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Immunotherapy For Cancerous Tumors By CAR-T Cell

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Abstract

T cells engineered with chimeric antigen receptors (CARs) are emerging as powerful immunotherapies for cancer. Remarkable efficacy has been demonstrated in treating B-cell malignancies using CAR-T cells, which led to the gene therapy being approved by the US Food and Drug Administration. Currently, several clinical trials on hematological malignancies and solid tumors are being conducted all over the world. The production of CAR-T cells with appropriate traits is essential for the success of CAR-T in vivo. Chimeric antigen receptor (CAR) T-cell therapy engineers T cells to express a synthetic receptor that redirects effector function to the tumor, to improve efficacy and reduce toxicity associated with conventional therapies, such as radiotherapy and chemotherapy. This approach has proven to be effective in treating hematological malignancies. However, the same effects were not observed in tumors. CAR T cell therapy has been successful in treating hematopoietic malignancies. However, its efficacy against solid tumors remains to be determined. In this paper, rapid advances in Immunotherapy for cancerous tumors by Car-T cell are discussed. There are several other limitations of CAR-T cell therapy which are; development of tumor resistance to single antigen targeting CAR constructs and CAR-T cell-associated toxicities.

Keywords: Immunotherapy, tumors, therapy, T cell, CARs.

ملخص البحث

تظهر الخلايا التائية المهندسة باستخدام مستقبلات المستضدات الخيمرية (CARs) كعلاجات مناعية قوية للسرطان. تم إثبات فعالية ملحوظة في علاج الأورام الخبيثة للخلايا البائية باستخدام خلايا CAR-T ، مما أدى إلى اعتماد العلاج الجيني من قبل إدارة الغذاء والدواء الأمريكية. حاليًا ، يتم إجراء العديد من التجارب السريرية حول الأورام الخبيثة الدموية والأورام الصلبة في جميع أنحاء العالم. يعد إنتاج خلايا CAR-T ذات السمات المناسبة أمرًا ضروريًا لنجاح CAR-T في الجسم الحي. مستقبلات المستضد الكيميري (CAR) يقوم العلاج بالخلايا التائية بمهندسة الخلايا التائية للتعبير عن مستقبل اصطناعي يعيد توجيه وظيفة المستجيب إلى الورم ، لتحسين الفعالية وتقليل السمية المرتبطة بالعلاجات التقليدية ، مثل العلاج الإشعاعي والعلاج الكيميائي. أثبت هذا النهج فعاليته في علاج أورام الدم الخبيثة. ومع ذلك ، لم تُلاحظ نفس التأثيرات في الأورام. كان العلاج بالخلايا التائية ذات مستقبلات المستضدات الوهمية ناجحة في علاج الأورام الخبيثة المكونة للدم. ومع ذلك ، لا يزال يتعين تحديد فعاليته ضد الأورام الصلبة. في هذا البحث ، تمت مناقشة التطورات السريعة في العلاج المناعي للأورام السرطانية بواسطة الخلايا التائية Car-T. هناك العديد من القيود الأخرى على العلاج بالخلايا التائية ذات مستقبلات المستضدات الوهمية وهي ؛ تطوير مقاومة الورم لمستضد واحد يستهدف بنيات CAR والسميات المرتبطة بخلايا CAR-T.

الكلمات المفتاحية: العلاج المناعي ، الأورام ، العلاج ، الخلايا التائية ، CARs.

1. Introduction

Over the past decades, “immunotherapy” has dominated the cancer research community, with American scientists James Allison and Japanese Tasuko Honjo sharing the Nobel Prize in Physiology or Medicine in 2018; for their contribution to the use of immunotherapy for the treatment of cancer. Immunotherapy, also called biological therapy, is a treatment method that stimulates the immune system to perform its functions more effectively to eliminate cancer. "Immunotherapy" has already succeeded in helping between 10% and 30% of cancer patients to survive in the long term, but it is still ineffective for the remaining percentage of patients, prompting researchers to continue their efforts to promote the use of "point-point inhibitors" Immunological Inspection", which awakens T cells to attack the malignancy (Hawkins, D'Souza, & Klampatsa, 2021).

Chimeric antigen receptors (CARs) are unique receptors designed to target specific tumor antigens to functionally reprogram T lymphocytes. Because T lymphocytes are genetically engineered to express these synthetic receptors to target cancer cells, the type of treatment can be called immunotherapy, gene therapy, or cancer therapy (Restifo, Dudley, & Rosenberg, 2012). The human defense system can efficiently identify both self and non-self-molecules, including bacteria, viruses, and non-tumor cells. Identification of cancer cells depends on antigens and acquired immunity by expression of foreign antigens (Galluzzi & Martin, 2017). Nevertheless, cancer cells have the potential to sabotage the immune system to their advantage, resulting in insufficient anti-tumor immunity, and tumor survival and progression. Some immunotherapies boost the immune system, while others target cancer cells directly (McGuirk, 2017).

CAR T cell therapy has been successful in treating hematopoietic malignancies. However, its efficacy against solid tumors remains to be determined. In this paper, rapid advances in Immunotherapy for cancerous tumors by Car-T cell are discussed (Mohanty, 2019).

2. Literature review

2.1 Immunotherapy

The discovery of cancer immunotherapy began in the late nineteenth century, specifically in 1981, when the American surgeon William Cooley discovered by chance that injecting cancerous tumors with certain strains of bacteria stimulates the immune system to destroy those tumors.

In the wake of Cooley's discoveries, the efforts of scientists in this field continued, until the discoveries of American scientists James Allison and Japanese Tsuko Honjo - recipients of the 2018 Nobel Prize in Medicine - in the late twentieth century, who were working independently on the use of some proteins on cells Immunosuppressants, known as "checkpoints," control the immune system and stimulate it to attack cancer cells. These discoveries led researchers to turn to immunotherapy, which is now one of the most exciting areas of cancer research. T cells are a type of immune cell that attack foreign cells and are a powerful weapon against cancer cells, but the adaptive immune system can mistakenly attack the body itself, causing many diseases called autoimmune diseases (Hawkins, D'Souza, & Klampatsa, 2021).

Immunotherapy is a type of cancer treatment that uses the immune system to fight cancer. The immune system is the body's defense against infection and disease, where it works to attack germs such as bacteria and viruses. The immune system also helps get rid of harmful or damaged cells in the body. Because the immune system is part of the body, immunotherapy is sometimes called biologic therapy or biological therapy. The basic idea of immunotherapy is simple: to help the body defend itself against harmful foreign bodies. But cancer cells can be deceptive. You often find ways to change so that your immune system doesn't detect them.

Several methods are also used to stop the body's defense when it is trying to attack it. In general, immunotherapies work by blocking some of these different ways that cancer cells evade, by (Fridman, 2012):

- Helping the immune system detect cancer cells so that it can attack them.
- Increasing the ability of the immune system to respond against cancer.

There are different types of immunotherapy, and each works in different ways to improve the immune response. T-cell immunity is called adaptive or acquired immunity because T cells are programmed to attack only after they have acquired necessary, specific information about the harmful cell. In other words, for T cells to receive the signal to "start" to attack the harmful cells, they first need to obtain information about the cell they are going to encounter. T cells target cells that identify them as body cells but show something to harm them, such as being infected with a virus. T cells do this by detecting a protein called an antigen on the cell surface and marking it as foreign or harmful. This antigen is detected by the T-cell receptor (Hawkins, D'Souza, & Klampatsa, 2021).

Most T-cell-based immunotherapies rely on the T-cell's ability to see antigen on the surface of the cancer cell. Once the T cells learn a particular type of cancer antigen, the body produces many more T cells that can recognize the antigen so that they can search for and attack other cancer cells that carry that particular antigen. Some T cells can also remember the antigen and respond again if they see it again. This 'memory' is an important way in which T-cell-based immunotherapies may prevent the recurrence (relapse) of T-cell-bearing cancer cells. Types of T-cell-based immunotherapies include immune checkpoint inhibitors, vaccinations, cytokines and T-cell transfer (Zhu, 2016).

CAR therapy is a type of cell therapy for some types of cancer. It is a form of immunotherapy and is sometimes referred to as “engineered cell therapy” or “immune cell therapy.” T-cell CAR therapy alters certain T cells in the body (components of the immune system) to improve the immune system's ability to fight cancer. Immunotherapy is one of the modern targeted treatment options in cancer treatment, and today we have a long list of cancers for which immunotherapy can be used, especially in those who have had limited treatment options or whose cancer cells have become resistant to the options currently available. Clinical studies have proven the success of this type of treatment in increasing patients' survival time." (Miliotou & Papadopoulou, 2018)

Cancer immunotherapy (sometimes called immuno-oncology) is the use of the immune system to treat cancer. This methodology takes advantage of the fact that cancer cells usually have molecules on their surface that the immune system can detect, which are known as tumor antigens; they are usually proteins or other minute particles (e.g. carbohydrates). Immunotherapy can be classified as active, passive, or hybrid (active and passive) therapy. Active immunotherapy directs the immune system to attack tumor cells by targeting tumor antigens. Passive immunotherapy improves existing antitumor responses and includes the use of monoclonal antibodies, lymphocytes and cytokines (Syn, 2017).

2.2 CAR T-Cells

T-cell therapy for adoption is a form of passive immunization by T-cell transfer (transferring cells for adoption). This type of cell is found in blood and tissues and is usually active when it finds external pathogens. They are particularly active when T-cell surface receptors converge with cells that display portions of exogenous proteins on their surface antigens. They are found in normal tissues and in neoplastic tissues, where they are known as infiltrative lymphocytes. These cells are active in the presence of antigen-presenting cells such as dendritic cells found in tumor antigens. Although these cells can attack the tumor, the environment surrounding the tumor is highly immunosuppressive, preventing tumor death by the immune system (Restifo, Dudley, & Rosenberg, 2012).

There are two main types of immunotherapies that have proven successful in treating carcinoid tumors. The first is checkpoint inhibitors, and the second is T-cell chimeric receptor (CAR), a type of treatment also known as T-cell immunotherapy that relies on gene-editing T-cells; the goal is to activate the immune system to identify and destroy specific cancers (Mohanty, 2019).

Cancer immunotherapy exploits the fact that cancer cells often have tumor antigens, which are molecules on their surface that can be detected by the immune system's antibody proteins, to which they bind. Tumor antigens are often proteins or other large molecules (such as carbohydrates). Natural antibodies bind to exogenous pathogens, but modified immunotherapy antibodies bind to tumor antigens that identify and stabilize or kill cancer cells. Immunotherapy can be classified as active or passive. Active immunotherapy specifically targets cancer cells via the immune system. Examples include cancer vaccines, CAR-T cells, and targeted antibody therapies. In contrast, passive immunotherapy does not directly target cancer cells, but rather enhances the immune system's ability to attack cancer cells. Examples include checkpoint inhibitors and cytokines (Quintarelli, 2018).

Conventional cancer therapies such as radiotherapy and chemotherapy are known to be effective in killing cancer cells, but they cannot effectively distinguish malignant tissue from healthy, rapidly spreading cells, resulting in a variety of severe adverse effects. Available treatments, the idea of cancer immunotherapy emerged. One approach to immunotherapy is cell therapy that takes advantage of beneficial immune functions including antigen specificity, the ability to expand activation, translocation to a region of interest, and memory formation toward the target antigen (Hawkins, D'Souza, & Klampatsa, 2021).

CARs are designed to recognize specific cancer-associated antigens and consist of an antibody-derived single-chain variable region (scFv) for antigen recognition and binding, a membrane-spanning domain and an intracellular signaling domain. Endogenous TCRs contain an intracellular CD3ζ domain that initiates downstream killing pathways upon receptor activation, in a process known as signal (Nurgali, Jagoe, Abalo, & Editorial., 2018). In normal physiology, TCR binding is not sufficient to activate T-cell signaling and to activate cost molecules on the T cell. Also required, termed signaling. This costimulation enables cross-linking of the TCR receptor and the costimulatory receptor, leading to T-cell activation (Berkey, 2010).

Three generations of CAR T cells have been extensively investigated, with the first generation designed to mimic TCR in function, using the intracellular CD3ζ domain. A preliminary study using first-generation CAR T cells found that CARs were able to induce antigen-specific cytotoxicity in vitro, but cytokine secretion was weak and transient in the absence of costly ligands on target cells (ong, 1999). although some early promise was shown. Investigations and follow-up studies found that first-generation CAR T cells produced little or no clinical benefit, targeted different antigens in a variety of cancers, and also had limited persistence after patient injection (Hawkins, D'Souza, & Klampatsa, 2021).

Subsequently, second-generation CAR T cells were developed, integrating the cost domain into the intracellular region of CAR to combine signals 1 and 2, with the goal of promoting T-cell activation and persistence. These compounds have been shown to act as effective mediators of antitumor functions besides showing remarkable efficacy with enhanced expansion, and in vivo cytokine secretion (Davila, 2013). Further investigations Clinical trials have shown that second generations CAR T-cells provide significant clinical benefit; as they suffer High percentages of patients have complete responses (Schuster, 2019).

It has been demonstrated that different cost domains have different effects on T cell function. For example, despite having similar clinical efficacy, a CAR with a 4-1BB cost domain produced more long-lasting T cells than using a CD28 cost domain. In contrast, another study found that the CD28 cost domain significantly increased CAR T-cell basal T-cell proliferation compared to the use of 4-1BB. Therefore, third generation CARs were developed to combine the signaling ability and T-cell functions of the two cost domains within a single CAR (Quintarelli, 2018).

Investigations into the third generation of CARs have provided evidence that the presence of two CARs can enhance anti-tumor CAR T-cell function and increase T-cell stability in vivo; enhanced efficacy, proliferation, and cytokine production in the clinic. Nevertheless, there is contradictory evidence about whether second- or third-generation T cells produce more significant responses in patients (George, 2020).

Second and third generation CAR T-cell therapies have shown promising clinical benefits in a range of hematological malignancies. Drug Administration and European Medicines Agency, for the treatment of B-cell lymphoma and acute lymphoblastic leukemia. To date, such success has not been observed in solid tumors, despite attempts to target many different antigens across a range of tumor types for CAR. T cells to target single malignant cells. In solid tumors, T cells have to overcome multiple barriers just to localize at the tumor site. T-cell penetration into the solid tumor mass proves an additional challenging hurdle, but even if this is overcome, T cells are countered by an immunosuppressive tumor microenvironment (TME) that inhibits the anti-tumor effect that CAR-induced T cells can elicit (Hawkins, D'Souza, & Klampatsa, 2021).

Within the solid tumor mass, there are a variety of cell types along with malignant cells that interact with each other using signals such as cytokines, chemokines, and growth factors. Collectively, they constitute TME which is immunosuppressive and supports tumor survival, growth and spread.

The cells in a solid tumor include immune cells, fibroblasts, and endothelial cells, each with different functions. Some immune cells within the TME are potent cytotoxic cells and high proportions of them have been associated with a good prognosis for patients. These include CD8+ cytotoxic T cells, helper 1 (Th1) CD4+ cells, B cells, natural killer (NK) cells, and 30 that secrete cytokines to enhance immune cell survival and function while aiding the immune system against cancer response. Examples of such cytokines are interleukin-2 (IL-2) and interferon- γ (IFN-γ) (Fridman, 2012).

To overcome the drawback of the TME on CAR T-cell therapy in solid tumors, a fourth generation of CAR T-cell has been developed. This generation, also known as armored CAR T-cells, are engineered to express proteins alongside a second- or third-generation CAR, shown in Figure 2, to reduce immunosuppression and further mediate anti-tumor efficacy (Hawkins, D'Souza, & Klampatsa, 2021).

A variety of therapies that use immunotherapy, to stimulate or help the immune system to fight cancer, have been in use since 1997. These include antibodies, and adoptive cell transfer. There are classes of drugs used in cancer chemotherapy, including the group of anthracyclines extracted from the sequence bacteria, which when present on the surface of the cell, enables the immune system to distinguish between cancer cells and healthy cells. This leads to the mobilization of the immune system, so its cells devour the cancerous cells and push the cancer to death, and the process is called the events of immune death. However, there are no studies confirming the efficacy of the substance, in addition, recently, anthracyclines have been subject to scrutiny due to their cardiotoxic effects (van Dalen, Raphaël, Caron, & Kremer, 2014).

Experimental cancer treatments are studied in clinical trials to compare a proposed treatment to the best existing treatment. Treatments that work for one type of cancer can be tested with others. Diagnostic tests are under development to target the right treatment to the right patients, based on their individual biology (Sleigh & Barton, 2010).

2.3 CAR T-Cells: T-Cell Cancer Immunotherapy

CAR is an emerging immunotherapy for many malignancies. This treatment approach is an experimental form of gene therapy that redirects T lymphocytes to eliminate cancer cells. The first step in this treatment is the isolation of the patient's peripheral blood (Miliotou & Papadopoulou, 2018). Apheresis is widely used to isolate blood from patients and separate it into its components, which are then genetically altered before being reinjected into the patient's body. Blood banks currently use apheresis to collect platelets and other blood components to treat many diseases, including blood diseases and renal disorders. Therefore, it is considered a safe practice for healthy individuals and patients (Vormittag, 2018).

The hypothesis of CAR-T immunotherapy is to modify T cells to recognize cancer cells in order to target and destroy them more effectively. Scientists collect T cells from humans, genetically modify them to add a chimeric antigen receptor (CAR) that specifically recognizes cancer cells, and then spew the resulting T cells into patients to attack their tumors (Hawkins, D'Souza, & Klampatsa, 2021).

The immune system stores in its memory all the antigens normally present in the human body. When a new antigen enters the body, the immune system recognizes it, attacks it, and "remembers" it. If this antigen enters the body again, it will be countered by trained and specific cells of the immune system. CAR T cells - A genetically modified type of white blood cell that can recognize cancer antigens and destroy tumor cells in a particular patient. This is possible thanks to the binding of the T cell to the chimeric antigen receptor, or CAR, that has been created in the laboratory (Pettitt, Arshad, Smith, Stanic, Holländer, & Brindley, 2017).

CAR-T (chimeric antigen receptor T) cell therapies use genetically modified individual T cells to combat malignancies1 and have shown success in patients with chemotherapy-resistant B-cell malignancies offered some hope for extending the overall life of patients with malignant B-cell tumors; However, they are unfortunately not curative interventions (Sinha, 2011). Alternative treatment modalities such as allogeneic hematopoietic stem cell transplantation (alloHSCT), although curative, are fraught with fatal complications, most notably graft-versus-host disease (GVHD), It is the leading cause of non-reversible mortality in patients with B-cell malignancies and accounts for a mortality rate of 15% to 40% (Kochenderfer & Rosenberg, 2013). CAR-T-cell therapies represent a safer treatment option that can be extended beyond this patient group. Although traditional approaches to targeting cancer cells (e.g., with chemotherapy or radiotherapy) appear to successfully target cancer cells, they have significant limitations including their inability to selectively target malignant cells. Advances in drug design have attempted to mitigate this through the use of monoclonal antibodies, for example, epidermis or blood diseases. Thus, there are many side effects associated with this therapeutic class (Kochenderfer & Rosenberg, 2013).

Their inability to selectively target malignant cells necessitates increased dose, long treatment periods, and reduced quality of life. This is supported by the paucity of data on successful outcomes (You, 2016). Immunotherapy has received significant attention, and researchers are gaining momentum by exploiting reprogrammable cells to target a growing range of disease targets. Unparalleled ability to recognize antigens displayed on the surface of pathogens. The adaptive immune system can generate lymphocytes with the ability to recognize disease-causing antigens expressed in bacteria, viruses, parasites and malignant cells that has not been previously encountered. The pool is thus a logical reserve to exploit in the development of targeted therapies such as CAR-T cells; the underlying principle of redirecting cytotoxic T lymphocytes to target cancer cells (Maude, 2014).

First-generation CAR-T cells comprise a single signaling domain, typically derived from the CD3z component of the T-cell receptor (TCR)/CD3 complex, CD28 and/or 4-1BB, which mediate T-cell activation via enhanced mechanisms of action and co-stimulatory pathways, leading to upregulation of anti-apoptotic protein genes and increased cytokine secretion (You, 2016).

Recently, there has been an increase in the number of clinical trials focused on regenerative medicine, particularly those examining stem cell therapies for indications including heart disease, hematological malignancies, bone or cartilage disease, traditional randomized controlled structures and systematic approaches. Powered by the growing presence of regenerative and precision medicine and technological advances in computational analysis and therapeutic strategies, researchers are moving away from traditional rules to explore more flexible clinical trial designs. Encouragingly, CAR-T cell therapies are advancing rapidly during phase I/II clinical trials (Quintarelli & Locatelli, 2016), with the support of appropriate regulatory frameworks in both the European Union (EU), the United States and broader global markets. To date, the majority of CAR-T cell clinical trials focus on hematological malignancies, although they are increasingly investigating solid tumor targets (Quintarelli & Locatelli, 2016).

In particular, they have demonstrated demonstrable clinical responses in B-cell malignancies and may induce a paradigm shift in the way relapsed and relapsed cancers are managed. Clinical successes to date have not been without difficulties and have been compensated to some extent by a complex adverse event profile personly. Notable adverse events include CRS (cytokine release syndrome) (Wang, 2015), which is a rapid immune reaction driven by massive release of cytokines (including interferon-g [IFN-g] and interleukin-6 [IL-6]) from targeting cancer cells, resulting in a potentially fatal outcome. Other side effects occur from 'off-target' activity, whereby the TCR recognizes non-cancerous antigens presented on normal physiological tissues and causes collateral damage. 'Ontarget' tumor toxicity can also occur. As a result of tumor-associated antigen expression in normal tissues, CAR-T cells may initiate autoimmune attacks on healthy tissue when their target is expressed in vital organs and a critical number of autoreactive T cells are reached (Kandalaft, 2012).

MART-1 (melanoma antigen recognized by T cells), for example, is a transmembrane protein found in normal melanocytes but also widely expressed in malignant melanoma; It has been reported to be toxic against melanocyte-rich tissues, including the skin, inner ear, and retina (Pettitt, Arshad, Smith, Stanic, Holländer, & Brindley, 2017).

2.3.1 Advanced features of CAR T cell therapy

Although tumor cells have multiple lineages and heterogeneity, they possess common target antigens, such as CD19, CD20, CD22 and many other antigens that allow CAR T cells to recognize tumor cells regardless of the cell lineage. Hence, recent advances in this technique include more precise target antigens expressed by cancer cells (Paietta, 2018), new studies of CAR T-cell therapy that characterize diverse CAR T cells that can promote tumor cell death. Some models and others are already being implemented in the case of clinical examination, including the NK CAR and the regularly pooled symmetrically short repeat (CRISPR) CAR Bi-private cars. A bispecific receptor is the receptor that has two distinct antigen recognition domains bound and localized with two distinct intracellular signaling domains that are expressed as different CARs on the surface of a single cell. At present, bispecific CAR CD19/CD20 has been presented as a new synthetic molecule that can recognize and bind to more than one target tumor antigen on the surface of cancer cells. Therefore, it can create a synergistic cascade of effector molecules when they encounter two tumor antigens (Zah, 2017). Furthermore, bispecific CAR maintains the cytolytic ability of T cells, for example, if one of the target molecules is inaccessible to CAR T cells due to a cellular hindrance such as mutation of a target antigen or loss of the target antigen normally present in malignant cells, a bispecific CAR can counterbalance tumor evasion (Majzner & Mackall, 2018). Therapies investigated include CD3 T-cells and tumor antigens, for instance CD19, on malignant cells. The therapeutic potential of blinatumomab, a bispecific T-cell fusion approved anti-relapse/refractory B ALL is demonstrated. Positive results have been reported in patients (Zhu, 2016).

The most notable advantage of CAR-T cell therapy over other cancer therapies is the abrupt intervention in time and the single infusion of T cells. In addition, 2-3 weeks of appropriate care and observation are sufficient for the patient. CAR-T cell therapy is seen as a 'medicine for the time being' and its efficacy may last for decades as the cells can survive in the host body over the long term, with an established ability to find and destroy cancer cells during relapse (Perales, 2018).

Numerous clinical trials are currently examining the use of CAR-T-cell therapy against solid tumors and other diseases. Reports indicate that T cells specifically engineered for CAR mRNA from mesothelin can induce antitumor activity in solid malignancies. Furthermore, CAR technology has been used in organ transplantation with two novel HLA A2 compounds, one representing the CD28CD3d signaling domain (CAR) and one deficient in the intracellular signaling domain (dCAR). Adoptive transfer of specific regulatory T cells (Tregs) provides better protection against graft rejection compared to transfer of polyclonal Tregs (Shen, 2018). CAR comprising the ICOS signaling domain communicates the potent antitumor effect on the epidermal growth factor receptor III (EGFRvIII) variant expressing glioma. Preclinical evaluation of CAR T-cell therapy targeting tumor antigen 5T4 in ovarian cancer was associated with a successful outcome (Owens, 2018).

According to the 2018 records on the total clinical trials conducted in the field of immuno-oncology, 220 trials involving CAR T therapy have been conducted to identify specific targets. It has successfully developed CAR T-cell drugs that are available on the market, including CTL019 (Kymriah), KTE C19 (Yescarta), and JCAR015 (Hey & Kesselheim, 2016). These were developed by companies known to have precedents for developing CAR T-cell therapy, such as Novartis in collaboration with the University of Pennsylvania, Kite Pharma with the National Cancer Institute, and Juno Therapeutics with Sloan Kettering, respectively, and are used to treat ALL, NHL, and ALL. These CAR T therapies represent a defining moment in 2017 in the field of oncology. The first two CD19-specific and FDA-approved therapies included Kymriah (tisagenlecleucel T) and Yescarta (axicabtageneciloleucel) by Novartis and Kite Pharma/Gilead Sciences, respectively (Rotolo, 2016).

2.3.2 Limitations of CAR-T cell therapy

Although CAR therapy has emerged as a promising anticancer approach, it is not without challenges that require improvement. For example, the enhanced persistence and enhanced cytotoxic profile of CAR T-cell therapy are active areas of research that require long-term follow-up in clinical trials (Kebriaei, 2017). In addition, a number of serious side effects are known to be frequently associated with CAR T-cell therapy, including these include neurotoxicity, cytokine release syndrome (CRS), B-cell hyperplasia, tumor lysis syndrome, and anaphylaxis. CAR T-cell proliferation produces cytokines in the body that kill cancer cells. Symptoms of toxicity associated with CRS range from mild symptoms of fatigue, nausea, headache, fever, and chills to serious symptoms including hypotension, tachycardia, and leaking capillaries. Another side effect is the presence of CAR T cells that target antigens on the surface of B cells or T cells that target not only cancer cells but normal cells as well, resulting in B-cell aplasia. Therefore, a comprehensive investigation to measure the characteristics of B-cell aplasia is necessary. Similarly, tumor lysis syndrome can lead to toxicity through the breakdown of dead cells generally at the start of cancer treatment. It can also cause organ damage and may be life-threatening (Neelapu, 2017).

One of the most challenging limitations of CAR-T cell therapy is the development of tumor resistance to a single antigen targeting CAR constructs. Although a single antigen targeting CAR-T cells can present high response rates, the malignant cells of a significant portion of patients treated with these CAR-T cells display either partial or complete loss of target antigen expression. This phenomenon is known as antigen escape (Majzner & Mackall, 2018). For example, although 70-90% of relapsed and/or refractory patients show durable responses to CD19-targeted CAR-T cell therapy, recent follow-up data suggest the development of a common disease resistance mechanism, including antigen reduction/loss. CD19 is present in 30-70% of patients with recurrent disease after treatment.

Similarly, downregulation or loss of BCMA expression has been observed in multiple myeloma patients treated with BCM-targeted CAR-T cells. Similar antigen escape resistance patterns have been observed in solid tumors. For instance, a case report of CAR-T cell therapy targeting IL13Ra2 in glioblastoma indicated that tumor recurrence resulted in decreased IL13Ra2 expression.

One challenge in targeting solid tumor antigens is that solid tumor antigens are often also expressed in normal tissues at different levels. Therefore, antigen selection is critical in CAR design not only to ensure therapeutic efficacy but also to reduce 'on-target off-tumour' toxicity. A potential approach to overcome antigen targeting on solid tumors also present in normal tissues is to target tumor-restricting post-translational modifications such as solid tumor overexpressing O-glycans such as Tn (GalNAca1-O-Ser/Thr) and sialyl-Tn (STn) (NeuAca2–6-GalNAca1-O-Ser/Thr). Four major CAR-T cell targets were investigated including TAG7228, B7-H3, MUC1 and MUC16. Although first-generation CAR-T cells targeting TAG72 in colorectal cancer did not produce any anti-tumor response, novel second-generation versions of TAG72-CAR-T cells and other tumor-restricted translational post-translational modifications are currently being investigated. . It will be necessary to develop more innovative strategies to reduce antigen escape and select antigens capable of inducing adequate antitumor efficacy, while decreasing toxicity concerns in order to expand the clinical use of CAR-T cell therapies in hematological malignancies and solid tumors.

Although checkpoint-CAR-T cell combination therapy is likely to be a new immunotherapy option, it is also important to realize that even this combination may still be insufficient to induce T-cell infiltration and effector function. Therefore, additional studies combining chimeric antigen-receptor T-cell therapy and checkpoint blockade with other immunotherapies/strategies may be necessary to induce T-cell infiltration and effector function in complex hematological malignancies or solid tumors. There are several other limitations of CAR-T cell therapy which are; On-target off-tumor effects, CAR-T cell trafficking and tumor infiltration, Immunosuppressive microenvironment, CAR-T cell-associated toxicities, Engineering CAR-T cells to ameliorate toxicity,Altering CAR structure (Sterner & Sterner, 2021).

3. Conclusion

At present, there is a significant research drive to increase the efficacy of CAR T-cell therapy in tumors, with many researchers focusing on developing new CAR-armored T-cell approaches. This rapidly advancing field of immunotherapy is promising CARs are modular synthetic receptors consisting of four major components: an extracellular target antigen-binding domain, a junctional region, a transmembrane domain, and one or more intracellular signaling domains. CAR-T cells have revolutionized the treatment of some hematological malignancies. However, there are still hurdles, which are discussed in this paper. Antigen selection is critical for CAR-T cell function. Neoplastic cells can downregulate antigens due to the selective pressure of CAR-T cells. Even with appropriate antigen targeting, off-target effects can occur and cause concomitant toxicity.

Despite these successes, this method (CAR-T) is still ambiguous results when fighting solid tumor diseases, and perhaps it is the most common among cancer diseases. Few of the patients responded to the treatment, while the majority did not, as some toxicity was observed that affects the patient, and attempts to exclude it from the drug or keep it away from the patient are very costly. But this method (CAR-T) is very useful in fighting hematopoietic cancers, and one of the attempts to overcome this is the synthesis of armored or reinforced CAR-T cells, where CAR-T cells are reinforced with some cytokines or links involved in the stimulus or antibodies that can block There are some unhelpful pathways in the cell, and research shows great promise for fighting cancer in this way. There are great scientific challenges with regard to immunology. Therefore, scientists are looking at measures to overcome clinical challenges in terms of regulations. CAR T cells are available in many scientific frameworks, which may vary greatly in different countries. These challenges and technology combined require standardization; However, CAR T cells offer patients hope for an advanced treatment, as there is potential for a specific and improved alternative to be made available in the coming decades.

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