CAR-T Cells

Xinxuan Huang

Abstract

CAR-T (Chimeric antigen receptor T) cell therapy is an immunotherapy especially effective in treating hematological tumors. It has become a relatively good method for treating cancer.

Keywords: CAR-T; Chimeric antigen receptor T cell; Cancer; Immunotherapy.

1. Introduction

Cancer is one of the leading causes of death worldwide; despite certain achievements in cancer treatment, humanity has not yet conquered cancer at all.

Immunotherapy is a therapeutic strategy that targets the immune system rather than tumor cells straightly, and by activating the patient's defenses, it can halt and destroy tumor cells [1].

CAR-T (Chimeric antigen receptor T) cell therapy is an immunotherapy especially effective in treating hematological tumors.

2. Origin of CAR-T cells

CARS were originally discovered in 1987 [2] and have proven helpful in cancer therapy [3]. In the laboratory, technicians use genetic engineering technology to activate T cells and install a localization and navigation device, the CAR (tumor chimeric antigen receptor), transforming T cells into CAR-T cells. He uses its "localization and navigation device" CAR to specifically identify tumor cells in the body and release many effector factors through immune action, which can efficiently kill tumor cells, thus achieving the goal of treating malignant tumors.

3. CAR-T cell structure and evolution

CAR comprises three major components: an extracellular domain, a transmembrane domain, and an intracellular domain [4,5]. The extracellular domain comprises a signal peptide, a tumor-associated antigen (TAA) recognition region, and a spacer. One characteristic feature of the extracellular domain is the single-chain variable fragment (scFv) region, which is similar to the variable part of heavy (VH) and light (VL) chains of the region of an antibody fused through a flexible linker [6,7,8]. The spacer is necessary to connect the antigen recognition region to the transmembrane portion, an alpha helix within the cell membrane that links the extracellular antigen-binding domain to the intracellular cytoplasmic domain [9].

The intracellular domain of the CAR is its functional terminus, which generally consists of activation and costimulatory domains. ITAMs (immunoreceptor tyrosine-based activation motifs) are the most abundant intracellular domain component found in the cytoplasmic domain of CD3 [9]. In particular, when an antigen recognition domain interacts with an antigen, an activation signal is sent to the T cell. Additionally, effective T-cell activity requires costimulatory signaling [10].

CAR T cells have been categorized into fifth distinct generations depending on the shape of the intracellular domain (Fig. 1). Commonly, the majority of effort in CAR engineering has been directed at understanding the effects of CAR co-stimulation to optimize the intracellular domain of CAR structures [11].

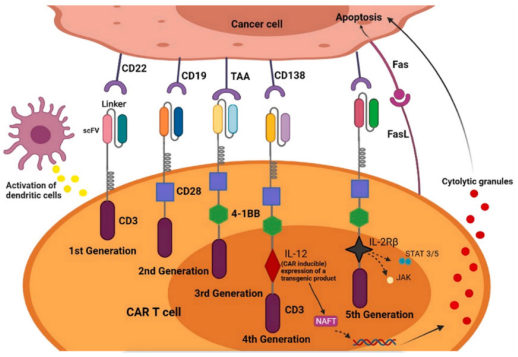

Fig. 1

Fig. 1. [12] illustrates the basic structure of five generations of CAR-T cells and their common targets on tumor cells. The core structure of a CAR displays the major components of the extracellular domain, transmembrane domain, and intracellular domain (endodomain). The first generation of CARs only contains the CD3ζ, but the second generation includes additional costimulatory signaling domains (CD28 or 4–1BB). The third-generation CARs were generated by combining multiple costimulatory domains, such as CD28–41BB or CD28-OX40, to enhance CAR-T cell potency. The fourth generation, also called T cell redirected for universal cytokine-mediated killing or TRUCKs, was generated by further genetic modification, including additional transgenes for cytokine secretion cytokines (e.g., IL-2, IL-

5, IL-12) or additional costimulatory ligands, to the base of the second-generation constructs. The fifth generation CAR-T cells contain an extra intracellular domain than their predecessors. The CARs comprise truncated intracellular domains of cytokine receptors (e.g., IL- 2R chain fragment) with a motif for binding transcription factors such as STAT-3/5 [12].

4. CAR-T cell therapy

CAR is a chimeric antigen receptor that gives immune cells a new ability to target specific antigen proteins; T is the T cells that kill tumor cells. CAR-T is a tailored T cell with unique receptors termed CARs on its surface. It is obtained by delivering chimeric antigen receptor genes into the cells using various carriers such as liposomes and lipid nanoparticles [13,14]. Such CAR-T cells are expanded and finally infused back into the patient. This therapy releases a large number of effector factors through immunity. It will effectively kill tumor cells in a non-MHC-restricted way, treating malignant tumors (Fig. 2) [15].

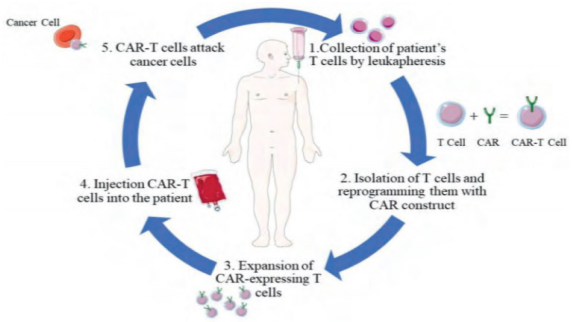

Fig.2

Fig. 2. The schematic illustration of preparing CAR-T cell therapy

5. Adverse effects of CAR-T cells

Despite promising therapeutic outcomes, CAR T cells also can elicit immune-pathologic effects, such as Cytokine Release Syndrome (CRS), Tumor Lysis Syndrome (TLS), on-target off-tumor toxicity, and other adverse reactions, which are listed below.

5.1. Cytokine Release Syndrome (CRS)

CAR-T cell therapy not only kills tumor cells but also results in the production of a considerable level of cytokines, including tumor necrosis factor-alpha (TNF- α), interferon γ (IFN- γ), IL-6, and IL-10 [16,17]. This cytokine production is called cytokine release syndrome (CRS) and leads to some clinical side effects such as fever, tachycardia, hypotension, and hypoxia, which may finally result in rapid death. CAR-T cell dosage and disease burden can predict CRS during CAR-T cell therapy [17,18,19].

5.2. Tumor Lysis Syndrome (TLS)

Destruction of many tumor cells causes a rapid release of intracellular substances. It brings about some metabolic disorders, including hyperuricemia, hyperphosphatemia, hypocalcemia, and metabolic acidosis, which result in acute renal failure and death [20].

5.3. On-target off-tumor toxicity

On-target off-tumor toxicity is an unavoidable side effect caused by the shared expression of the target antigen on normal tissues. For instance, some target antigens, including CD19, CD20, and CD22, are expressed on some normal blood cells, creating an obstacle in applying CAR-T cells in hematologic tumors [21].

6. Limitations of CAR-T cell therapy and the challenges it faces in solid tumors [22, 23]

The limitations include antigen escape [24, 25], CAR-T cell toxicity [26, 27], antigen heterogeneity [28], CAR-T cell trafficking and tumor infiltration [29, 30, 31], poor stability [32], immunosuppressive microenvironment [33, 34], and ineffectiveness in B cell-associated malignancies [35].

6.1 Antigen escape

One of the most challenging limitations of CAR-T cell therapy is the development of tumor resistance to single antigen-targeting CAR constructs. Although initially, single antigen targeting CAR-T cells can deliver high response rates, the malignant cells of many patients treated with these cells display either partial or complete loss of target antigen expression. This phenomenon is known as antigen escape.

6.2 Antigen heterogeneity

Solid tumors tend to display a large degree of antigen heterogeneity. Many tumors have only a subset of cells that express the target antigen. Even in the setting of a uniformly expressed TAA, there is the possibility of antigen loss or antigen escape.

6.3 CAR-T cell trafficking and tumor infiltration

Compared to hematological malignancies, solid tumor CAR-T cell therapy is limited by the ability of CAR-T cells to traffic to and infiltrate solid tumors as the immunosuppressive tumor microenvironment and physical tumor barriers such as the tumor stroma limit the penetration and mobility of CAR-T cells.

7. CONCLUSION

CAR-T cells are T cells synthesized using CAR technology and can self-replicate, making significant progress in cancer treatment. In recent years, the new generation of CAR-T cells has attracted great attention in cancer treatment.

The success rate of CAR-T Cell immunotherapy depends on the type of cancer. The role of CAR-T cells in cancer treatment depends on their ability to effectively manufacture and safely use. Despite recent success in many clinical studies, CAR-T cell therapy has led to a significant incidence and death of related toxicity. In addition, cytokine release syndrome and neurotoxicity are the main reasons for limiting the use of CAR-T cell therapy in clinical practice. With further understanding of the toxicity mechanism, the toxicity of CAR-T cell therapy will be effectively controlled, weakened, or even disappeared.

Although CAR therapy has shown significant effectiveness in hematological malignancies, our main goal is to investigate its potential in solid tumors, and we need to find new methods to overcome many obstacles faced by CAR-T cell therapy in solid tumors.

CAR-T cell therapy has rapidly moved from the initial stage to the rapid development stage. Toxicity management of CAR-T cell therapy requires more research to eliminate shortcomings of the present approaches or introduce new methods. We can try and develop from the following aspects:

1. We can develop approaches to engineer more powerful CAR-T cells, improve anti-tumor activity, and decrease toxicity; the new CARs can increase the safety of cancer treatment using CAR-T cells and overcome its present weaknesses.
2. Develop corresponding drugs before CAR-T cancer treatment to alleviate or neutralize toxicity and protect beneficial cells during treatment.
3. We can combine CAR-T cell therapy with other anticancer therapies to improve anti-tumor efficacy, expand clinical efficacy, and limit toxicities.
4. Develop universal CAR-T cells, improve the production failure of CAR-T cells, reduce prices, and increase the clinical efficacy of CAR-T cells, making it universally applicable to most patients.

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