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Existing methods to improve immunotherapy's limitations: CAR-T cell therapy and checkpoint inhibitors

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Abstract. Immunotherapy is a form of treatment for cancer that works by provoking the immune system of the body into tracking down and destroying cancer cells. CAR-T-CT is a treatment that makes use of CAR-T cells (CARs), which are T cells (T-Cs) that have been modified in some way by the incorporation of engineered synthetic receptors. This therapy is designed to destroy cells that express a specific target antigen, and its primary objective is to do so by locating and killing those cells. Due to the fact that Immune CPI inhibits the production of specific proteins (checkpoint protein) on immune cells as well as on cancer cells thereby preventing the immune system from combating cancer, Immune CPI are used to treat cancer. By inhibiting the activity of these proteins, CPI is able to contribute to the process of stimulating the immune system to specifically target and destroy cancer cells. However, there are still some limitations that exist, and these have the potential to reduce the effectiveness of the treatment or produce some side effects that are life-threatening. This article makes a few suggestions for innovative steps that could be taken in order to both improve the current state of affairs and find answers to any problems that may arise in the near or distant future. The article makes these suggestions in order to improve the current state of affairs and find answers to any problems that may arise in the future.

Keywords: immunotherapy, CAR-T cell therapy, checkpoint inhibitors.

1. Introduction

Immunotherapy uses drugs to enhance or restore the immune system's ability to fight and defeat disease. Immunotherapy seeks to normalize the body's immune system so that it can destroy cancer cells without also causing an autoimmune inflammatory response, which would reduce the treatment's efficacy [1]. Cancer vaccines, CAR-T-CT and checkpoint inhibitors (CPI) are among the immunotherapeutic approaches that have been investigated. Each of these immunotherapies aims to improve immune function and can be achieved through different mechanisms of action [2]. The following studies will focus primarily on CAR-T-CT and CPI-enhancing immunotherapies.

CPI are drugs that destroy cancer cells by inhibiting the binding of checkpoint proteins. The immune response can be inhibited by common checkpoint proteins, such as PD-L1 and PD-1 (Collectively referred to as CP-1). In other words, when CP-1s bind, they aid T-cell receptors in binding to tumor cell antigens and inhibit T-cells from eradicating cancer cells. CP-1s are examples of normal checkpoint proteins. However, Immunological CPIs, such as anti- CP-1s, block one CP-1 from binding to the other CP-1, unleashing T-Cs to assault and kill cancer cells [3].

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In the CAR-T-CT method, part of the white blood cells, including T-Cs, are removed in order to grow CARs. To do this, the T-Cs are genetically modified to produce another receptor, called chimeric antigen receptor. That's because the transformed T-cells can better identify antigens of cancerous cells, thus activating their ability to destroy the cancerous cells [4]. What's more, the graduate development of CARs has contributed significantly to the efficiency of T-Cs. It has been difficult to guarantee the accuracy and success of natural T-Cs in the human body in detecting and killing cancer cells, since cancer cells use a number of confounding factors that interfere with T-C function, such as increasing the number of surface antigens or disguising them as different cell types, making them unrecognizable. However, these two immunotherapies still have their specific limitations, drawbacks and side effects. Again, different immunotherapies have different specific strategies to improve their effectiveness and reduce potential side effects.

The main disadvantage of CAR-T-CT is antigen escape [5]. Several CAR-T-CT approaches have been developed to address this issue, such as detecting multiple antigens from cancer cells to avoid antigen leakage [6]. There are also potentially fatal side effects in addition to the aforementioned restrictions. One of these is cytokine release syndrome

Large amounts of cytokines are circulated throughout the body when CARs proliferate, which can stimulate the immune system. Serious side effects may include the following [7].

For CPI: In the not-too-distant future, immunotherapy may be confronted with challenges such as primary and acquired drug resistance, as well as irAE. Cancers that exhibit primary resistance to immunotherapy do not respond favorably to treatment. The ineffectiveness of a previously effective drug in a particular patient is referred to as acquired resistance to immunotherapy. [8]. Immunological side effects of CPIs range from normal to severe. Severe side effects include autoimmune reactions. By targeting checkpoint proteins, these drugs neutralize one of the immune system's defense mechanisms. Sometimes the immune system responds by attacking other organs and tissues, which can cause serious or even fatal problems in the kidneys, liver, lungs, intestines and other organs [9].

2. Analysis of the problems

2.1. For CAR-T cell therapy

2.1.1. Antigen escape. The first issue with CAR-T-CTs is antigen escape, which occurs when tumors become resistant to treatment due to the single antigen-directed CAR construct. [5]. Antigen leakage is the most common difficulty in CAR-T CTs, which leads to inadequate treatment, including cancer recurrence. According to the results, 10-20 percent of relapses in young B-ALL after CD19 CAR are due to antigen leakage [10]. In the study of Kymriah, 15 of 16 patients having the symptoms again were CD19-negative. At least 15 of 61 (25%) complete responders relapsed as CD19 negative or partially negative, indicating the need for improved techniques and antigen escape [6].

CARs -associated toxicities

Patients who were given CD19-directed CARs, which were the primary CAR-T-CT treatment to be approved by the FDA, have had the most extensive characterization of the toxicities associated with the treatment [5]. However, the toxicities from the CARs can cause diseases, including Cytokine Release Syndrome (CRS).

Mechanism (Pathophysiology) and clinical data

The interaction of the CARs with their targets activates the T-Cs and triggers a systemic response that is related to inflammation symptoms, which is the reason of CRS. The stimulated T-Cs then secrete cytokines and chemokines. The general state of immune activation is furthered by cytokine production by neighboring immune cells, such as dendritic cells, monocytes and macrophages, all of which contribute to this condition. Acute lymphoblastic disease is the most severe and lethal form of the disease, but its response rate is extremely high and of great importance to patients [11]. Almost all patients treated with CAR-T-CT for acute lymphoblastic leukaemia exhibit at least mild toxicity, with

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23-46% also experiencing serious paraneoplastic cytokine release and extensive T-cell proliferation in vivo [5]. This is because CAR-T-CT is a relatively new therapy.

Symptoms

Patients will initially exhibit constitutional symptoms, such as a high temperature. In addition to those, you may also have malaise, rash, myalgias, and fatigue. Those who have a severe case of CRS, on the other hand, may exhibit symptoms such as hepatosplenomegaly, hepatic dysfunction, coagulopathy and so on [11]. Patients who have received CAR-T and experience symptoms that are consistent with CRS should be checked for other causes as well, since it given that fever, hypotension, and respiratory failure are symptoms of a severe immune response that can have many causes [11].

Diagnosis

In fact, according to the most recent definition, a sizable percentage of patients with severe CRS will satisfy the clinical requirements for sepsis, which are a suspected infection coupled with organ dysfunction. Due to their high lactate levels and need for vasopressors, many of these people will also meet the criteria for septic shock [12].

Treatment

The clinical management of CRS is still a challenging problem with plenty of unknown questions. But currently, it recommended that a grading scheme for the severity of CRS most widely used, which was developed by the National Cancer Institute (NCI). The monitoring and treatment of CRS use a grade- and risk-adapted method. Antihistamines, antipyretics, and fluids are used to treat the symptoms of low-grade CRS. While severe CRS is a circumstance that poses a threat to life and necessitates quick, urgent treatment, BiTE blinatumomab that has been used to prevent the development of severe CRS [12].

2.1.2. CARs trafficking and tumor infiltration. **Immunosuppressive microenvironment.**

It is a limitation that mainly focuses on solid tumor treatment. Numerous immune-suppressive cell types, including tumor-associated macrophages (TAMs), regulatory T-Cs (Tregs), and myeloid-derived suppressor cells (MDSCs), which have the ability to infiltrate solid tumors within the tumor micro-environment (TME). These results of infiltration and cancer cells induce the production of growth factors, chemokines, and cytokines, all of which contribute to the formation of tumors [5].

Immune-suppressive cell types

Tregs, also known as CD4-CD25-FOXP3 cells, are responsible for suppressing the immune system. They do this by producing cytokines that work against the immune system, competing with effector cells for immune-stimulating cytokines, and making direct contact with invading effector cells. Moreover, Tregs increase the quantity of the immunosuppressant transforming growth factor beta (TGFb) that is produced by the tumor. TGFb is a mediator of immunosuppression that interferes with adaptive immune priming as well as effector responses [13].

TAMs are the antigen-presenting cells that are most common in the TME. It is able to distinguish between macrophages with the M1 and the M2 phenotype. M1 is responsible for the secretion of cytokines that promote inflammation, such as IL-12. Whereas M2 is associated with the synthesis of the anti-inflammatory IL-10 and the arginase I enzyme. Arginase has the ability to downregulate the z chain of the T-Cs receptor, which prevents T-Cs from becoming activated [13].

MDSCs are created abnormally and drawn to the TME in order to assist in the production of an immunosuppressive (IMS) TME that promotes tumor escape. Thus, MDSCs are essential for the development and upkeep of the tumor-suppressing TME in solid tumors. In models in which MDSCs are absent or destroyed, the TME disintegrates, so allowing immune effector cells access and the ability to become activated [14].

CARs trafficking and tumor infiltration

CAR-T-CT is utilized to eradicate the tumor cells and completely eradicate the TME. However, the capability of CARs to penetrate and transport to solid tumors is limited by the IMS TME as well as physical obstacles such as the tumor stroma, tumor-associated fibroblasts (CAFs), and blood vessels,

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which indicates that the efficiency and effectiveness of the treatment cannot be guaranteed under these circumstances [5].

2.2. For Checkpoint inhibitors

2.2.1. Immune-related adverse events (irAEs). When receiving CPI medication, many patients develop an anticancer T cell response along with enhanced immunologic activation, which may lead to unfavorable immune-related complications (irAEs), whose mechanisms include exacerbation of preexisting organ-specific autoimmunity, cross-reactivity and environmental triggers between tumor and organ-specific antigens. But it's still difficult to predict who will contract the disease [15]. Numerous disorders, such as pneumonitis, dermatologic toxicity, and gastrointestinal toxicity, may manifest [11].

Dermatologic toxicity

For the most prevalent irAE linked with CTLA-4 or CP-1 inhibition treatment- the dermatological toxicity, it has been reported that between about 35 percent of people who received CP-1 blocking experienced most dermatologic damage [11].

Gastrointestinal Toxicity

Among the clinical manifestations of the irAE, diarrhea is a common adverse effect of CPI treatment, and its prevalence is increased in patients who are also receiving CTLA-4 antibody therapy. Diarrhea was reported in 27 to 54 percent of patients. While, another side effect is Colitis, which was recorded in 8 - 22 percent of patients treated with anti–CTLA-4 medication, according to a comprehensive review that analyzed the results of 10 clinical studies [11].

Pneumonitis

The most frequent pulmonary hazard of CPI treatment is pneumonitis. Despite the low overall prevalence of pneumonitis, any patient who experiences new respiratory symptoms should be evaluated for the condition because it has the potential to be fatal. Pneumonitis was the underlying cause of 35 percent of deaths that were connected to anti-CP-1 treatment, as determined by a meta-analysis of fatal CPI-AEs [11].

2.2.2. Primary and acquired resistance. **Primary & secondary resistance.**

Immune CPI resistance in cancer: primary and secondary mechanisms, Primary resistance refers to the inherent lack of responsiveness of certain tumor cells to immune CPI, while secondary resistance refers to the development of resistance in previously responsive tumor cells over time. They have broad activity against various malignancies and have transformed cancer therapy. However, due to primary resistance, their effectiveness is still limited in many cancers [16].

Primary resistance CPI is an abbreviation for cancer progression index, which describes the failure of cancer cells to respond favorably to therapy with CPI. It occurs when cancer cells have some host factors, such as intrinsic or acquired genetic mutations or an altered microenvironment that reduces the effectiveness of CPI. The efficacy and toxicities of CPI may be significantly impacted by host factors in some patient populations, such as those with conditions such as histories of organ or bone marrow transplants, deficient organ capability, exceedingly age, childbearing, viral hepatitis, bacterial/fungal infections. This includes pat.ients who have undergone organ or bone marrow transplantation in the past [16].

Acquired resistance

acquired resistance to CPI is a condition when a tumor that originally responded to therapy with CPI might subsequently develop a resistance to these medications, whose typical mechanisms include defects in antigen presentation, neoantigen depletion, IFN-g signaling, tumor-mediated immunosuppression/exclusion, and additional inhibitory checkpoints [17].

Because antigen recognition on MHCs of antigen-presenting cells is essential for the activation of T cell-mediated immunity, major histocompatibility complex (MHC) class I or B2M mutations or loss can result in the absence of TCR engagement and the loss of tumor antigen presentation [17]. This

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emphasizes the significance of intact MHC class I expression and antigen presentation in anti-tumor immune responses. Therapeutic strategies aimed at restoring or improving MHC class I expression and antigen presentation have the potential to improve anti-tumor immune responses and clinical outcomes in cancer patients.

IFN-g produced by effector T-Cs activates the JAK-STAT signaling pathway in tumor cells. This pathway regulates MHC class I and PD-L1 expression and has multiple mechanisms for inducing tumor cell death. The binding of IFN-g to the IFNGR1/IFNGR2 heterodimer, which activates the JAK1 and JAK2 kinases, is the first step in this pathway. Mutations or loss of JAK1/2or IFNGR1/IFNGR2, on the other hand, can result in IFN-g insensitivity in the TME and resistance to anti-PD-1 mediated T cell response [17].

When an anti-PD-1 blockade is effective against a diverse tumor, it can result in the loss of clones containing valuable neoantigens due to selective pressure. To regulate the body's response to ICIs, neoantigen-specific T-Cs play a crucial role. Therefore, the absence of tumor-specific neoantigens encoded by somatic mutations can result in immune evasion and clinical progression [17].

Upregulated WNT signaling can result in PTEN loss or beta-catenin stability. PTEN is a tumor suppressor that regulates phosphatidylinositol 3-kinase activity. T cell-mediated infiltration and immunity are hindered when PTEN is lost, due to increased expression of IMS cytokines and decreased synthesis of the T cell effector IFN-g which is caused by the fact that PTEN regulates phosphatidylinositol 3-kinase activity [17].

During the acquisition of resistance, there is an increase in the expression of several immunological T cell checkpoints, including TIM3, LAG3, and VISTA. This could point to a permanent reduction of effector function and eventual weariness [17].

3. Suggestions

3.1. For CAR-T cell therapy

3.1.1. Antigen escape. **Target more than one antigen.**

To address the issue of antigen loss after CAR-T-CT, various strategies have been proposed, such as utilizing dual CAR constructs or tandem CARs that incorporate two scFvs within a single CAR construct, which aim to target multiple antigens simultaneously in cancer cells. Surprisingly, exploratory clinical trials utilizing bidirectional targeting CAR-T have shown promising outcomes. Patients who have diffuse large B-cell lymphoma and adult ALL, for instance, showed promise, according to Dai [18]. In 2017, Fisher developed a CARs with a DAP10 and an anti-GD2-scFv. Typically, TCR and NKG2D must work together to provide a costimulatory signal; nevertheless, neuroblastoma may down-regulate or inhibit the activity of NKG2D, leading to immune escape. However, the CAR developed here can replace for NKG2D to transmit signals, avoiding the occurrence of immune escape [19].

Combination Immunotherapy

Besides, Combination immunotherapy with CARs is a promising approach to addressing the issue of immunological escape in cancer [20], which involves combining CAR-T-CT with other treatments such as radiation, vaccinations, or immune agonists to promote epitope spreading and prevent tumor cells from evading immune detection [6]. To explain this, we should first know that by reinvigorating a worn-out immune response, checkpoint blocking (CPB) therapy can produce long-lasting therapeutic effects; CARs have the potential to deliver both the necessary immunological infiltration of the tumor as well as a highly targeted immune response against the tumor. In this way, the addition of CPB agents into the CAR-T-CT, which work to combat the immune-inhibitory milieu that undermines optimal CARs performance, can further amplify the performance [20].

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3.1.2. CARs -associated toxicities. **Altering CAR structure.**

To reduce toxicity, one potential strategy is to decrease the affinity of the antigen-binding domain on CARs. This may result in a higher threshold for activation, meaning that higher concentrations of antigen on tumor cells would be required to trigger a significant level of CAR activation. As a result, decreasing the antigen affinity may help to prevent healthy tissue from being targeted by a minimal amount of antigen [5].

One potential solution to the toxicity caused by CAR-T-CT is to use activated CARs to control cytokine release by altering the hinge and transmembrane areas. This approach has shown promise in reducing cytokine release and CAR proliferation in a CD19-targeted CAR. However, it is not an ideal solution and may only be applicable in phase 1 clinical trials. Nevertheless, this method has resulted in a 54.5 percent remission rate in B cell lymphoma patients treated with modified hinge and transmembrane CARs [5].

The costimulatory domain of CARs is a more versatile approach compared to traditional targeting methods, as it can be tailored to specific tumor types, sizes, and antigen densities. The choice of costimulatory domain can also account for potential toxicity issues and the antigen-antigen binding domain pair. For instance, the inclusion of 4-1BB domains in CAR design has been linked to lower toxicity risk, longer-lasting T cell activity, and more controlled T cell expansion. On the other hand, CARs with CD28 costimulatory domains tend to have faster onset and decline of T cell activity [5].

3.1.3. CARs trafficking and tumor infiltration. **Equipping T cells.**

One approach to enhancing antitumor IMS TME involves equipping T-Cs with synthetic TGF-targeting receptors that can block or modify their natural response to soluble substances, which contain various types, including the TGF dominant-negative receptor (DNR) and so on. These receptors can encode various TGF-responses, enabling them to compete with endogenous TGF receptors for ligand binding and block endogenous TGF signaling. The TGF CAR can also activate T-Cs by transmitting signals that stimulate their activity, making TGF a potent T cell stimulant [21].

Expressing chemokine receptors on CARs

A promising strategy to enhance CAR trafficking is the incorporation of chemokine receptors onto CARs. For this approach to be effective, the receptors must be compatible with tumor-derived chemokines. Recent studies have shown that CARs overexpressing CXCR1, CXCR2, or integrin v6, and CARs transformed to express CXCR2, have improved trafficking and greatly enhanced antitumor activity. CARs ' ability to migrate to the tumor site is crucial for achieving effector activity. However, inadequate chemokine receptor expression and physical barriers can hinder CARs ' homing to tumor locations [22]. While trying to infiltrate tumors, CARs must first destroy heparin sulphate proteoglycan (HSPG), a important component of the extracellular matrix that comprises the stroma. The reason for the improvement of tumor infiltration and anti-cancer activity is that CARs can express the enzyme heparanase, which degrades HSPG [5].

3.2. For Checkpoint inhibitors

3.2.1. Immune-related adverse events (irAEs). Researchers are working on preclinical models to better understand irAE processes, which could help with customized diagnosis and treatment. A genetic mouse model has been developed to simulate ICI myocarditis, enabling researchers to explore therapeutic strategies. This model provides an opportunity to study the effects of CTLA-4 and PD-1 deletion, the correlation between these genes, the etiology of myocarditis, and the efficacy of abatacept in delaying its advancement. Due to the numerous challenges associated with managing irAEs, the focus has shifted to prevention at this point. While, Biomarkers (Bio-M) that have the ability to predict irAEs are receiving an increased amount of investigation [23]. There are various types of Bio-M that have the potential to improve the precision of diagnosing, predicting, and preventing irAEs, which include blood-based predictive Bio-M, tissue Bio-M, DNA and gene expression Bio-M, and microbiome Bio-M [24].

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3.2.2. Primary and acquired resistance. **Primary resistance.**

To overcome primary resistance to CPIs, combining immunological CPIs with other cancer therapies has shown promise. This includes combinations with chemotherapy, radiation therapy, targeted therapies, and other immunotherapies, including cytokines and vaccines. Some combination therapies have been found to enhance the immune system's response to cancer cells and improve treatment outcomes, such as the use of radiation, which has been shown to result in an abscopal effect. Clinical trials have demonstrated that combining radiation with granulocyte-macrophage stimulating factor (GM-CSF) can result in a 27 percent ablative effect in solid tumors that have failed multiple therapies. Nivolumab and low dose ipilimumab have demonstrated high TMB and excellent PFS and OS in the treatment of non-small cell lung cancer, melanoma and renal cell carcinoma. Studies have demonstrated that adding pembrolizumab to chemotherapy can increase survival rates for patients with metastatic first-line non-small cell lung cancer, which has led researchers to explore the effectiveness of combining chemotherapy with targeted drugs, adoptive cell therapy, and cancer vaccines in clinical trials. These trials have shown promising results, leading to increased interest in combination therapies for cancer treatment [16].

Acquired resistance

MDSCs inhibit T-Cs and create an IMS environment in the TME that reduces the immune response against tumors by establishing a network of interactions with immune and non-immune cells, resulting in multiple positive feedback loops that have negative effects on the TME, which leads to the mobilization of IMS cells, activation of angiogenesis, and hypoxia, all of which enhance acquired resistance to immune CPI. That’s the reason why targeting MDSCs may be a promising therapeutic method to overcome this limitation [24].

The inhibitory effect of MDSCs is mediated by a number of different methods. Through direct cell-cell interactions or indirect environmental readjustment effects, the suppression emanating from MDSCs impairs proper T-cell activity. The functions of MDSCs are listed below, which are classified into three categories that influence their resistance to immune CPI. (1) Directly attack T-Cs, causing T cell dysfunction. (2) Predisposed to encourage tumor growth. (3) TME development by means of MDSC-mediated IMS cellular and molecular networks [24].

In both preclinical cancer models and actual patients, the combination of immune CPI and MDSC treatments has produced favorable outcomes. Targeting MDSCs after immune CPI infusion can disrupt their suppressive functions and enhance the immune response against cancer [25].

4. Conclusion

The analysis in this article revealed that there are now a number of options available to improve certain aspects of the immunotherapies that have been identified. By targeting more than one antigen and integrating CAR-T-CT with other immunotherapies, it is feasible to improve the limitations of antigen escape. Changing the shape of T-Cs to lessen the targeting of healthy tissue and cytokine production is one method of reducing the toxicities associated with CARs. It is possible to solve the problem of CARs transportation and tumor invasion by expressing chemokine receptors on CARs and fitting T-Cs with the appropriate receptors. While, in the case of immune CPIche, Bio-M contribute to the avoidance of irAEs, which are adverse effects caused by the therapy; combinations of different cancer treatments can overcome primary resistance, and targeting MDSCs can put an end to acquired resistance. The overcoming of immunotherapy limitations improves the treatment's effectiveness for a wider range of malignancies and other illnesses. It can make the process of targeting cancer cells with greater specificity and precision, which ultimately leads to better outcomes for patients. In addition, enhancing the treatment has the potential to lessen the severity of these adverse effects and make it a more attractive choice for patients. More importantly, overcoming immunotherapy's limits can also progress medical research, leading to new discoveries and treatments for diseases other than cancer. This will contribute to the future advancement of medical science and the treatment of additional diseases. Improvements to the restriction have yet to be developed. For example, for immune-related adverse effects, it is just the technique to avoid illness progression or to limit it as much as feasible.

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However, it cannot completely avoid the possibility of immune-related side effects from the use of CPI.

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