Research Progress of CAR-T Therapy in Tumor Therapy

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Abstract. New progress is constantly being made in the field of tumor treatment, and new advances are constantly being made. Among them, chimeric antigen receptor T cell (CAR-T) immunotherapy is a gene therapy method that expresses transmembrane chimeric antigen receptors by gene editing and redirects T cells to recognize tumor cells specifically. CAR-T cells can kill tumor cells effectively so as to achieve the aim of treating malignant tumors. This is a highly promising approach to cancer immunotherapy that is precise, rapid, efficient, and has the potential to cure cancer. This paper summarizes the development course and research progress of CAR-T therapy and illustrates important targets of CAR-T cells in tumor treatment, such as CD19, prostate specific membrane antigen, human epidermal growth factor receptor-2, etc. Meanwhile, the paper presents the current problems facing CAR-T cell immunotherapy, such as the toxicity of CAR-T therapy, the exhaustion of CAR-T cells and their safety, as well as the corresponding effective solutions. The paper will use tumor specific antigen as a target or design double target CAR-T cells to deal with off-target toxicity. Besides, it regulates CAR-T cell activity in vivo to reduce CRS. The results indicate that blocking checkpoints or inhibiting exhaustion-related transcription factors can resist exhaustion. Further process optimization can improve the carrier's safety.

Keywords: CAR-T therapy · tumor · CAR construction · targets · problems and solutions

1 Introduction

So far, malignant tumors are one of the main causes of human death. It has been considered a huge threat to human health. According to the 2020 cancer data report released by the World Health Organization, the number of new cancer patients in the world in 2020 was about 1.93 million, the crude incidence rate was 247.5/100000, and the age-standardized incidence rate by world standard population (ASIRW) was 201.0/100000. The number of new deaths is about 9.96 million, the crude mortality rate is 127.8/100000, and the age-standardized mortality rate by world standard population (ASMRW) is 100.7/100000 [1]. For a long time, the treatment of malignant tumors has been mainly surgical treatment, chemotherapy, and radiotherapy. However, these commonly used treatments have some bad effects. The side effects of patients taking treatment will seriously affect the health and normal life of patients. With the rapid development of modern

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oncology, immunology, and molecular biology, the rise of tumor immunotherapy has brought dawn to the treatment of malignant tumors.

Immunotherapy has been a hot spot in cancer medical research in recent years. It aims to use the activity of immune cells to specifically kill malignant tumors containing certain antigen phenotypes. Chimeric antigen receptor T cell (CAR-T) immunotherapy combines the antigen-antibody recognition specificity with T cell potential cytotoxicity so that T cells have new tumor targeting, killing activity, and persistence.

This paper, through the method of literature review, illustrates the research progress of CAR-T therapy in cancer treatment. This paper introduces specifically what is called "chimeric antigen receptor T cell immunotherapy" and the evolution and optimization of the structure of the four generations of CAR, including important and common targets in CAR-T therapy as well as their characteristics. In addition, the paper outlines some problems faced by CAR-T therapy so far and puts forward possible solutions. This paper aims to provide a theoretical basis for tumor immunotherapy and offer ideas for enhancing the applicability of CAR-T therapy. In order to provide some referential contributions for human beings to overcome tumors.

2 Overview of Car-T

2.1 CAR-T Therapy

CAR-T therapy is the abbreviation of chimeric antigen receptor T cell immunotherapy. The goal of CAR-T therapy is to treat the patient's T cells in vitro, add specific antigens, namely chimeric antigen receptor (CAR), then stimulate them by using cytokines so as to screen and amplify a large number of CAR-T cells with highly specific immune effects, and then reinfuse them into the patient's body to kill tumor cells or viruses. The clinical application is mostly based on autoimmune cells.

T cells, also called T lymphocytes, are a type of white blood cell in humans that are derived from bone marrow pluripotent stem cells and mature in the thymus under the induction of thymic hormones. After maturation, it metastasizes into the human blood, lymph, and tissue fluids, where it exerts immune functions and is able to defend against and eliminate tumor cells. However, tumor cells express programmed cell death-ligand1 (PD-L1) on the cell surface, which binds with programmed death-1 (PD-1) on the T cell surface, making T cells unable to recognize and effectively kill tumor cells. PD-L1 protein is the ligand of PD-1, and their combination can transmit inhibitory signals, thereby inhibiting the function of the immune system. Once combined, PD-1 and PD-L1 will transmit a negative regulatory signal to T cells, which can trigger the inhibition of PIK3CA/AKT and other signal pathways, induce T cells to enter a resting state, make them unable to recognize tumor cells, generate immune escape, promote tumorigenesis, and effectively relieve the immune response of the body [2]. The CAR of CAR-T cells can recognize tumor cells specifically and effectively prevent the body's immunity from being hindered because of the combination of PD-1 and PD-L1, which makes T cells unable to recognize tumor cells. CARs are composed of three domains: an extracellular domain which could specifically bind to target molecules on the surface of tumor cells; a transmembrane domain which could regulate expression of the CAR on the surface of T cells; and an intracellular domain which generates signal molecules of activation [3].

The extracellular domain is usually composed of a single-chain variable fragment (scFv) and a hinge region (hinge) that functions as a linker. The scFv is composed of a heavy chain variable region and a light chain variable region linked by short peptides of 15–20 amino acids. The scFv provides targeted antigen specificity to CAR-T cells. In contrast to native T cell receptors, antigen recognition by scFv of car does not require antigen processing and peptide epitope presentation in MHC molecules, which greatly expands the applicability of a single designed car vector for different patients. The transmembrane regions of transmembrane domains are mainly type I dimeric transmembrane proteins such as CD4, CD8, and CD28. The intracellular domain is usually T cell receptor (TCR) / CD3ζ The immunoreceptor tyrosine-based activation motif (ITAM) of the intracellular domain is involved in intracellular signal transduction.

2.2 Construction of CAR

CAR was first proposed in 1989. CAR molecular structures are continually optimized, and so far, CAR molecules have progressed to the fourth generation. The first generation of CAR contained only one intracellular signal activating receptor, CD3ζ. Due to the lack of costimulatory molecules, CAR-T cells cannot transduce proliferation signals and induce cytokine production. Therefore, CAR-T cells cannot effectively achieve continuous proliferation in vivo and are thereby unable to completely clear tumor cells, leading to tumor recurrence. Second generation CARs have been generated with the intracellular addition of a costimulatory molecule, such as B7-1 (CD80), B7-2 (CD86), CD27, CD28, or inducible co-stimulator (ICOS), which allows T cells to continuously proliferate and release cytokines even without exogenous costimulatory molecules. Third generation CARs incorporate two costimulatory molecules that further enhance cytokine secretion and inhibit tumor growth. On the basis of second-and third-generation molecular structures, fourth generation CAR molecules integrate the expression of immune factors or costimulatory ligands (e.g., IL-12) and, once bound to the target antigen, activate nuclear factor of activated T cells (NFAT) to induce the expression of IL-12, thereby recruiting other immune cells in the environment and participating in the clearance of tumor cells that do not have the target antigen. At the same time, immune cells that are recruited in the vicinity of the tumor can also contribute to the pathogenesis of cancer by secreting certain cytokines (such as IFN-α, IL-5, TNF-, IL-4, etc.) to regulate the microenvironment near the tumor, to relieve its immunosuppressive property, and to participate in the killing effect on tumor cells by mobilizing the body's own immunity [4].

3 Targets of Car-T Cells

3.1 Tumor Associated Antigens

Tumor associated antigens are those which are highly expressed on the surface of tumor cells and lowly expressed in normal tissues. This is the case for most of the currently applied tumor antigen targets. Tumor associated antigens can be classified into different types. Immune cell antigens are often associated with their Cluster of Differentiation (CD) typing, including CD19, CD20, CD22, CD70, and others; classical tumor markers,

such as prostate-specific membrane antigen (PSMA), carcinoembryonic antigen (CEA), and others; growth factor, cytokine, and hormone receptors, as well as mutants and receptor classes, such as human epidermal growth factor receptor 2 (HER-2), vascular endothelial growth factor (VEGF), and others; cancer-associated glycoproteins, proteins, and glycolipids, such as mesothelin (MSLN), glypican 3 (GPC3) and others.

3.1.1 CD Targets

The best-known targets among the CD class of targets are CD19. CD19 is a surface protein expressed on B lymphocytes and follicular dendritic cells and belongs to the immunoglobulin (Ig) superfamily. It is a type I transmembrane glycoprotein with a molecular mass of 95 KD. CD19 regulates B cell development, proliferation, and differentiation through B cell receptor (BCR) - dependent and independent mechanisms. Together with CD21, CD81, and cd225, CD19 forms the BCR complex that reduces the threshold for BCR mediated B cell activation, in which CD21 provides a bridge to surface immunoglobulins, CD81 regulates CD19 expression, and CD19 plays a major signaling role. CD19 acts as a coreceptor in B cell activation as well as signaling, regulates B cell activation and proliferation, participates in the signaling function of B cells, and mediates target cell killing by T cells.

CD19 has been mainly used in targeted therapy of B cell lineage tumors, including chronic lymphocytic leukemia (BLL), B cell lymphoma, and acute lymphoblastic leukemia (ALL) [5]. Five patients with relapsed refractory B-cell non-Hodgkin's lymphoma (R/R B-NHL) with bone marrow invasion were treated with CD19 CAR-T cells from November 2017 to May 2018 at the Department of Oncology, the First Affiliated Hospital of Zhengzhou University. The near-term efficacy was evaluated 28 d after infusion and bone marrow examination was performed. Four patients achieved complete remission (CR) and minimal residual disease (MRD) transformation negativity. One patient achieved partial remission (PR). Bone marrow biopsy showed no lymphoma bone marrow invasion. Therefore, it was concluded that CD19 CAR-T cell therapy had a good long-term outcome in patients with R/R B-NHL with bone marrow invasion [6]. On August 30, 2017, the FDA approved Kyrmiah, a CAR-T cell product manufactured by Novartis, for the treatment of patients under the age of 25 who have relapsed or refractory B-ALL. This is the world's first CAR-T product approved for clinical therapy, while also opening a new paradigm of "treating immune cells with gene modification" for tumor therapy. Subsequently, a trial to treat pediatric ALL was initiated with FDA approved CD19 CAR-T cells, which has breakthrough progress: 72 patients with refractory relapsed ALL were treated, resulting in an objective response rate (ORR) of 81% at 3 months, and all responders achieved negative results for minimal residual disease (MRD); event free survival (EFS) was 73% at 6th month and 50% at 12th month, and overall survival (OS) was 90% at 6th month and 76% at 12th month [7].

3.1.2 Classical Tumor Marker Targets

Prostate-specific membrane antigen (PSMA) is a kind of enzyme that can bind to membranes with high specificity and membrane association. Because of its high expression in

more than 90% of prostate cancer lesions, it has become an important target for molecular imaging of prostate cancer [8]. The prostate-specific membrane antigen (PSMA) gene maps to 11p11-12 and expresses a type II intrinsic membrane protein composed of 750 amino acids. Ma et al. generated first- and second-generation PSMA CAR-T cells using this target, demonstrating that the second generation was more capable of killing tumors and secreting more cytokines (for example, IFN- and IL-2) [7].

Carcinoembryonic antigen (CEA), a glycosylated macromolecular polypeptide protein secreted by mucosal epithelial cells and capable of being expressed in the gastrointestinal tract, liver cells, squamous epithelium, endometrium, spleen, and prostate, is a broad-spectrum tumor marker [10]. The application of CEA CAR-T cells in 10 patients with advanced colorectal cancer was studied by Professor Qian Cheng [11] of the Third Military Medical University. Seven patients had stable disease (SD) after receiving treatment, and two patients had SD for more than 30 weeks. Significant tumor shrinkage was observed in two patients, and a variable decrease in serum CEA was observed in all patients.

3.1.3 Growth Factor, Cytokine, Hormone Receptors and Their Mutants and Receptors Targets

Human epidermal growth factor receptor-2 (HER-2) is a large type I transmembrane protein, and HER-2 can bind to other receptors of the ErbB family, such as EGFR, to form homodimers or heterodimers, which regulate intercellular signaling pathways and promote cell proliferation, angiogenesis, and tumor development. Early experiments of HER-2 CAR-T cells were trapped in the dilemma of lethal adverse effects, and subsequent HER-2 CAR-T cell research focused on safety designs that enhanced safety and efficacy by, for example, targeting dual targets, reducing costimulatory molecules, and dose escalation injections. Wang et al. [12] replaced the four amino acids LHMQ at the C-terminal of the CD3ξ chain with YRHQ. By DNA synthesis, DNA fragments containing coding antigen receptor H28ζ or H28ζ (YRHQ) targeting HER-2 were obtained by DNA synthesis. H28ζ CAR-T cells and H28ζ (YRHQ) CAR-T cells targeting HER-2 were prepared by the lentivirus vector. H28ξ CAR-T cells and H28ξ (YRHQ) CAR-T cells can specifically recognize and effectively kill tumor cells expressing the HER2 antigen. The ability of H28ξ (YRHQ) CAR-T cells to specifically kill tumor cells and the STAT3 protein phosphorylation level were better compared with those of H28ξ-CAR-T cells. To some extent, H28ξ (YRHQ) CAR-T cells have higher antitumor activity.

3.1.4 Cancer Associated Glycoproteins, Proteins and Glycolipid Targets

Mesothelin (MSLN) is a cell surface glycoprotein whose molecular weight is 40 KD, which is highly expressed on cancer cells including mesothelioma, pancreatic, gastric, ovarian, and lung cancers. High expression of mesothelin regulates multiple cell signaling pathways and is strongly associated with tumor proliferation, invasion, and poor prognosis. Mice with malignant pleural mesothelioma (MPM) were compared with different modes of systemic versus local administration. It showed that intrapleural mesothelin mediated CAR-T efficacy was greatly better than systemic infusion of

CAR-T, with the former infusing less CAR-T than the latter to induce long-term complete remission in mice, and the local route of administration also prompts the effective elimination of extrathoracic tumor sites [13]. Studies of Qin Hai Ming [14] found that tumor infiltrating T cells subjected to the tumor microenvironment had decreased plpp1 expression, causing abnormal T cell lipid metabolism and impairing the proliferative capacity and effector function of T cells. MSLN CAR-T stably expressing PLPP1 was able to enhance the level of T-cell activation in vitro, exert a stronger killing function on tumor cells, and better inhibit tumor growth.

3.1.5 Tumor Specific Antigens

Tumor specific antigen is only expressed on the surface of tumor cells, but not in normal cells, which is the ideal antigen. Because of it, CAR-T cells can specifically target specific tumor cells and do not act on normal cells, thus reducing the body's adverse effects. Tumor-specific antigen targets account for a small proportion of CAR-T cell targets due to their specificity.

The EGFR287-302 epitope is only found on the surface of overexpressed EGFR in tumor cells and EGFR variants such as epidermal growth factor receptor type III variant (EGFRvIII), but it is not found in normal cells. Therefore, this is a very ideal tumor-specific antigen target. According to Chen Muhua's [15] research, it showed that CAR-T cells targeting EGFR can specifically kill EGFR-positive triple negative breast cancer cells E0771-EGFR and 4T1-EGFR in vitro, and have a certain effect-target ratio dependence.

4 Issues Facing Car-T Therapy

4.1 Toxicity

4.1.1 Off-Target Toxicity

As tumor specific antigens are scarce, most of those targeted by CAR-T are tumor associated antigens. Therefore, while recognizing and killing tumor cells, CAR-T cells can also damage normal tissues with low expression of target antigens and show off target effects, which can seriously endanger patients' lives. One colon cancer patient received targeted erbB2 CAR-T therapy. After 5 days of CAR-T therapy, the patient developed progressive hypotension and bradycardia, and then died of cardiac arrest, which is due to CAR-T cells recognizing and attacking lung epithelial cells with low ERBB2 expression [16].

In most cases, tumor-associated antigens are generally selected as targets for CAR-T cells. Tumor cells and normal tissues express all of them, inevitably causing off-target toxicity. Therefore, tumor specific antigen is an ideal target for CAR-T therapy, and there is no off-target effect. Or the scFvs targeting the two different antigens were connected to the activation signal and the co-stimulation signal, respectively. CAR-T cells can only target and recognize the tissues or cells expressing the two antigens at the same time, enhancing their specificity and thus avoiding the off-target effect.

4.1.2 Cytokine Release Syndrome

Cytokine release syndrome (CRS) is an abnormal immune response caused by the release of excessive cytokines (especially IL-10, IFN-γ, IL-6) by activated immune cells during CAR-T treatment, which can cause multiple system organ damage and even death. Haitao et al. [17] reported the results of CAR-T therapy in 15 patients with recurrent and refractory hematological malignancies. All patients developed severe cytokine release syndrome after reinfusion. The clinical manifestations were persistent high fever, low blood pressure, and low oxygen. 14 patients were discharged from the hospital after their body temperature, blood pressure, and blood oxygen saturation returned to normal. However, some patients had poor liver function, renal insufficiency, nausea, vomiting, and diarrhea. One patient died of multiple organ failure.

The CRS after CAR-T reinfusion can be alleviated by regulating the in vivo activity of CAR-T cells. For example, suicide genes can be co-expressed in CAR-T cells, and once CRS occurs, suicide genes can be used to clear CAR-T cells. Zhang et al. [18] constructed CD19 CAR-T cells overexpressing the suicide gene iCasp9, and the chemical inducer AP1903 could effectively terminate iCasp9-CD19 CAR-T cytotoxic function in vitro and in vivo.

4.2 CAR-T Cell Exhaustion

T cell exhaustion (Tex) refers to the reduction of the normal effect level of T cells and the decrease of their proliferation and survival time under the continuous stimulation of tumor antigens. This phenomenon also exists in CAR-T cells. When Tex occurs, their biological functions are mainly manifested as: the expression of inhibitory receptors such as LAG-3, PD-1, TIM-3, and CTLA-4 continues to increase or co-express multiple inhibitory receptors; cytokine release (IFN-γ, IL-2), and perforin, granzyme secretion decreased; proliferation and self-renewal capacity (dependent on IL-7, IL-15) decreased; mitochondrial activity, glycolysis, and metabolic reserve of exhausted T cells decreased with metabolic changes [19].

In recent years, one of the most commonly used and effective methods to resist Tex is checkpoint blocking. Drugs acting on CTLA-4, PD-1, and PD-L1 have been developed and put into clinical use. These drugs are combined with CAR-T therapy, which has achieved good results in many patients. Inhibition of exhaustion-related transcription factors can also effectively resist T cell exhaustion.

4.3 Virus Delivery Safety

So far, CAR-T cell products have been listed on the virus as the carrier to make T cells get CAR. Like Kymriah, Yescarta uses lentiviral vectors. The viral vector still has potential carcinogenicity, and the viral vector carrying gene fragments has certain limitations, which cannot accommodate large genes. At the same time, the viral vector may lead to insertion mutations during integration [20].

Therefore, further mechanism research, process optimization, and awareness improvement are needed to gradually improve the R & D level and risk awareness of viral carrier raw materials in the CAR-T cell production process so as to promote the clinical transformation and application of cell therapy products.

5 Conclusion

With the development of CAR-T therapy and its application in the clinical treatment of tumors, it brings hope for the cure of tumor patients. This paper reviews the development of CAR-T therapy and some important targets, such as carcinoembryonic antigen, CD19, mesothelin, prostate specific membrane antigen, epidermal growth factor receptor, and human epidermal growth factor receptor-2. Hopefully, this will provide ideas for the discovery of new targets. At the same time, the current problems of CAR-T therapy, including toxicity, T cell exhaustion, and virus delivery safety of CAR-T cells, are mentioned. Additionally, some possible solutions are proposed. Using tumor specific antigen as a target or designing double target CAR-T cells to deal with off-target toxicity. CRS was reduced by regulating the activity of CAR-T cells. Blocking checkpoints or inhibiting exhaustion-related transcription factors can resist exhaustion. Further process optimization can improve the carrier's safety. However, this article only provides a general review of CAR-T therapy, which does not contain specific details and does not involve all targets and problems. The follow-up will continue to supplement the content of this article.

In short, CAR-T therapy has a very good development prospect in tumor treatment. By constantly optimizing and adjusting the design scheme, it will eventually be applied to a wide range of cancer treatments, bringing hope to more patients and improving the quality of human life.

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