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CAR-T therapy for breast cancer

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Abstract. The most common form of cancer among women is breast cancer. With the increasing negative impact of breast cancer on human life and health, scientists have devoted more detailed research on breast cancer treatment and there has been the discovery of a novel CAR-T cell immunotherapy method. Based on the results of the research on CAR-T therapies for breast cancer, this paper summarizes the targets of the therapy for breast cancer, discusses the challenges faced by the treatment of the cancer, and proposes effective strategies to solve the difficulties and overcome the challenges. So far, studies found that breast cancer cells have multiple target sites that they can be combined with. Moreover, such difficulties as weak efficacy and lack of target antigen specificity could be addressed by strategies like dual targeting CAR-T cells and synthetic receptors that combine targeted antigens. These studies provide an effective basis for better understanding the key points and specifics of CAR-T immunotherapy for breast cancer.

Keywords: CAR-T, Breast Cancer, Clinical Trials.

1. Introduction

Statistical analysis of World Health Organization data from 2015 to 2020, as many as 7.8 million women have breast cancer, while 0.5% - 1% of men have breast cancer [1]. As a result, breast cancer is a major threat to human life and wellness. There is innumerable research based on breast cancer, and the number of breast cancer patients worldwide is continually increasing yearly. One of the most passionately contested scientific issues in the medical community is breast cancer treatment. Currently, breast cancer is divided into four major categories according to different ways of cancer spread. They are ductal carcinoma in situ, invasive ductal carcinoma, inflammatory breast cancer and metastatic breast cancer [2]. The inner wall of the breast milk duct develops cellular cancer in a non-invasive malignancy called ductal carcinoma in situ [2]. As its name suggests, invasive ductal carcinoma is an aggressive kind of cancer in which cancer cells invade other areas of the breast tissue by traveling through the milk ducts [2]. The cell canceration of inflammatory breast cancer appears on the skin and the breast lymphatic vessels, with severe invasion and rapid growth [2]. Breast cancer that has spread to other regions of the

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body, such as the brain, lung, or bone, is known as metastatic breast cancer [2]. It can be seen that every type of breast cancer should not be underestimated. Therefore, the therapies of breast cancer are also the urgent research focus in the field of cancer treatment.

At the moment, breast cancer treatment approaches include surgical therapy, adjuvant therapy such as chemotherapy and radiotherapy, as well as immunotherapy. Surgical therapy is the most basic treatment. Surgical therapy has relatively stable treatment results and relatively complete technology. However, it can only achieve local control of breast cancer, and the use of surgical resection also has no small side effects on the human body [3]. Chemotherapy drugs inhibit the spread of cancer throughout the body. Radiotherapy uses radiation to kill cancer cells at specific locations. However, these non-specific treatment methods have inevitable side effects [4]. They will cause damage to other organs, tissues, and cells. The more serious side effect is that the white blood cells in the patient's body are removed together with cancer cells, leading to a weaker patient's immune system. Monoclonal antibody therapy in immunotherapy is highly targeted. However, this therapy has no immune response to some rare breast cancers, such as triple negative breast cancer (TNBC) [4]. So, a new type of immunotherapy, CAR-T therapy, is coming into the picture.

CAR-T therapy is a type of immunotherapy that combats cancer by utilizing the immunological capabilities of T cells. Compared to other therapies, it has the unique advantage of maximizing the immune activity of T cells and being able to target therapy more accurately. For breast cancer, a complex and common cancer, it is undoubtedly one of the most effective treatments. As a result, the focus of this review will be on the workings, approaches, and difficulties of CAR-T therapy for breast cancer. It will additionally investigate and lay out the connection between CAR-T cells and cancer cell therapeutic targets to better illustrate the full profile of CAR-T therapy for breast cancer.

2. Mechanism

2.1. Structure of CAR

The structure of CAR consists of three parts. They are extracellular domain, intracellular domain and transmembrane domain. CAR extracellular domains are generated from tumor antigen specific monoclonal antibody fragments [4]. The transmembrane domain of CAR can regulate the surface expression level of CAR, thus controlling the degree of CAR signal transmission [4]. The intracellular domain is the most important structure. It is the main structure that promotes T cell immune effect.

2.2. Mechanism and function based on the architecture of CAR-T cells

CAR-T extracellular domain is a targeted domain that can connect the external and transmembrane domains to promote signal transmission [4]. The transmembrane domain of CAR-T cells also plays a role in controlling signal transmission and has a more direct impact. The CAR-T therapy procedure is extremely dependent on the intracellular domain of CAR-T cells. The intracellular domains of CAR-T cells contain co-stimulatory components that stimulate T cell activation [4]. In addition, intracellular expression inducers that cause CAR-T-cell-mediated tumor cytokines are present in the endodomain, promoting the targeted delivery of cytokines [4].

3. Application

The processing of CAR T immunotherapy on breast carcinoma, from preclinical investigation through underway clinical trials, will be covered in this section. We specifically reviewed tumor-associated antigens in breast cancer and current therapeutic studies.

3.1. HGFR/cME

There is RTK's four participation in the ERBB family which contain the intracellular tyrosine kinase domains, transmembrane protein domains, and external domains that could bind ligands of epidermal growth factor receptor (EGFR/HER1), ERBB2 (HER2), ERBB3 (HER3), and ERBB4 (HER4) [5]. The FDA-approved medications, such as tyrosine kinase as an effective molecular inhibitor and monoclonal

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antibodies aimed at the exterior layer of the membrane, target HER2 and EGFR, members of the ERBB family, which, among other malignancies, breast cancer typically exhibit overexpression. (mAbs).

Abnormal RTK signaling has a role in several human cancer. Many changes have been found in genes that code for RTKs, for the identical scenario under the circumstances of reality in case, EGFR, HER2, or ErbB2 under similar conditions, and MET which occurs in recent molecular genomic experiments. mutations that increase function, genomic enhancement, rearrangements of chromosomes, and/or autocrine activation are the four basic ways by which RTKS is abnormally activated in human malignancies [5, 6].

Carpenter and colleagues discovered the EGF binding receptor on human fibroblasts more than 4 decades later the time, and subsequent research by virtue of varying categories have been determined EGF binding receptor is for RTK [6]. The significance of RTKs in the occurrence or growth of malignancies has come to light in recent years as a result of mounting data. For several malignancies, including breast cancer, targeted medicines that target RTKs have been created, tested in clinical trials, and given the green light [7]. These developments have greatly improved the acknowledgment of the role of RTK signaling and the descending pathways that regulate essential biological operations like Cell proliferation, differentiation, migration, metabolism, and survival are all aspects of cell biology.

The University of Pennsylvania researchers created automobile t-cell targets for TNBC based on the TnMUC1 antibody E5E. Car T cells were developed to precisely recognize TNBC cells based on the TnMUC1 antibody E5E [8]. A promising method for identifying TNBC cells is Penn's design of a CAR T structure, which allows T cells to precisely deploy CAR T cells to redirect to the MUC1 sugar type in TNBC therapy.

3.2. HER2

The target that follows, would discuss the treatment that is still recruiting. Firstly, the paragraph would talk about the potential protein target called HER2, it is an erbb-like oncogene family that includes the oncogenes HER2/neu and epidermal growth factor receptors, which are similar but different. Enhancement of the HER2 gene results in the overexpression of HER2/neu, a 185-kDa surface membrane protein, in about 25% of human breast tumors. This gene's overexpression causes HER2 kinase to be activated without the need for a ligand, which boosts mitotic signaling and cell growth. It’s already demonstrated that these patient-derived cell lines have this gene amplification [9].

Binary oncolytic adenovirus in accompaniment with HER2-specific autologous CAR VST, advanced HER2 positive solid tumors, also known as a tailored CAR, was recently developed in collaboration with researchers at Baylor College of Medicine. This immunotherapy shall identify the targeted biomarkers by virtue of antibody fragments with the scFV section. The ByTE antibodies, a viral epitope recognition receptor, can also be treated as a variable domain of heavy chain of heavy-chain analogs, and these biomaterials are generated from hypoimmunogenic induced pluripotent stem cells (NCT03740256).

3.3. CD70

A transmembrane glycoprotein type II identified as CD70, along with CD154 and CD95, is a constituent of the superfamily of tumor necrosis factors (TNF). both mouse and human T cells express the ligands to CD70 and CD27. While others, the remaining T, B, and NK cells naturally express CD27, antigen-stimulated activated T lymphocytes, B lymphocytes, and NK cells encourage the CD70 expression [9]. Antigen-specific cytotoxic T lymphocyte liveness and T cell multiplication are induced by CD27/CD70 interactions. Antigen presentation cells (APCs) presented their unique antigens to naive T lymphocytes by using a combination of CD28/CD80 co-stimulation, which was followed by an up-regulation of CD27 and a high expression of CD70. On T lymphocytes, the CD27 and CD70's interaction leads to the clonal proliferation of this cells [10].

CD70 has been discovered to own one potential therapy since 2016, and until last year it was still suspended. Nevertheless, at the beginning of 2023, a trial was launched that involved providing periphery blood cells engineered with a CD70-binding chimeric antigen receptor to people the carrier

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of cancer that expressed CD70. The researchers used CD27, CD70's natural ligand, as a binding component to create a CAR that binds within CD70. This CAR transduces peripheral blood lymphocytes (PBL) to transmit the major histocompatibility complex (MHC) to detect cd70-expressing target cells, such as renal cell carcinoma and other malignancies, independently. Anti-HCD70 CAR transduction T cells released a significant amount of highly specific in- when co-cultured with CD70+ target cells (NCT02830724).

4. Challenges

As a novel treatment, CAR-T has faced many new problems in treating breast cancer compared with treating hematological tumors. This is caused by characteristics of breast cancer. As one type of solid tumors, breast cancers often form solid masses in a certain organ at an early stage. As for antigens, hematologic tumor cells carry similar levels of tumor associated antigens, whereas breast cancer cells vary in their levels of antigen expression. Therefore, the efficacy of CAR-T therapy is much less than that for hematologic tumors and is often accompanied by toxicity.

4.1. Lack of target antigen specificity

Unlike the antigens of hematological tumors that are mostly single and specific (CD19, BCMA), there are few tumor-specific antigens (TSAs) in breast cancer. Instead of TSAs, antigens highly expressed in solid tumors are mostly tumor-associated antigens (TAAs), which can appear in normal cells. This poses a high off-target risk, and safety becomes a critical issue. Even worse, even if specific targets for breast cancer are found, some cancer cells will escape the supervision of immune system by reducing specific targets, which is termed as antigen escape [11]. Antigen escape is one side effect of single antigen targeting CAR-T cells.

4.2. Tumor heterogeneity

Tumor heterogeneity refers to the fact that a single breast cancer contains a diverse collection of cells with distinct genotypes and phenotypes. Heterogeneity contributes to tumor differences and tumor environment. Tumor heterogeneity increases obstacles in breast cancer, in terms of tumor classification and tumor microenvironment. For one thing, the heterogeneity of breast cancer phenotypes accompanied by the dynamic tumor microenvironment makes breast cancer classification a difficult task. For another, the heterogeneity of cancer cell markers can impair the therapeutic effectiveness of CAR-T treatment.

4.3. Tumor microenvironment

In the immunosuppressive tumor microenvironment, cell types that infiltrate breast cancer can help tumor cells suppress CAR T cells. These cell types have the potential to increase the production of tumor-promoting cytokines, chemokines and transforming growth factor beta (TGFβ) [12]. This immunosuppressive environment inhibits CAR-T cell proliferation and short-term CAR-T cell persistence, as well as CAR-T cell homing and colonisation of tumor tissue. Thus, it’s less likely for CAR-T cells to infiltrate breast cancer or recognize the antigens. The tumor microenvironment of breast cancer largely decreases the efficiency of CAR-T therapy.

4.4. Toxicities

Despite the fact that CAR-T is a potential treatment for breast cancer, severe toxicities and clinical fatalities have precluded it from becoming a first-line or early treatment [11]. The two most common clinical effects are cytokine release syndrome (CRS) and neurotoxicity. Patients with CRS typically present with fever, hypotension and respiratory failure within the first week after CAR-T treatment, as well as elevated blood cytokine levels [13]. Neurotoxicity can result in temporary memory loss, disorientation, convulsions, and, in rare cases, severe cerebral edema. The fast activation and proliferation of cytokine secreting T cells has been linked to both CRS and neurotoxicity. In addition, the cytokines generated by the CAR T cells and the ligand-receptor contacts stimulate other immune

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cells in the myeloid compartment, which in turn release more cytokines, thus triggering a cycle of inflammation.

5. Strategies

CAR-T therapy has surfaced as a groundbreaking immunotherapy method, transforming cancer treatment by tapping into the patient's immune system's capabilities. This cutting-edge therapy entails genetically altering T-cells to precisely target and eliminate cancer cells, showing extraordinary efficacy in treating blood malignancies. Nevertheless, its use in solid tumors, especially breast cancer, continues to face challenges due to factors like tumor diversity, antigen evasion, and immunosuppressive tumor settings. This section intends to examine contemporary approaches designed to surmount these obstacles and unleash the complete potential of breast cancer treating.

5.1. Development of Multi-Antigen Targeting CAR-T

CAR-T development capable of targeting multiple antigens has shown significant potential in overcoming the challenges with traditional CAR-T treatment for breast cancer. CAR-T treatment can be enhanced by engineering the cells to recognize multiple TAAs simultaneously. This innovative approach reduces the risk of tumor escape due to antigen loss or heterogeneity, while also increasing therapeutic effectiveness.

This method involves modifying T cells to carry chimeric receptors capable of recognizing various TAAs - proteins or glycoproteins typically present on cancer cells. When these CAR-T cells bind to their specific antigens, they become activated, leading to proliferation, cytokine release, and selective eradication of cancer cells. Recent advances in this field have explored programmable and multi-targeted CARs, which allow for increased precision and flexibility in targeting different antigen combinations.

Numerous clinical trials have evaluated the effectiveness of therapies targeting multiple antigens in the treatment of breast cancer. For example, a phase I/II trial employed T cells designed to target both HER2 and MUC1, two common breast cancer TAAs [14]. The results of this trial were promising, with manageable toxicity profiles in patients with relapsed/refractory breast cancer. Breast cancer metastasis in the brain was effectively treated by delivering HER2-targeting CAR-T cells regionally, according to another study [15]. Disis et al. investigated multi-antigen vaccines targeting breast cancer proteins such as HER2, IGFBP-2, and IGF-1R [16]. Hirabayashi et al. developed cells with dual-targeting abilities, optimized co-stimulation, and metabolic fitness to enhance anti-tumor activity and prevent tumor escape in breast tumors [17].

CAR-T cells targeting multiple antigens offer several advantages. By targeting various TAAs, these modified T cells can address tumor heterogeneity, a significant limitation of conventional CAR-T therapy. This approach may also help prevent tumor escape resulting from antigen loss or downregulation, which frequently results in treatment resistance and recurrence. Incorporating ideal combination of co-stimulation and metabolic fitness properties that can improve their persistence and function in the immunosuppressive tumor microenvironment.

5.2. Advancements in Therapy through TCR Engineering

Recent advancements in TCR-engineered T therapy offer promise in overcoming the challenges in T therapy process for breast cancer treatment. Genetically modified T cells from the patient are utilized in TCR-T therapy to express a T cell receptor that specifically targets human TAAs. This enables precise targeting and destruction of cancer cells that display these antigens on its surface, together with molecules of the MHC (major histocompatibility complex).

The effectiveness of TCR-modified T cells in treating breast tumors demonstrated in multiple studies. Li et al. showed that TCR-engineered T cells targeting the PLAC1 antigen effectively combated breast cancer. T cells that were engineered with a TCR targeting the prostate antigen TARP were found to selectively eradicate breast and prostate tumors that express HLA-A2 by Hillerdal et al. [14, 18]. Clinical trials have demonstrated promising results for TCR-engineered T therapy in breast cancer treatment as well. The use of autologous lymphocytes in a phase II pilot trial that were mutation-reactive showed

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immunogenicity in breast cancer patients, underscoring the potential of TCR-engineered T in this context [19].

Compared to CAR-T therapy, TCR-T therapy provides several advantages in the context of breast cancer. Firstly, it enables targeting of intracellular antigens presented by MHC molecules, broadening the range of antigen targets and overcoming the limitations of CAR-T cells, which only recognize cell-surface antigens. This is particularly significant since many cancer-specific antigens in breast cancer are intracellular. Another advantage of TCR-T cells is that they identify and eliminate cancer cells through an MHC-dependent mechanism, potentially mitigating the off-tumor, on-target toxicities often observed in T cell therapy. Lastly, TCR-T cells have demonstrated a higher affinity for target antigens compared to CAR-T cells, which could potentially result in a stronger immune response against tumors. In order to maximize the potential of TCR-T therapy for breast cancer treatment and enhance patient outcomes, it is imperative to conduct ongoing clinical trials and immunogenomic studies.

5.3. Application of Interleukin-6 Receptor Antagonists

The use of interleukin-6 (IL-6) receptor antagonists has emerged as a promising approach to tackle the obstacles posed by the immunosuppressive tumor microenvironment (TME) and resistance to immunotherapy. IL-6 is a multifunctional cytokine that plays crucial roles in inflammation, immune regulation, and cancer progression. In breast cancer, IL-6 signaling promotes tumor growth, angiogenesis, metastasis, and immune evasion by recruiting immunosuppressive cells and suppressing T cell activation.

IL-6 receptor antagonists can be administered to block IL-6 signaling, thereby reducing the recruitment of immunosuppressive cells and enhancing the CAR-T therapy effectiveness. Specifically, IL-6 receptor antagonists can either prevent IL-6 from binding to its receptor (IL-6R) or interfere with the signal transducer gp130, ultimately inhibiting the downstream pathway involving the transcription factor signal transducer and activator of transcription 3 (STAT3) and Janus Kinase, known as JAK. As a result, there is a decrease in inflammation that supports tumor growth, a reduction in tumor proliferation, and an improved immune response.

The potential of combining IL-6 receptor antagonists with CAR-T therapy for breast cancer has been shown in various clinical trials. In a preclinical breast cancer model, Kampan et al. (2018) discovered that combining the IL-6R antagonist tocilizumab Using CAR-T cells that target human epidermal growth factor receptor 2 (HER2) markedly decreased tumor burden and enhanced survival [20]. The study by Fu et al. (2019) showcased the synergistic effect of combining the selective estrogen receptor modulator bazedoxifene, which also functions as an IL-6 inhibitor, and the chemotherapeutic agent paclitaxel. This combination treatment demonstrated the ability to significantly inhibit cell viability, migration, and the formation of colonies in vitro, and effectively suppressed tumor growth in vivo in breast cancer xenograft models [21].

This approach's benefits arise from its ability to counteract the immunosuppressive impact of tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs) within the TME. By inhibiting IL-6 signaling, IL-6 receptor antagonists can create a more favorable TME, enabling CAR-T cells to exert their antitumor effects effectively. In addition, inhibition of IL-6 signaling can improve the cytotoxic efficacy of CAR-T cells and reduce the possibility of tumor recurrence. Future clinical trials should focus on optimizing the combination of IL-6 receptor antagonists and CAR-T therapy to maximize therapeutic benefits for breast cancer patients.

5.4. Progress in Inducible Safety Switches for CAR-T Therapies

Inducible safety switches are a promising development in CAR-T therapy as they allow for selective activation or deactivation of CAR-T cells in response to specific stimuli, such as external cues or small molecules. The switchable CAR-T technique is a prime example of this innovation, in which a distinct targeting molecule, such as a bispecific antibody, promotes interaction between tumor and CAR-T cells. This approach enables precise regulation over the activation of CAR-T cells, allowing customization based on the patient's response or adverse events.

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Clinical trials have extensively explored the application of inducible safety switches in breast cancer treatment. Cao et al. (2021) demonstrated that switchable CAR-T cells were more effective than traditional antibody-redirected therapies in targeting breast cancers [22]. Dees et al. (2020) examined the potential of newly developed CAR-T therapies for the management of triple-negative breast cancer (TNBC), which is a difficult and resistant subtype [23]. Xie et al. (2020) assessed the viability of CAR-T therapy for TNBC and discussed the obstacles and future prospects for clinical implementation [24].

The integration of inducible safety switches into CAR-T therapy offers several benefits. Firstly, it provides better regulation over the activation of CAR-T cells, potentially reducing toxicities on target cells and increasing treatment safety. Secondly, it offers an approach to address tumor heterogeneity by facilitating the targeting of multiple antigens, decreasing the likelihood of tumor escape due to antigen loss. Finally, inducible safety switches can support the creation of "universal" therapy, which can be easily used across various patients and cancer types, lessening the need for personalized manufacturing, and accelerating the provision of T cell treatments. Overall, the potential of inducible safety switches to improve the safety and effectiveness of CAR-T therapies has been exhibited in clinical trials regarding for breast cancer, signaling a new era of cancer treatments.

6. Conclusion

This review points out that CAR-T treatment for breast cancer has a unique role and efficacy. For the abnormal signal of RTK gene in breast cancer cells and the tumor development promoted by transmembrane surface glycoprotein, the treatment method guided by CAR-T mechanism has become an important application in clinical treatment. In addition, the challenges faced by CAR-T therapy, such as lack of target antigen specificity, tumor heterogeneity, tumor microenvironment, and toxicity, can also be effectively solved and treated through strategies such as multi antigen development, TCR engineering, interleukin-6 receptor antagonist, and inductive safety switch targeting CAR-T cells. As a result, CAR-T therapy has therapeutic potential in the treatment of breast cancer and is becoming increasingly essential in the treatment of breast cancer. At the same time, with the deepening of research, the treatment could be integrated into the treatment of more cancers and become an indispensable mainstream treatment in clinical treatment. This review scientifically investigated the mechanism and application of CAR-T therapy in the clinical treatment of breast cancer, as well as recommended viable solutions to address the therapy's existing problems. It is of great significance to systematically solve the treatment difficulties of CAR-T therapy, and also provides a certain reference value for understanding the CAR-T development for clinical breast cancer therapy. Finally, future studies might focus on the targets of CAR-T cell treatment, the hurdles faced by breast cancer, and investigate and summarize effective solutions to the problems, in order to further the development of CAR-T immunotherapy for breast cancer.

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