

Therapy Using CAR-T Cells for Lung Cancer: Mechanism, Application and Further Development

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Abstract. Cancer, a formidable medical challenge, arises when body cells proliferate uncontrollably, deviating from their normal growth patterns. With over a hundred unique types, each variant of cancer is characterized by its specific causes, symptoms, and treatment modalities. Virtually no organ or tissue in the human body is immune to the potential onslaught of this disease. Among the myriad of treatments available, CAR-T cell therapy stands out as a revolutionary approach, especially in the realm of lung cancer treatment. This cutting-edge immunotherapy harnesses the body's own immune system to combat cancerous cells. This review delves deep into the intricacies of CAR-T cell therapy, elucidating its underlying mechanism and its specific role in targeting lung cancer. Furthermore, the article sheds light on the current applications of this therapy, its potential side effects, and its prospective advancements, offering hope for a future where lung cancer can be more effectively managed or even eradicated.

Keywords: Cancer, lung cancer, CAR-T therapy, immunotherapy.

1. Introduction

The most fatal and second-most prevalent type of cancer, lung cancer, has an estimated 2 million new diagnoses (11%) and 2 million fatalities (18%), according to recent data [1]. Based on their microscopic appearance, NSCLC is divided into three subtypes: lung adenocarcinomas (40%) squamous cell carcinomas (25–30%), and big cell carcinomas (10–15%) [1]. Lung cancer often does not cause symptoms in the early stages. Most people with lung cancer find out they have it when it is already advanced (stage III/IV) [1]. The average age of patients is 70 years, and most of them are between 65 and 75 years old [1]. Many of them have cancer spreading locally or not locally [1]. The International Association for the Study of Lung Cancer (IASLC) reported that only 6% of people with stage IV NSCLC survive for five years, compared to 36% of those with stage IIIA NSCLC [1]. This means that lung cancer is very hard to treat when it is found late, and many older people cannot tolerate aggressive treatments because their organs are weaker due to aging. Therefore, it is very important to find ways to screen and detect lung cancer early and to develop new treatments for tumors that are advanced. The treatment of lung cancer depends on how far the tumor has spread when it is diagnosed.

With the continuous advancement of science and technology, researchers are committed to developing the latest and most effective therapies to combat cancer. By utilizing genetic engineering technology, chimeric antigen receptors (CAR) with specific antigen recognition capabilities are introduced into T cells, enabling them to autonomously reproduce and kill tumor cells. Since its inception in the early 1990s, ALL and DLBCL are two examples of hematological malignancies that have been successfully treated using CAR T-cell therapy, which has completed three generations of development [1]. This therapy is a technique for genetically manipulating T cells, a kind of white blood cell, that can identify and eradicate tumors [1]. This is accomplished by giving the T cells a synthetic receptor that can bind to protein in the cancer cells. This therapy modifies the genes within T cells to increase their capacity to fight cancer, and can also be seen as a type of gene therapy. Therefore, the mechanism and the application will be mainly summarized in the essay.

2. Mechanism

CAR-T cell therapy is a revolutionary therapy in immunology that uses a patient's immune system to combat cancer. The mechanism behind this therapy involves a series of sophisticated steps to engineer, activate, and deploy the patient's T cells in a highly targeted manner.

The process begins by extracting T cells in the blood through leukapheresis. These cells are crucial components of the immune system responsible for recognizing and eliminating foreign invaders, including cancer cells. Once collected, the T cells are transported to a specialized laboratory for genetic modification.

In the laboratory, the isolated T cells undergo genetic engineering to introduce chimeric antigen receptors on their surface. These CARs are synthetic receptors created by fusing the antigen-recognition domain of an antibody with signaling domains derived from T cell receptors and co-stimulatory molecules. The design of the receptors is tailored to learn specific antigens present on the exterior of cancer cells while bypassing the usual requirement for major histocompatibility complex (MHC) presentation. The choice of the antigen target is critical as it determines the therapy's specificity and effectiveness.

Once the CARs have been successfully integrated into the T cells, they are now referred to as CAR-T cells. These genetically modified cells are then expanded in large numbers in the laboratory over several days. This expansion phase ensures that a sufficient population of potent cells is generated for infusion back into the patient.

The cells are given intravenously back to the patient once they have achieved the desired number. The cells keep circulating in the patient's circulation after this one-time infusion, seeking out cancer cells that express the particular target antigen.

Cytotoxic pathways are activated by the cell once it binds to the antigen, as a result of a cascade of signaling events. The cells are activated as a result, launching a potent and precise onslaught versus the cancer cells that kills them and stops the growth of the tumor.

Long-term efficacy depends on cell proliferation and persistence in the body. To do this, several cell therapies have been developed to incorporate co-stimulatory domains like CD28 or 4-1BB, which offer extra signals to boost cell proliferation and survival.

Lung cancer and other types of solid tumors pose special difficulties. The hostile microenvironment of solid tumors and the scarcity of suitable antigens can limit their penetration and function. Researchers continue to explore strategies to overcome these obstacles, such as developing multi-antigen targeting CARs or combining cell therapy with other treatment modalities.

Additionally, the activation of CAR-T cells and their interaction with target antigens on tumor cells play a role in the mechanisms of this therapy. It releases soluble factors that can help with the anti-tumor response when they interact with the target antigen. The bystander myeloid cells that are activated by these soluble factors, however, can also release inflammatory cytokines like IL-6 and IL-1 β . The inflammatory toxicities seen in patients receiving this therapy are caused by the release of inflammatory cytokines and the activation of myeloid cells [2].

Different stages of CAR-T cells have been created, each with unique changes and advancements.

The stages of the cells are as follows:

(1) First stage: The initial cells are made up of an interior signaling domain, usually CD3, and an exterior antigen recognition domain (scFv). Due to poor CAR-T cell activation and durability, this generation had limited efficacy [3].

(2) Second stages: In addition to the CD3 domain, second stage cells also contain another domain. The introduction of costimulatory domains improves the anticancer responses of these cells by promoting their activation, proliferation, and persistence [3].

(3) Third stage: Along with the CD3 signaling domain, third-generation cells also integrate other costimulatory domains. Through the provision of synergistic signals, this generation attempts to improve overall cell performance and persistence [4].

(4) Fourth stage: Fourth-generation cells are designed to release particular cytokines. These cells are also referred to as T cells redirected for universal cytokine-mediated killing (TRUCKs). These

cytokines support the overall anticancer immune response by attracting and activating more protective cells in the tumor's microenvironment [4].

(5) Fifth stage: Research is ongoing to develop fifth-generation CAR-T cells, which incorporate extra components such as the IL-2 receptor (IL-2R) to improve cell performance and persistence [3].

Moving on to how this therapy works to treat lung cancer, it should be noted that radiation, chemotherapy, and surgery may not be effective in treating the disease's later stages. This cancer is also one of the major causes of cancer-related fatalities globally. Fortunately, this therapy presents a new strategy to deal with this lethal cancer.

To summarize, this therapy combines T cell collection, genetic modification, antigen recognition, signaling and activation, target cell recognition, cytotoxic effect, target cell elimination, and persistence and memory mechanisms to harness the power of the immune system against cancer. Continued research and development in this field hold great promise for advancing the effectiveness and applicability of this therapy.

3. Application in Lung Cancer

The application in many cancers like lung cancer had been more challenging due to various factors, including the complexity of the lung tumor microenvironment, the lack of tumor-specific antigens, and the potential for off-target toxicities.

Nonetheless, researchers have been actively investigating the application of this cell therapy in lung cancer and exploring ways to overcome these challenges. Several strategies are applied to overcome these challenges.

First, one method used by researchers to treat lung cancer is the identification of target antigens. Finding appropriate tumor-specific antigens that are substantially displayed on lung cancer cells but scarcely present in healthy tissues is one of the key components of successful therapy. Finding these antigens can improve the cells' affinity for cancer cells while reducing side effects. Several antigens, including mesothelin and the EGFR, have been proposed as targets for the treatment in lung cancer.

Moreover, overcoming the immunosuppressive tumor microenvironment (TME) is also essential for treating lung cancer. Solid tumors, including lung cancer, often create an immunosuppressive microenvironment that hinders the function and infiltration of immune cells, including CAR-T cells. Researchers are exploring combination therapies that involve using immunomodulatory agents or checkpoint inhibitors to counteract this immunosuppression and enhance CAR-T cell activity within the tumor.

Considering these, lung cancer treatment using this therapy has demonstrated great possibilities. Clinical trials and investigations have produced favorable findings.

One study looked at the possibility of these cells that target B7-H3, an antigen that is overexpressed in lung cancer [5]. In a melanoma model, injection of B7-H3 CAR-T cells dramatically suppressed tumor growth and prolonged survival, indicating the potential usefulness of these cells in lung cancer [5].

A review paper also covered this therapy for lung cancer. The use of the cells in immunotherapy treating solid tumors, such as lung cancer, was underlined. Despite difficulties including the absence of suitable antigens specific to the tumor and an immunosuppressive tumor microenvironment, the encouraging outcomes of early trials offer a theoretical basis for this therapy in the treatment of lung cancer [3].

The review study also addressed ongoing trials testing cells targeting scheduled death-ligand 1 (PD-L1) in NSCLC that has relapsed or been treated unsuccessfully. Lung cancer and other malignancies have higher levels of PD-L1, an immunological checkpoint that prevents T cell activation. Zeushield cytotoxic T lymphocytes and the cells that target PD-L1 are being tested for their efficacy and safety [6].

The viability and safety of CAR-T cell therapy in the treatment of lung cancer have also been established by another investigation. The scientists carried out a phase I clinical experiment in patients

using CAR-T cells that were specifically engineered to target the tumor-associated antigen mesothelin. The research demonstrated that this therapy was not risky and had positive therapeutic effects, such as tumor shrinkage and lengthened survival [7].

The use of cells that target EGFRvIII, a mutant version of the EGFR, in lung cancer has also been investigated in a study. In preclinical models, the researchers showed that EGFRvIII-targeted cells efficiently identified and eliminated lung cancer cells that expressed EGFRvIII. This suggests that this treatment may be able to target particular mutations in lung cancer [8]. The effectiveness of this therapy in treating lung cancer is being examined in ongoing trials. These trials are analyzing the safety and effectiveness of this treatment in several subtypes of lung cancer while examining various target antigens, such as HER2, MUC1, and CD30.

Nevertheless, the application of this therapy in lung cancer is still facing plenty of challenges that will limit the efficacy of it.

The difficulties that this treatment for lung cancer is encountering are mostly focused on overcoming the immunosuppressive microenvironment of the tumor and focusing on lung cancer-specific antigens. Due to the heterogeneity of lung cancer and the requirement to uncover antigens that have a strong effect on tumor cells while sparing healthy tissues, it is still challenging to identify suitable antigenic targets. As a result, the promise of the therapy may be limited by toxicity, in which the cells assault normal cells expressing modest levels of the targeted antigen. The cell function and anticancer activity may be inhibited by the immunosuppressive tumor microenvironment, which is defined by elements like regulatory T cells and inhibitory checkpoint chemicals. Furthermore, only a small percentage of the cells may penetrate solid tumor tissues, particularly lung tumors, which can reduce their effectiveness. To overcome these difficulties, scientists are currently investigating several approaches, such as the discovery of novel lung cancer-specific antigens, the reduction of toxicity, the modulation of the TME, and the improvement of cell trafficking and infiltration into the tissues of the tumor. These initiatives have the potential to enhance the efficiency of this therapy and advance its use.

To sum up, although lung cancer has several great challenges to encounter, it is effective and has a large potential to effectively treat lung cancer. Researchers are also providing strategies to overcome the difficulties and enhance the efficacy, which implies the prospect of this therapy in treating lung cancer.

4. Obstacles and Further Development

Before it may be extensively employed in clinical practice, CAR-T therapy for NSCLC must overcome a number of obstacles. Several of these difficulties include:

(1) The absence of tumor-specific antigens that CAR-T cells can target without endangering healthy organs when they go off-target. For instance, NSCLC cells do not express CD19, a common antigen employed in this therapy for hematological malignancies. Therefore, novel antigens have been investigated as possible targets for CAR-T cell treatment in NSCLC, including mesothelin (MSLN) and many other targets [9].

(2) The immune-suppressive tumor microenvironment (TME) can prevent the cells from entering solid tumors, activating, and remaining there. The TME contains a variety of elements that can harm cell function and survival, including hypoxia, an acidic pH, and other elements [9].

In extreme circumstances, this therapy's potential negative effects can be fatal. These include neurotoxicity, which is a neurological dysfunction brought on by the disruption of the blood-brain barrier, cytokine release syndrome (CRS), which is an inflammatory response in the body brought on by abandoning a large number of cytokines by CAR-T cells, and on-target off-tumor toxicity, which is the harm of healthy tissues that express tiny quantities of the target antigen [9].

To overcome these challenges, several strategies have been proposed and tested in studies. These include:

(1) The engineering of the cells with enhanced features such as dual or switchable specificity, inducible expression or activation, co-stimulatory domains, cytokine secretion, checkpoint blockade, or suicide genes. These features can improve many aspects of this therapy in NSCLC [10].

(2) The use of multiple other ways in conjunction with CAR-T cell therapy. In order to promote tumor antigen expression, decrease immunosuppression, increase CAR-T cell infiltration and activation, and guard against resistance and recurrence, these approaches can work in concert with this therapy [10].

CAR-T cell therapy is a new way to treat NSCLC that has shown great promise and fast growth. It has some drawbacks and dangers, but it also has more advantages than the usual treatment, such as stronger binding to targets, longer-lasting effects, and faster results [11]. CARs can overcome some of the challenges of cancer therapy, such as avoiding the immune system's recognition and response, but they still face other obstacles. To make CARs safer and more effective, researchers have modified them in different ways, such as making them target more than one antigen, respond to drugs, switch on and off, block signals, or work for different patients [11]. These new types of CARs are being tested in animals and humans to deal with the diversity of tumor antigens, and they may become the next era of cells [11]. The final aim of developing the cells is to cure all kinds of cancers.

5. Conclusion

CAR-T cell therapy, a type of immunotherapy, involving genetically altered T cell, to identify and target cancer cells. Though problematic, the use of this therapy for solid tumors such as NSCLC still needs more study and development.

There are two main subtypes of NSCLC, which is one of the most prevalent and lethal tumors in the world. Surgery, chemotherapy, radiation, molecular-targeted therapy, and immunotherapy are currently available therapeutic options for NSCLC. These therapies do, however, have drawbacks such as harmful effects, resistance, recurrence, and restricted response rates. Therefore, there is an urgent demand for new and potent therapy for people with NSCLC.

By using the immune system of the patient to target certain antigens on the outermost layer of cancer cells, CAR-T therapy holds an opportunity to overcome certain drawbacks of conventional therapies. When the cells bind, they get activated and begin to multiply, secrete cytokines, and eliminate tumor cells.

In conclusion, this therapy is an intriguing strategy for treating NSCLC that has the potential to deliver tailored and strong anti-tumor responses. Before this therapy for patients can be used broadly, there are still a lot of challenges to be solved. The creation, administration, and fusion of this therapy require additional study and development.

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