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Mechanism And Application Status Of CAR-T Cell Immunotherapy

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Abstract. With the continuous increase in the incidence and mortality of cancer, finding more accurate and effective treatment methods has become an important direction of medical research. As an important technological breakthrough in the field of tumor treatment in recent years, chimeric antigen receptor T cell (CAR-T) immunotherapy transforms T cells through genetic engineering to enable them to specifically recognize and kill tumor cells, overcoming many limitations of traditional treatment methods such as chemotherapy, radiotherapy and surgery. This article systematically introduces the basic principles and mechanisms of CAR-T cell immunotherapy, and reviews its clinical application and initial results in hematological malignancies. At the same time, this article also deeply analyzes the challenges currently faced by CAR-T therapy in clinical promotion, including the impact of immunosuppressive tumor microenvironment on efficacy, the difficulty in controlling side effects such as cytokine release syndrome (CRS) and neurotoxicity, and the high cost of treatment. To address these challenges, researchers are actively exploring improvement strategies such as multi-target CAR-T cells and "armored" CAR-T cells. Looking to the future, CAR-T cell therapy is expected to achieve a wider range of disease applications, and make greater breakthroughs in ensuring safety and improving treatment effects, becoming one of the core forces in anti-tumor treatment.

Keywords: CAR-T cells; immunotherapy; tumor microenvironment.

1. Introduction

At present, cancer is one of the main causes of death and also a major public health burden worldwide. According to data from the International Agency for Research on Cancer (IARC) and reports from the WHO global cancer fact sheet, it was estimated that there were 20 million new cancer cases and 9.7 million cancer-related deaths worldwide in 2022. This means that nearly one in five people will develop cancer at some point in their lives, and the IARC predicts that approximately 35million people will have cancer by 2050, a 77% increase from the number in 2022 [1]. Because there is no definite cure, and cancer patients have long been facing severe psychological and physical burdens. Although existing treatment methods, such as chemotherapy and surgery, have been effective, there is still a risk of recurrence and metastasis. Compared with traditional treatment methods such as chemotherapy, radiotherapy and surgery, Chimeric Antigen Receptor (CAR)-T cell immunotherapy has significant advantages in both treatment methods and effects. Although chemotherapy and radiotherapy can kill rapidly dividing cancer cells, they usually fail to distinguish between cancer cells and normal cells, causing damage to healthy cells as well, and cannot avoid the possibility of recurrence and the development of drug resistance. Surgery can only remove local tumors and has limited effect on metastatic cancers that cannot be operated on. Moreover, the trauma it causes requires a long recovery period and poses a relatively high risk. Therefore, CAR-T cell immunotherapy is renowned for its efficacy and specificity because it modifies T cells to enable them to recognize and eliminate pathogens and cancer cells more accurately. However, CAR-T cell immunotherapy is still a very new technology and still faces multiple challenges. Such as sustainability and security issues [2].

Meanwhile, the use of this therapy may also face the problems of cytokine storm (CRS) side effects and high costs. Therefore, this article will further explore the current situation and prospects of CAR-T therapy with readers by explaining the principle and mechanism of CAR-T cell immunotherapy,

reviewing previous clinical applications and successful cases, the current challenges and limitations faced by this technology, as well as future trends.

2. CAR-T technology Principle

T cells are white blood cells that recognize and target pathogens and cancer cells and play an important role in the immune system. When T cells encounter pathogens and cancer cells, T cell receptors recognize and respond. T cells release cytokines that direct other immune cells to destroy virus-infected cells and cancer cells. This led to the creation of CAR-T cell therapy, a treatment that genetically engineered a patient's own T cells to kill cancer cells.

The process of making CAR T cells is divided into four steps: First, T cells are collected from the patient; The T cells are then activated and the edited CAR gene is inserted into the T cells via a viral vector. Then, the number of T cells was increased and the quality was measured. Finally, CAR T cells are injected back into the patient to help the immune system destroy the cells it needs to kill.

3. Mechanism of Action

In CAR-T cell therapy, antigen recognition is a key step to achieve targeted therapy, and its core lies in the chimeric antigen receptors on the surface of CAR-T cells. This receptor structure is modified from the patient's own T cells through genetic engineering and consists of four parts: antigen recognition region (scFv), Hinge region, transmembrane region (TM), Co-stimulatory domain and signal transduction domain (CD3ζ).The antigen recognition domain is used to recognize antigens on infected cells and cancer cells, the costimulatory domain is used to enhance T cell activation, and the signal transduction domain is used to deliver signals to the T cell interior. The hinge region and the transmembrane region, the former is used to connect the antigen recognition region and the transmembrane region, the latter is used to ensure that the CAR is located in the T cell membrane [3]. Unlike the original T cells, the CARs of the modified T cells achieve recognition by directly targeting specific antigens on the surface of tumor cells. This mechanism bypassing the dependence of traditional T cell receptors on antigen-presenting cells and major histocompatibility complexes (MHC). Take CD19 as an example. Researchers introduced an antigen recognition region capable of recognizing CD19 into T cells. Through CAR-T cells, it can be eliminated by binding to CD19-positive tumor cells. This technology greatly enhances the specificity of treatment, reduces damage to normal cells and also increases efficiency.

After CAR-T cells recognize and bind to antigens, the signal transduction domain (CD3ζ) within the cells will be activated. In addition, costimulatory molecules such as CD28 will also be activated. Subsequently, CAR-T cells will release perforin and granzyme to eliminate the bound antigens. Meanwhile, CAR-T cells will also release some cytokines, such as interferon -γ (IFN-γ) and tumor necrosis factor -α (TNF-α). These cytokines are used to summon more immune cells to clear cancer cells and change the local environment to avoid recurrence as much as possible.

However, this immune activation is contact-dependent. Cytokines need to come into contact with cancer cells to be activated and initiate a series of actions. As a benefit, the frequency of mistakenly damaging normal cells is reduced.

Natural T cells need to recognize antigens through T cell receptors and must have antigen-presenting cells present the antigens in the form of MHC molecules for a series of immune responses to be activated. Due to the local nature of the form of MHC molecules, some cancer cells may not be recognized and eliminated. The recognition mechanism of CAR-T cells is different from that of natural T cells. The recognition method of CAR-T cells directly using antibodies has higher efficiency and can directly recognize the antigens on the cell surface. Furthermore, the costimulatory molecules, after optimization, can enhance the proliferation ability and survival time of T cells to achieve a sustained anti-tumor effect.

4. Clinical Application and Successful Cases

In recent years, CAR-T cell immunotherapy has made breakthrough progress in the field of hematological tumor treatment, among which the more significant ones are acute lymphoblastic leukemia (ALL), non-Hodgkin's lymphoma and multiple myeloma. CD19 is a molecule expressed on B cells. Due to the success of CAR-T therapy in the treatment of CD19, it has become an ideal target for B-cell malignant tumors. For instance, tisagenlecleucel (Kymriah) has been approved for the treatment of patients under 25 years old with relapsed or refractory B-cell ALL, while axicabtagene ciloleucel (Yescarta) is used for the treatment of adult patients with large B-cell lymphoma. In terms of multiple myeloma, some CAR-T therapy products, such as idecabtagene vicleucel (Abecma)

The effect is also very remarkable. In ELIANA's clinical data, the complete remission rate of tisagenlecleucel in the treatment of adolescents and children with relapsed or refractory B-ALL was 81% [4]. Similarly, in the clinical data of ZUMA-1, the overall response rate (ORR) of Yescarta in the treatment of relapsed/refractory large B-cell lymphoma reached 82%, and even 54% of the patients achieved complete remission [5]. The KarMMa study data demonstrated that the ORR of Abecma in patients with severely pretreated multiple myeloma reached 73%, among which 33% achieved complete remission (CR). These clinical data further illustrate the effectiveness of CAR-T therapy and its great potential for treating malignant tumors in the hematological system [6].

In addition to these studies, the data of ciltacabtagene autoleucel (Carvykti) in the CARTITUDE-1 trial were also quite outstanding. Some patients with multiple myeloma who had at least experienced it participated in this study. The vast majority of them had developed resistance to proteasome inhibitors, immunomodulators and anti-CD38 monoclonal antibodies. But surprisingly, the experimental results showed that the effective response rate of this product was as high as 98%, and the percentage of patients achieving complete remission after strict screening also reached 83% [7].

However, this therapy still has the problem of recurrence. Although the conditions of most patients have been alleviated, new disease progression will occur successively in the subsequent period. Due to the insufficient persistence of CAR-T cells, problems such as the loss of CD19 antigen occur, which is the tumor cell escape mechanism.

5. The Challenges

Although CAR-T cell therapy has achieved remarkable results in hematological malignancies, there are still some challenges in practical applications. A common side effect, cytokine storm, is caused by the excessive release of pro-inflammatory cytokines such as IL-6 and IFN-γ after the massive activation of T cells, leading to a systemic inflammatory response. Symptoms such as high fever, fatigue, and breathing difficulties may occur. In severe cases, it may cause organ function damage and even endanger life. In addition, immune effector cell-related neurotoxicity syndrome is also a very common side effect, which can lead to symptoms such as consciousness disorders, language disorders, and epilepsy. In severe cases, it can cause cerebral edema, which is quite unfavorable for treatment.

In terms of technical challenges, CAR-T therapy still has some limitations. Among them, the selection of the target is one of the most critical technical challenges at present. The ideal therapeutic target should be highly expressed only on the surface of tumor cells and lowly expressed in normal tissues. However, in actual tumors, very few can truly reach the ideal therapeutic target. Secondly, tumors are highly heterogeneous. The antigens on the cell surfaces of different patients and even different regions within a tumor vary greatly, which makes it impossible to eradicate cancer cells by using only a single target [8].

Apart from side effects and technical challenges, the high cost and production complexity have also made it difficult for this therapy to be popularized now. At present, CAR-T therapy is customized according to the condition of each patient. The customization process takes a long time and has high requirements for craftsmanship. To ensure safety and effectiveness, a large number of strict

screenings are needed. This further promotes the increase in treatment costs. The high prices usually make it unaffordable for many patients, which is often caused by various disputes such as among hospitals, patients and doctors due to patients' dissatisfaction with the fairness of treatment and hospital resources.

6. Research and Future Trends

Although CAR-T cell therapy has achieved considerable results in hematological malignancies, due to factors such as antigen inhibition and limited tumor antigen targets, CAR-T cell therapy still faces significant challenges in practical operations. To address these risk issues, there are many different solutions available at present. Dual-target CAR-T cells are a very good solution. Tumor cells with two targets that can simultaneously express multiple antigens are regarded as promising therapeutic strategies, and can also improve the specificity of treatment. In 2024, researchers from the University of Pennsylvania published a study on dual-target CAR-T cell therapy in Nature Medicine. For the first time, CAR-T cells targeting both EGFR and IL13Rα2 were tested in six patients with recurrent glioblastoma. The results showed that the tumors of some patients shrank significantly, suggesting that the dual-target strategy might overcome the heterogeneity of tumor antigens and improve the therapeutic effect.

In addition, another study is that "Armored" CAR-T cells are a way to enhance therapeutic effects by genetically engineering CAR-T cells to express specific factors. Because it can not only enhance its own persistence and effectiveness, but also activate the surrounding immune cells, this method is also a promising approach. In 2025, researchers developed a collagen-bound IL-12-expressing STEAP1-targeted CAR-T cell and found that this cell showed significantly enhanced cytotoxicity in the mouse model, suggesting that autocrine IL-12 could enhance the anti-tumor ability of CAR-T cells [9,10].

7. Conclusion

CAR-T cell therapy, as one of the major technological breakthroughs in the field of oncology, genetically engineering T cells to endow them with the ability to specifically recognize and kill tumor cells, breaking through traditional limitations and opening up a new era for tumor treatment. However, CAR-T cell therapy still faces a series of challenges in the process of clinical promotion. First of all, its individualized customized therapeutic effect is far from being achieved in curing hematological malignancies. Some factors, such as the immunosuppressive microenvironment, limit the performance of the therapy. Secondly, the side effects generated during the treatment process are still difficult to be fully controlled, such as cytokine release syndrome and neurotoxicity. To address these challenges, a variety of improved methods are being actively studied by researchers. Among them, dual-target CAR-T cells and "Armored" CAR-T cells are two of the most promising approaches. Looking forward to the future, CAR-T cell therapy is expected to have greater breakthroughs and can be used in the treatment of a wider range of diseases. Although this therapy still needs continuous exploration and improvement at present, becoming a core force in treating tumors and achieving safer and more efficient medical means is a foreseeable future.

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