promptly, it can progress to neurotoxicity. To ensure the safety of treatment, optimizing the design of the constructed cells and improving clinical management strategies are particularly crucial. For instance, IL-6 receptor antagonists can be introduced to reduce the incidence of adverse reactions. At the same time, clinicians need to closely monitor patients' responses so as to take effective management measures in a timely manner [11].

4.2. Tumor heterogeneity

The high heterogeneity of antigen expression in lung cancer cells poses a challenge for single-target therapy, which could escape. To solve this issue, researchers are developing dual-target and switchable CAR-T cells. These methods are expected to enhance the immunotherapy's ability to cope with tumor heterogeneity and more effectively eliminate cancer cells [12].

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4.3. Microenvironment impact

There are various immunosuppressive factors present in the lung cancer microenvironment, which may impair the function of constructed cells. The combination of gene editing technology and immunomodulators may address this challenge [12].

4.4. T-cell depletion

For safety, this therapy may cause several severe adverse reactions. A relatively common one is CRS, which results in releasing substantial

5. Conclusion

This therapy holds great potential in treating NSCLC. The numerous targets have been experimentally proven to significantly inhibit tumor growth and improve patient survival rates. However, it still faces problems such as limited targets, tumor heterogeneity, microenvironment influence, and T cell exhaustion. To address these, it is necessary not only to combine CAR-T with traditional treatment methods and conduct combined treatment research, but also to develop multi-target CAR-T cells in the future, optimize delivery methods, and utilize gene editing technology to enhance its safety and efficacy.

In addition, medical research is developing personalized CAR-T therapy schemes, which precisely design attack targets through analyzing tumor antigens and genomic sequencing. Liquid biopsy and imaging techniques can also provide guidance for this. The integration of these techniques can enhance the specificity of treatment, bringing hope to patients. However, the challenge of cost cannot be ignored.

As of now, there are numerous current clinical trials utilizing CAR-T therapy for NSCLC, yet most have not demonstrated effective outcomes. It remains crucial for major hospitals worldwide to actively recruit volunteers and conduct prospective experiments to advance the genuine clinical application of this therapy. Although it is still in its exploratory phase, it holds immense potential. In the future, efforts should be intensified in basic research, translational medicine, and clinical research to promote its widespread application, ultimately enabling more NSCLC patients to recover.

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