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CRISPR/Cas9-Enhanced CAR-T Cell Therapy for Hematological Malignancies

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Abstract: CRISPR/Cas9 technology has brought revolution to the field of gene editing, offering precise and efficient tools for genetic modifications. One of its most promising applications lies in improving CAR-T cell therapy for treating hematological malignancies. Among approaches to treating blood cancers, CAR-T therapy, which programs T cells to recognize and eliminate cancer cells, has shown some success for B-cell malignancies such as diffuse large B-cell lymphoma (DLBCL) and B-cell acute lymphoblastic leukemia (ALL). However, challenges such as immune evasion, cytokine release syndrome (CRS), neurotoxicity, and limited CAR-T persistence remain significant barriers. CRISPR/Cas9 can optimize CAR-T therapy by precisely inserting CAR genes into specific loci, knocking out inhibitory genes like PD-1 to enhance persistence, and enabling multi-targeting strategies to overcome tumor immune escape. Clinical trials demonstrate the feasibility and potential of CRISPR-edited CAR-T cells, showing improved safety, durability, and efficacy. This study explores the synergistic application of CRISPR/Cas9 in CAR-T therapy, addressing its current limitations and providing a pathway to safer and more effective treatments for hematological malignancies.

Keywords: CRISPR/Cas9, hematological malignancies, CAR-T therapy, immune evasion.

1. Introduction

CRISPER/Cas systems, nowadays as a significant gene editing technology in modern biological research and therapeutic applications has made breakthroughs. Among all three systems, Cas9 proteins in type II systems becomes a leading tool for precise genetic modifications. It originates from the adaptive immune system of prokaryotes. And the principle of how Cas9 works is through single-guide RNA (sgRNA) and the Cas9 endonuclease to target and cleave specific DNA sequences [1]. There are few obvious advantages of this system, including simple to conduct, low cast, and able to induce targeted gene mutations, which makes it a powerful method for modifying the genomes of organisms, including human cells [2]. Therefore, this gene editing tool becomes a revolutionary tool for researchers to have more methods to explore more possible cures for genetic diseases [3].

One of the most promising fields of applying CRISPER/Cas9 is cancer immunotherapy, in which chimeric antigen receptor T-cell (CAR-T) therapy has the most outstanding behaviour [4]. What CAR-T therapy is the genetic engineering of T cells that express chimeric antigen receptors which enables them to recognize and destroy cancer cells that express specific antigens. This treatment has demonstrated remarkable success in treating hematological malignancies in recent years, like B-cell

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acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL) [5,6]. As for specific therapies, in 2017, the first CAR-T therapies were approved by the U.S. Food and Drug Administration (FDA)—Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel)—for treating specific types of leukemia and lymphoma. These two therapies are a milestone of a new era in personalized cancer therapy [7].

CAR-T therapy showed appreciable outcomes in the treatment of numerous hematological malignancies, while there are some issues that still require a solution. One of the main problems is immune escape and cancer cells may be able to mask themselves from the immune system by changing or reducing their surface memorial antigens. Also, an immune reaction that might be lethal — cytokine release syndrome (CRS) — may occur due to the activation of CAR-T cells [8,9]. Mild to moderate side-effect of CRS may be fever, hypotension, shortness of breath, multiple organ dysfunction and even life-threatening complication such as shock and acute respiratory distress syndrome (ARDS). And another drawback is low persistence of CAR-T cells in the patient's body and therefore less long-term CAR-T cell products [10].

For this purpose, it was then applied CRISPR/Cas9 technology to modify CAR-T cells to improve their function ability and reduce the side effect [11]. Now, some side effects are able to diminish. For example, the PD-1 gene has been knocked out with CRISPR/Cas9, a technique that enables T cell activation augmentation and CAR-T cell persistence and activity against tumors [12]. Moreover, CRISPR/Cas9 system also can be used to engineer T cells to bear multiple targets, thereby minimizing the risk of tumor immune escape [13]. Regarding clinical manifestations, trials have recently shown that CRISPR edited CAR-T can be successfully used on patients, which does provide good results. However, off target effects and editing efficiency remained unoptimized challenges [14, 15].

In this study, the aim is to delve into how CRISPR/Cas9 technology can lend itself to the advancement of CAR-T cell therapies, which in particular, intends to address the downsides and negative side-effects of standard manner CAR-T therapy when regulating hematological malignancies. Through a thorough analysis of the most up to date advances and clinical results, this research aims to showcase how CRISPR/Cas9 can enhance CAR-T therapy to make it a more effective and widespread hematological malignancy treatment [16].

This study is important because it provides a means to overcome existing critical challenges to the use of CAR-T therapy, including immune evasion and safety concerns, that can then be overcome by the use of CRISPR/Cas9 technology to a large extend. Integration of these technologies could not only improve therapeutic outcome in patients with refractory or relapsed hematological malignancies but also decrease or reduce side effects of these therapies [17]. In the end, this work intends to help advance safer and more efficacious gene editing approaches in cancer immunotherapy.

2. Mechanism of CRISPR/Cas9

Originally from the adaptive immune system of bacteria, the CRISPR/Cas9 is a gene editing tool. It allows precise editing of DNA sequences through targeted recognition and cutting, facilitated by its two main components: single-guide RNA (sgRNA) and the Cas9 enzyme [1–3].

First, a single guide RNA (sgRNA) is designed to bear a sequence that matches on target DNA region (tracrRNA), and the target recognition process begins [3]. Complementary base pairing allows the sgRNA to bind to the target DNA, allowing for very specific targeting [5]. Cas9, a DNA cutting enzyme, generates a complex with the sgRNA, and how the sgRNA inside the complex directs the Cas9 – sgRNA complex to a specific location in the DNA (specific nucleotide sequence) or target site by recognizing a sequence known as the Protospacer Adjacent Motif (PAM). DNA cleavage begins when the Cas9-sgRNA complex binds the target DNA. Cas9 introduces a double-strand break (DSB) at specified location [1,5]. This break stimulates the cell's inherent DNA repair processes,

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which can be used for gene disruption or precise gene modifications: Homology-Directed Repair (HDR) and Non-Homologous End Joining (NHEJ).

NHEJ is a DNA repair mechanism that does not rely on a template; it directly ligates the broken ends of DNA double-strand breaks (DSBs) and is common across all cell cycle stages, particularly in the G1 phase and early S phase. The process begins with the KU70/KU80 complex, which recognizes and binds to the DNA break ends. At this point, the DNA ends often contain irregular bases or single-stranded overhangs, which are processed by nucleases (e.g., Artemis) and polymerases to trim or fill the ends. DNA ligase IV, in association with the XRCC4 complex, then ligates the DNA ends together. While this repair method is fast and effective in repairing DNA damage in non-dividing cells, the lack of a guiding template often results in insertions, deletions, or frameshift mutations, thereby disrupting the function of target genes [3,5]. Therefore, NHEJ is frequently utilized in gene knockout experiments.

In contrast, when sister chromatids are accessible as templates throughout the S and G2 phases of the cell cycle, a high-fidelity repair mechanism known as HDR (Homology-Directed Repair) takes place. It is dependent on a homologous DNA template. The process begins with the cell recognizing DNA damage and recruiting repair proteins. Nucleases, such as CtIP and the MRE11-RAD50-NBS1 complex, create 3' single-stranded DNA (ssDNA) overhangs by processing the ends of the DNA breaks. RPA proteins then bind to the ssDNA to prevent destruction. RAD51 mediates the pairing of the ssDNA with a homologous sequence, such as a sister chromatid or donor DNA template. DNA polymerase uses this template to synthesize new DNA, filling the gap, and DNA ligase completes the repair, restoring the DNA double-helix structure. HDR requires a homologous DNA template and has lower efficiency, but with a much higher accuracy of repair, introducing few errors. Precise gene editing applications benefit from HDR, since a specific sequence can be inserted or corrections of mutations made if a repair template is present, leading to HDR being ideal for precise gene therapy work [16].

3. CAR-T Therapy

3.1. Construction and Function of CAR-T Cells

CAR-T therapy is a revolutionary mode of anticancer therapy for hematological malignancies. In CAR-T therapy, T cells from a patient are genetically modified to be able to produce chimeric antigen receptors (CAR), which enables them to recognize and eliminate cancer cells. Typically, this would start off by collecting the patient's T cells, then genetically modifying them [4,6]. To provide these cells new targeting capabilities, patient's T cells are fistly collected. CAR-T cells then should be modified, or constructed, by integrating a chimeric receptor gene into T cells. The CAR is an extracellular antigen binding domain (usually from an antibody specific to tumor associated antigens), intracellular signaling domain, and co stimulatory. In this case, the CARs on the modified CAR-T cells are modified so that CARs can specifically target antigens on cancer cells, inducing T cell activation, proliferation and release of cytotoxic agents to destroy the cancer cells [4,5]. The CAR-T cells are once expanded, and then reintroduced back into the patient. Engineered T cells can have a longer persistence in the body continuously monitoring residual and recurrent cancer cells [6].

3.2. CAR-T Therapies Approved by FDA for Hematological Malignancies

There are many treatments for tumors, among which CAR-T therapy is quite effective in the treatment of blood tumors. The U.S. Food and Drug Administration (FDA) has approved a number of CAR-T treatments for the treatment of blood malignancies. Two outstanding CAR-T therapies include Tisagenlecleucel (Kymriah) and Axicabtagene Ciloleucel (Yescarta) [18,19]. In 2017, Kymriah became the first CAR-T treatment approved by the FDA for paediatric and Adult patients with

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relapsed or refractory diffuse large B cell lymphoma (DLBCL) and young adults with B cell acute lymphoblastic leukemia (ALL) [19]. Using lentiviral vectors, this therapy embeds the CAR gene into T cells which can then recognize CD19 antigen expressed on the surface of B cells [19]. On the other hand, Yescarta is for the treatment of adult patients with large B cell lymphoma, including DLBCL, in those who have not responded to previous treatments or who have relapsed within one year of initial therapy [20]. Retroviral vectors comprise the means used in this therapy to introduce the CAR gene into patient T cells. CAR molecule is composed of an anti-CD19 single chain antibody fused to T cell activation signalling domains, to facilitate T cell specific recognition and targeting of B cells that express the CD19 antigen [20]. The approvals in these cases were based on very high response rates, with many patients achieving complete remission, from clinical trials. Although, this is not without risk, especially in cases of side effects caused by CAR-T therapy, such as cytokine release syndrome (CRS) and neurotoxicity that has to be determined and managed rigorously [8,9].

CAR-T therapies are a positive example of how we fight hematological cancers. It provides a new approach for patients for whom other traditional therapies have proven ineffective, demonstrating the potential for durable responses and cures in some patients [6]. Meanwhile, with expanding research, CAR-T cell design is getting better, toxicities are being better managed and CAR-T cell treatment may be spread to other types of cancer [10].

3.3. CRISPR in CAR-T Therapy: Applications and Progress

Genetically engineered T cells have been an important advancement in the technology that has enabled the precision and success of CAR-T cell therapy, which was accomplished by the CRISPR/Cas9 technology. CRISPR can stretch the persistence of CAR-T cells in the body and boost their anti tumor activity by knocking out specific inhibitory receptors [11, 12]. The production of Programmed Cell Death Protein 1 (PD-1) inhibits T cell function like inhibiting conventional CAR-T cells and it is not sustained against tumor cells. Removing this inhibitory pathway using CRISPR/Cas9 technology such as in the tumor context, knocking down the PD-1 gene leads to prolonged progression-free survival and higher response rates. CRISPR can also enhance the co-stimulatory molecules' expression and the pathways of immune checkpoints to greatly increase the time of existing of CAR-T cells in the body and so induce a more durable therapeutic effect [11,15]. CAR-T cells have been modified so they are more resilient and more effective at targeting and destroying cancer cells [12]. Extended CAR-T cell persistence not only extends hematological oncology, but additionally, provides novel opportunities for treating solid malignancies [10].

Additionally, targeting T cells specifically by CRISPR/Cas9 can changing a cell's genetic makeup with extreme precision, enhancing T cells' ability to home in on particular targets (cancer cells) and destroy them. It allows researchers to do multiplex gene editing on T cells by adding several genetic modifications, at the same time. For example, CRISPR can simultaneously knock out several immune checkpoint molecules, boosting the anti tumor capability of CAR-T cells [11]. This strategy increases the ability of T cells to respond to tumors with many antigens, thereby making the treatment more effective for cancers with large numbers of different antigen cancers [15].

Clinical trials has results using CRISPR-modified CAR-T cells have been promising, with superior safety and efficacy, and in treating refractory as well as relapsed cancers. It matters especially for cancers resistant to standard treatments, extending new hope for patients with few treatment options. Proven in trials, CRISPR modified T cells have found a way to get past resistance mechanisms that limited the efficacy of traditional CAR-T therapy. Because CRISPR edited T cells can be successfully infused into patients and response at a high reflect rate even in the difficult to treat cases, the groundbreaking potential is apparent. [12]

CRISPR technology and CAR-T cell therapy combine to make treatment much more precise and safer, and offer far superior outcomes to the patient, who has a higher survival rate and a better quality

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of life. With the technology evolving, it can be expected that the synergy between CRISPR and CAR-T therapy is expected continue to push the bounds in cancer and produce more personalized and effective methods of cures for many cancers.

4. Challenges and Optimization

CRISPR-Cas9 technology and CAR-T therapy have impressive potential as treatments for a variety of cancers, and especially hematological malignancies. Despite their successes, these therapies have significant hurdles to overcome if they are to reach greater levels of safety, precision, and long term efficacy.

4.1. Side Effects

One of the major problems in CAR-T cell therapy is that cancer cells can escape immune detection. Common tumor cells can mutate or downregulate their surface antigens populated by CAR-T cells, such as CD19 of B cell tumors, which prevents CAR-T cells recognition and killing of these cells [5,6]. One of the major reasons for relapse in patients who respond initially to CAR-T therapies like Kymriah and Yescarta, both directed towards CD19, is this immune escape mechanism [19,20]. To combat this, researchers are trying dual targeting CAR-T cells or CRISPR to engineer T cells with better recognition [10, 12].

Cytokine release syndrome (CRS), the other serious side effect of CAR-T cell therapy, is noted. When activated CAR-T cells, they will release substantially large amounts cytokines which may cause the symptoms such as fever, in some cases, life threatening multiorgan failure [8,9].

The second issue to worry about is Neurotoxicity, its full name is Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). The exact mechanisms aren't fully understood, but they're probably linked to the large quantities of cytokines released when CAR-T cells multiply in the body. This can be more severe, causing things like headaches, seizures and confusion [8]. In taking these efforts to further optimize CAR-T cell therapy, methods include modifying CAR constructs and using CRISPR to fine-tune immune responses, all aiming to reduce these side effects [4,10].

4.2. Off-Target Effects / Editing Efficiency

Precision is one of CRISPR-Cas9's hallmarks, but off-target effect—cas9 enzymatic cutting of certain DNA sequences not intended—is a risk especially in clinical treatments [11]. Somewhat, off target modifications can result in unwanted mutations that may induce oncogenic changes or other unwanted consequences for treated patients [11]. To combat this, researchers have created high fidelity Cas9 variants and guided RNA design improvements to enhance the specificity of CRISPR Cas9 editing [14].

For the success in therapy of CRISPR modified CAR-T cells, high editing efficiency is indeed the key point. Low editing efficiency can result in a heterogeneous population of modified and unmodified cells, reducing the overall effectiveness of the therapy [15]. Currently, improved delivery systems like viral vectors and lipid nanoparticles and optimizing editing conditions are methods that are optimal CRISPR editing in T cells [15].

4.3. Optimization Strategies

When coupled with CRISPR, it can be engineered CAR-T cells that attack multiple tumor antigens in one go, thus bypassing immune evasion. For example, dual targeting CAR-T cells may overcome antigen loss in tumors such as CD19 negative relapses in DLBCL [20]. A multi antigen targeting

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approach cuts cancer cells' chances of escaping by making cancer cells more difficult to adapt for such a pathway.

Another way of reducing CRS side effects is by refining the design of CAR constructs. To create safer and more controllable therapies, the affinity of CARs for their antigens can be altered by using CRISPR or switch mechanisms that control CAR-T cell activity can be introduced [10].

Improved delivery of CRISPR components into T cells is essential for high editing efficiency. Current techniques rely on electroporation, an advanced procedure, to increase the uptake of CRISPR machinery into cells while minimizing cell damage [15], but researchers are looking into other methods as well. We expect better delivery methods will yield improved gene editing outcomes in clinical applications.

CRISPR technology can improve therapies like Tisagenlecleucel (Kymriah) and Axicabtagene Ciloleucel (Yescarta). Lentiviral vectors are used for production for Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), but CRISPR technology allows for the precise insertion of the CAR gene into predetermined places, such as the TRAC locus, thereby avoiding the safety risk of random insertion [21].

5. Conclusion

CAR-T cell therapy integrating CRISPR/Cas9 technology represents a breakthrough development in hematological malignancy treatment. Clinical success of CAR–T therapies such as Tisagenlecleucel (Kymriah) and Axiabtagene ciloleucel (Yescarta) in treating relapsed or refractory B cell malignancies including acute lymphoblastic leukemia (ALL) and diffuse large B cell lymphoma (DLBCL) has been outstanding. Nevertheless, immune evasion, CRS, neurotoxicity, and lack of T cell persistence are nevertheless major obstacles to the wider application and sustained efficacy.

The limitations addressed by CRISPR/Cas9 technology are the inability to make any predetermined mutation and the lack of control over exactly where in a cell’s DNA the mutation occurs, as evidenced by these mutations being placed at random loci throughout the genome. CRISPR/Cas9 enables targeted CAR insertion at selected loci, such as the TRAC gene to improve expression stability and minimize random insertional mutagenesis. Additionally, immune checkpoint regulator knockout, such as PD1, increases T cell persistence and anti tumor activity bypassing tumor immune escape mechanisms.

The combination of CRISPR with CAR-T therapy improves efficacy and decrease treatment related toxicity. CRISPR-edited CAR-T cells fine tune the immune response and minimize off targeted effects. Compared to other approaches in development, this approach has shown improved safety profiles, fewer side effects, and more tumor clearance in clinical trials.

While it is clear that CRISPR engineered CAR-T therapies have a promising future, relative to the many technical challenges, including potential off target effects, delivery efficiency and scalability, future challenges include how to overcome these hurdles en masse. Ethical and regulatory considerations, however, have to be carefully managed to maintain safety and acceptance by the public and the patient. Consistent with further research and innovation, CRISPR/Cas9 technology has the capacity to refine CAR-T therapy to deliver more successful, obtainable, and long-lived treatments for hematological tumors and farther.

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