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Current Progress of Chimeric Antigen Receptor T cell Cell Therapy

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Abstract: Cancer is a disease characterized by uncontrolled cell growth, has become one of the leading causes of death worldwide. Cancer is the result of the transformation of normal cells into tumor cells in a multi-stage process. Chimeric antigen receptor T cells (CAR-T) have emerged as a new approach to cancer treatment. Recent advances in CAR-T therapy include the development of multiple generations of CARs, each of which modifies the CAR receptor to enhance anti-tumor activity. Despite these advances, CAR-T therapy still faces challenges such as antigen escape, where tumors develop resistance through downregulation or loss of target antigens. This review provides an overview of the principles, procedures, and current achievements of CAR-T therapy while highlighting its limitations and potential improvements. It explores strategies to mitigate side effects, improve the safety and efficacy of CARs, and expand the indications of CAR-T therapy to solid tumors. This article aims to provide valuable insights into the current status and future prospects of this transformative cancer treatment.

Keywords: CAR-T cell therapy, Cytokine release syndrome, tumor microenvironment, HIF.

1. Introduction

Cancer cell-related disease is a common yet severe problem involving a wide variety. According to the data of WHO, in year 2020, cancer-related deaths caused nearly 10 million death cases, affecting organs like mammary glands, lung, colon, etc. Cancer cells, due to their phrasal progression, have a high rate of relapse [1]. Although scientists have made significant progress on conventional methods, cancer disease hasn't been resolved. Traditional methods involving surgery, radiotherapy, and chemotherapy have critical limitations. Surgery is highly restricted to solid tumors that have not spread extensively. Radiotherapy can damage DNA in cancer cells to inhibit their growth but also has side effects on normal tissues around the tumor. Chemotherapy uses drugs to kill dividing cells but also affects normal cells. Because of all those restrictions, curing cancer disease has become a conundrum for the medical field. However, a newly invented method with unprecedented effects may bring some turnovers. CAR-T cell therapy, an edge-cutting technology, entails genetically modifying a patient's own T-cells to produce a synthetic receptor known as a CAR, which identifies a particular antigen on the surface of cancer cells, triggers T-cell activation, and eventually inducing cancer cell apoptosis [2]. Benefits of CAR-T cell therapy include a high rate of cancer shrinkage and the potential of long-term remissions (decrease of cancer characteristics in some hematological malignancies [3]. This treatment has been successfully used in recent years with a decrease in remission rate of up to

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80% for hematologic cancer [4]. Chimeric antigen receptor T-cell (CAR-T) immunotherapy, aiming at inducing cancer cell apoptosis, combines the CARs used to target the cancer with T cells in vitro. The guide, CARs, has been continuously modified to enhance the efficacy and safety of CAR T treatment [5]. These CARs have various properties to overcome the limitations of previous generations [5]. The distinct features of these CARs enhance CAR function through various mechanisms. For instance, the Universal CARs, classified as split universal, programmable (SUPRA), and biotin-binding immune receptor (BBIR) CARs, each have distinct antigen-targeting epitopes that reduce immune escape with distinctive structures [6].

CAR-T cell therapy works by a process from excretion of T cells, expression of CARs to the T cells, replication, to reinsertion of it back into the human body. Once the CAR-T cells are released back into the human body, they will start targeting the cancer cells as well as activating the immune system inhibiting in human body.

This paper aims at explaining the CAR-T cell therapy's current function procedure, some of its unresolved fatal side effects like cytokine release syndrome, false targeting, and tumor microenvironment, as well as branching out some possible near-future improvements like expanding indicators. This paper would give a brief overlook at to the current situation of the novel CAR-T cell therapy as well as focusing on its currently-facing major problems.

2. Function

CAR-T cells are T cells (a kind of white blood cell called lymphocytes) naturally presented in patients genetically engineered to express particular chimeric antigen-specific receptors that target and eliminate cancer cells [7].

It is commonly divided into three areas, the extracellular antigen recognition domain, the transmembrane domain, and the intracellular signaling membrane [8]. The extracellular domain is related to the identification of cancer cells. The single-chain variable fragment (scFv) is a common yet essential particle in the extracellular domain. It can identify tumor-specific antigens, conduct CAR-T reproduction, and activate the anti-tumor functions. The higher affinity CAR-T cell represents, the better the ability to identify cancer cells.

Another kind of particle present in the extracellular domain is the extracellular vesicles (EV) [9]. It is responsible for intercellular communication, carries nutrients like protein and lipids, and binds and penetrates specific antigens.

The intracellular domain activates the T cells. The transmembrane domain acts as a hinge to complete the structure of CAR.

Four phases are typically included in CAR-T therapy: T cell collection, CAR-T cell modification and reproduction, infusion back into the body, and side effect monitoring [10]. The first step, the collection of T cells from the patient's body, is also known as apheresis, or sometimes leukapheresis. The blood of the patient would be transmitted through a machine, separating the blood into groups, like platelets, plasma, red blood cells, etc. The T cells will be collected and the rest will be returned back. After that, a new gene containing CAR is introduced to transform the T cells into CAR-T cells. It has the intracellular domain, mostly by viral transduction, and the previously stated antigen binding domain. Then, the CAR-T cells are cultivated in a lab under ideal conditions for quick development and reproduction.

While the T cells are still manufactured outside of the body, other methods are quickly taken actions, like chemotherapy, to prevent the disease from further spreading. Before CAR-T cells are infused, chemotherapy is required to make room for CAR-T cells. Finally, CAR-T cells will be imported back into the body, usually taking about 30 minutes, and doctors and nurses will be closely monitoring the patient's condition [10]. The major difference between CAR-T cell therapy and conventional methods is that it modifies cells inside human body to trigger natural responses to cancer

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cells, instead of inducing medicine to kill cancer cells. The former one has presented high specificity to cancer pathogens, without harming any normal cell. However, it has also proposed several life-threatening side effects, like high-level-cytokine related cytokine release syndrome, as well as a series of threatens related with the complicated tumor microenvironment.

3. Cytokine Release Syndrome (CRS)

Cytokine release syndrome (CRS) is one of the most prevalent, extreme side effects in the CAR-T therapy. It is brought by the hyperactivation of CAR-T cells and immune cells such as dendritic cells and macrophages, and results in a systemic inflammatory response [11]. When CAR-T cells are reinserted into the body, they activate and begin to proliferate. In this process, they release a kind of protein called the cytokine. It is responsible for cell communication and immune system regulation. However, the presence of high-density cytokines will conduct systemic inflammatory response syndrome (SIRS), with symptoms like fever, low blood pressure, or high heartbeat rate. The severity of CRS varies from mild, flu-like symptoms to organ failure and even death-threatening conditions [12].

CRS usually manifests with fever, and proceeds with general symptoms like malaise, headache, fatigue, etc. More serious symptoms include hypoxia and hypotension, which could result in shock cardiovascular organ dysfunction, causing death. Currently, patients inserted with Car-T cells are under close monitoring, especially focusing on heartbeat and temperature to ensure that actions can be taken in time. Scientists are also trying to modify better methods to decrease this side effect.

The first effort is the development of predictive models, a simulation of the CAR-T cell's movements and reactions inside patient's body. It could predict CRS occurrences and help doctors to take action in advance. One of the examples is a deep learning prediction model called the PrCRS, based on U-net and Transformer [13]. It has successfully forecasted the probability and timing of patients developing severe CRS at least one day in advance, thus helping clinicians to decide whether or not to take more aggressive drugs. However, limitations do remain. Due to the shortage of CRS patients, scientists have used data of COVID-19, a similar disease, which may result in bias [14].

Another field is the modification of T-cell genes. According to research, using clustered regularly interspaced palindromic repeats–associated protein 9 (CRISPR–Cas9) to regulate T cell activation states and differentiation, primary T cells and engineered T cells, such as CAR-T and TCR-T, can be edited both in vivo and in vitro. This has enabled T cells to better adapt to certain microenvironments [14]. Further developments also include modifying controllable CAR-T cell with induced cell apoptosis to address with serious side effects, increasing CAR-T cell's antigen specificity to reduce its harm to surrounding cells like B cells, and producing multi-targeted Car-T cells.

4. Overcoming Tumor Microenvironment

The complex region known as the tumor microenvironment (TME) is home to immune cells, vasculature, cancer-associated fibroblasts (CAFs), and cancer cells [14]. It is an ideal environment for tumor development, created by the engagement and interaction of immune cells and cancer cells. It is like a shield protecting the internal tumor cells. The TME contains a low PH condition due to metabolic change, which results in the inhibition of immune cell activation [15-18]. In addition, cancer cells express signals to prevent immune cell activation and promote immune escape [19-21]. What's more, the TME possesses a low-oxygen level condition, termed hypoxia [22]. All these characteristics of immune protection contribute to tumor cell growth.

TME has proposed great convenience and protection for tumor growth. One of its functions is to stimulate the growth of additional blood vessels, a process known as angiogenesis. The angiogenic factors, most notably vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF),

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would manipulate and send fake signals leading to vessel proliferation and mitigation, resulting in an extra supply of energy to the tumor and ultimately to tumor expansion [23].

Another major characteristic is hypoxia. Hypoxia in TME is caused by the turbid structure of tumor neo vasculature, which fails to meet the high metabolic needs of cancer cells that are with uncontrolled growth [24-26]. Malignant tumors frequently possess an average oxygenation level below 2.0%, whereas normal tissues express an oxygen level between 3.0% and 7.4% [27]. Although for clinicians, this is an unfavorable environment, it is an ideal place for cancer cells as they can tolerate and evolve while other cells are induced to apoptosis. A constitutively expressed β subunit (ARNT) and an oxygen-sensitive α subunit make up the heterodimer known as hypoxia-inducible factors (HIFs). Prolyl hydroxylase domain (PHD) enzymes hydroxylate HIF-α subunits (including HIF-1α and HIF-2α) under normal oxygen circumstances, preparing them for the degradation of von Hippel-Lindau (VHL) protein complex [28,29]. However, in hypoxic environments, the absence of oxygen inhibits hydroxylation, leading HIF-α subunits to stabilize and accumulate. The HIF family of transcription factors is thus activated, modifying gene expression in immune cells and tumor cells inside the TME to affect tumor growth and treatment response [30]. Activities of HIF-1α inhibitors greatly influence tumor to migrate, invade, and metastasize surrounding cells [31,32].

For now, overcoming the tumor microenvironment is still a formidable challenge as it is a complex system involving the existence and interactions between tumor cells, immune cells, and normal cells, while also drastically reducing the efficacy of cancer treatments.

5. Conclusion

This review focuses on an innovative method of treating cancer—CAR-T cell therapy. It is a method for expression of the CAR receptors on T cells' surface, to enable it with the ability to recognize tumor cells by specific characteristics. Then the review explains the basic function process of CAR-T therapy, from the collection of T cells, modification, replication, to reinsertion. CAR-T cell therapy, different from normal ones, which boosts the immune system's ability to kill cancer, focuses on endowing T cells with the ability to recognize and kill cancer cells. It dramatically reduced the mortality rate while increasing recovering rate. Although with outstanding effects, it also encompasses numerous problems. The review focuses on two of the major side effects, the CRS and TME. The former is caused by a high density of cytokine while the latter presents multiple side effects heavily influenced by the HIFs. Other deficiency includes neurotoxicity, personalization-lead high price, false target effect, etc. We believe that this article can give a rough overview of CAR-T therapy, the newest strategy of treating cancer.

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