

CAR T-Cell Therapy: Current Progress, Challenges and potential Strategies

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Abstract. In recent years, the unexpected development of immune system resistance in cancer cells has initiated development for new drug therapies that combat resistant cancer cells. One important issue is the mutation of antigens, which are able to help the cancer cells avoid immune system detection. As a result, the development of effective new therapies free from these problems is still a heavy focus in the medical community. Chimeric Antigen Receptor T-cells therapy is a new potential treatment that uses the infusion of genetically engineered immune system T-cells to recognize specific threats with the help of artificial T-cell receptors. Through extracting and engineering the blood sample of patients, foreign pathogens and cancer cells that aren't yet able to be identified by the immune system can be recognized and detected by the CAR T-cells. This review paper aims to examine CAR T-cell treatments against ALL, focusing on the target antigens used in CAR design, variations in CAR generations, clinical trials and FDA approvals for CAR T-cells, obstacles in CAR T-cell treatments, and the best ways to overcome them.

Keywords: CAR T-cell, cancer therapy, strategy, challenge.

1. Introduction

Under normal circumstances, the human immune system can defend against foreign threats by monitoring substances in the body. T-cells can detect foreign threats and even mutated cancer cells with the help of T-cell receptors located on their surface. These lymphocytes are formed from common lymphoid progenitors in bone marrow along with B lymphocytes [1]. The lymphocytes subsequently migrate to the thymus and develop specific receptors to recognize antigens. Once matured, T-cells bind to antigen determinants on the surface of antigen-presenting cells (APCs), which are immune cells that develop recognition towards potential antigen by specifically presenting as antigens. The activation of T-cells can also vary, since helper T-cells and cytotoxic T cells (two variants of lymphocytes) require several molecules such as CD28 to become fully activated and thus be able to identify assigned antigens. The developed lymphocytes will then spread around the immune system and create cell-mediated immunity by releasing chemicals that initiate an immune response once pathogens or other foreign threats are detected.

In general, 3 main types of T-cells can be found in the human immune system: helper T-cells, regulatory T-cells and the cytotoxic T-cells. To provide immunity, the immune system has to have a strong response to foreign antigens. T-cells with high efficacy in recognition will receive survival signals from molecules such as ICOS and OX40, which are expressed on the membrane surface following binding with the antigen. After activation, cytokines will assist in communication between lymphocytes and other immune cells as well as initiating further differentiation into other responder forms. Helper T-cells can further be identified as Th1, Th2, or IL-17 types, which all have specific roles in continued development of further immune responses. Figure 1 shows a summary of the identification and function of these 3 types of T-cells.

T-Lymphocyte Variant	Identification and Function
Cytotoxic T-cells (CD8+)	Cytotoxic T-cells (Tc-cells) have a special type of co-receptor attached to their surface called CD8. By combining with other T-cell receptors like the class I MHC molecules, CD8 can recognize a variety of antigens from both pathogens and infected cells. The cytotoxic T-cell becomes activated when it recognizes the infected cell, producing toxic molecules that kill all nearby organisms, destroying the pathogen.
Helper T-cells (CD4+)	Helper T-cells (Th-cells) are characterized by a co-receptor called CD4. CD4 interacts with T-cell receptors as well, but with class II MHC molecules instead of class I MHC molecules. As a result, helper T-cells can recognize pathogen peptides displayed by antigen-presenting cells. Upon binding, helper T-cells make cytokines, which signal the immune system to facilitate rapid growth and launch a more extensive immune response. There are multiple subtypes of Th-cells (Common types include Th1, Th2, and Th17). Each subtype of helper T-cell produces its own set of cytokines based on the type of pathogen it has recognized. As a result, some cytokines are more effective at eliminating specific invaders than others.
Regulatory T-cells	T-cells that function as regulators (Treg-cells) are similar to Helper T-cells because they include CD4 on their surface, but do not activate the immune system. When the immune response is no longer necessary, regulatory T-cells deactivate, therefore dividing more slowly than helper T-cells. This prevents excessive damage to the normal cells and tissues in the body when resources are over-extended. There are several ways in which regulatory T-cells suppress the immune response, including: • Suppressing lymphocyte and other immune system responses by releasing anti-inflammatory cytokines. • Producing molecules that destroy and initiate apoptosis activated immune cells. • Cutting off communication between the immune system to prevent T-cells activation.

Figure 1. Summary of the identification and function of the 3 main types of T-cells [2]

2. Production Procedure of CAR T-cells

Chimeric antigen receptor (CAR) T-cell therapy is a modern medical cell-based gene therapy that genetically modifies extracted T-cells into CAR T-cells before infusing them back into the patient where the CAR T-cells can detect, recognize and destroy harmful pathogens and other unidentifiable threats. By altering the genes, T-cells are engineered to be more effective against cancer cells that evolve to deceive the immune system by overcrowding their antigens (which block T-cell receptors from binding) or disguising their antigens.

There are 4 steps to producing Chimeric Antigen Receptor T-cell infusion and production, before being able to infuse it into the patient for treatment. These 4 steps are explained in figure 2.

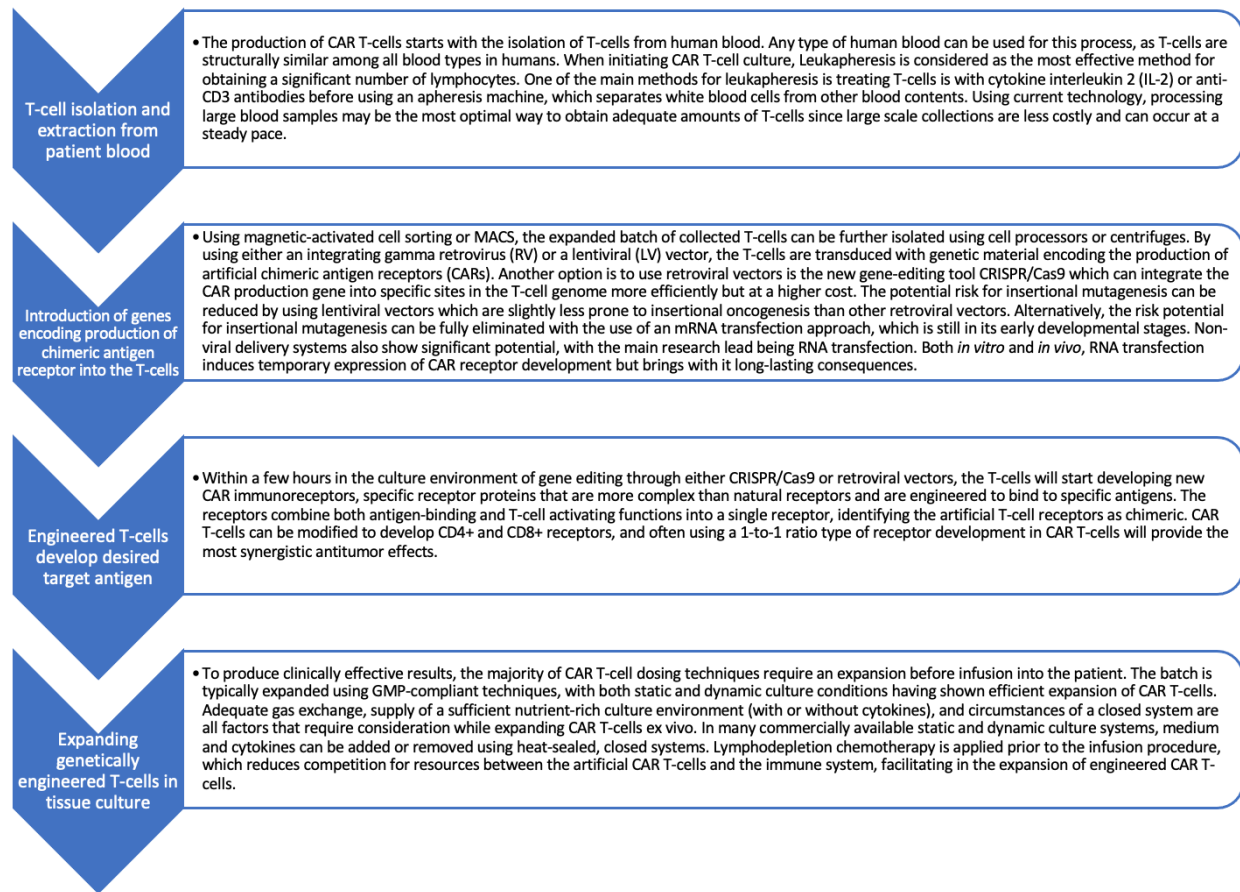


Figure 2. The 4 steps to produce CAR T-cells [3-5]

3. The Approved CAR T-Cell Therapy

As of 2022, the U.S. Food and Drug Administration (FDA) has given approval to six CAR T-cell therapies that specifically target variants of blood cancers. Figure 3 provides a summary of these six therapies.

Name	Targeted Patients	Target Antigen
Tisagenlecleucel (Kymriah)	Adults with specific forms of relapsed or refractory B-cell non-Hodgkin lymphomas	CD19
	Patients under the age of 25 with relapsed or refractory B-cell acute lymphoblastic leukemia	
Axicabtagene ciloleucel (Yescarta)	B-cell non-Hodgkin lymphoma	CD19
	Adults with relapsed or refractory follicular lymphoma	
Brexucabtagene autoleucel (Tecartus)	Adults with relapsed or refractory mantle cell lymphoma	CD19
	Adults with relapsed or refractory B-cell acute lymphoblastic leukemia	
Lisocabtagene maraleucel (Breyanzi)	Adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy,	CD19
Idecabtagene vicleucel (Abecma)	Adults with relapsed or refractory multiple myeloma after four or more prior lines of therapy	BCMA
Ciltacabtagene autoleucel (Carvykti)	Adults with relapsed or refractory multiple myeloma after four or more prior lines of therapy	BCMA

Figure 3. Summary of the 6 FDA-approved CAR T-cell therapy

4. Limitations and Potential Strategies

4.1. Antigen Escape

One of the most difficult aspects of CAR T-cell treatment is the resistance of tumor to single-antigen CAR constructs. Malignant cells exhibit a partial or total loss of expression of the target antigen in a great majority of patients who receive these CAR T-cell therapies. This process is known scientifically as "antigen escape." Even though CD19 targeted CAR T-cell therapy can produce long-lasting responses in 70–90% of patients with relapse or who are refractory, as shown in modern research [6]. Tandem CARs, a single CAR construct made up of two scFvs, or dual CARs can simultaneously target several target tumor antigens [7].

4.2. On-Target Off-Tumor Effects

Antigen selection is necessary for CAR design in order to ensure efficacy of the therapy and reduce "on-target off-tumor" damage. A way to avoid targeting antigens found in both solid tumors and normal tissues may be targeting truncated O-glycines expressed by solid tumors through post-translational modification [8]. TAG72, B7-H3, MUC1, and MUC16 have been identified as the four primary targets that can be exploited to generate CAR T cells. To reduce safety issues while selecting antigens with high anticancer activity and limiting antigen escape, fresh strategies will need to be developed.

4.3. CAR T-Cell Trafficking and Tumor Infiltration

Due to the immunosuppressive tumor microenvironment and actual tumor barriers, which impede their penetration and mobility relative to hematological malignancies, CAR T-cells are less able to infiltrate and colonize solid tumors than hematological malignancies. Local administration, as an alternative to systemic delivery, can lessen toxicities that may arise when there is no longer a need for CAR T-cells traveling to locations of the diseases due to CAR T-cells that do not function as intended. This is since that their on-target activity will reduce contact with healthy tissues and concentrate on tumor cells [9].

4.4. CAR T-Cell-Associated Toxicities

Despite its ground-breaking nature, CAR T-cell therapy is not used as the first-line treatment for cancer because of high rates of toxicities, some of which are fatal. CAR design, target identification, and types of tumor are crucial variables that affect the severity and prevalence of CSR, HLH, and/or ICANS [10]. Serious, life-threatening outcomes have happened in patients even in treatment studies with the highest response rates. In certain patients, life-threatening situations have happened (FDA) [11]. To reduce CAR-induced toxicities, it is essential to improve CAR engineering and utilize alternative techniques in order to prevent the aforementioned toxicities.

5. Conclusions

CAR T-cell therapy is a modern genetic cancer treatment therapy designed to counter antigens and cancer cells that are unidentifiable to the natural immune system. T-cells are extracted from samples of blood, then genetically engineered to develop a new chemical immune receptor called a Chimeric Antigen Receptor, abbreviated to CAR. The new artificial CAR receptors are modified to equip the CAR T-cells with the ability to recognize a specific type of antigen that the human immune system is struggling to detect. Chemotherapy is currently the first line of defense against Acute lymphocytic leukemia (ALL). Hematopoietic stem cells exhibit flexibility, repeatability, and multipotency, making them a potential strategy for the treatment of ALL. This is why the transplantation of hematopoietic stem cells has been viewed as a secondary line in ALL treatment. The understanding of immunotherapy and its related techniques has led to increasing efficacy in cancer treatment. Particularly, CAR T-cell technology is recommended as an excellent choice for ALL treatment as an

immunotherapy-based method. Therefore, there is a lot of potential for this technique in the treatment of cancer, with total of six FDA approved CAR T-cell therapies as of 2022.

In conclusion, CAR technology and its combined usage in other contexts allow CAR T-cell therapy to be a reliable and effective alternative ALL treatment strategy following the failure of chemotherapy therapy. Despite this, CAR T-cell therapy still faces significant difficulties such as cytotoxicity, cytokine release syndrome, neurotoxicity, and ICANS. As a result, future research should be warranted to unlock the full potential in this field of medical treatment.

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