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Harnessing the Power of CAR-T Cell Therapy for Triple-Negative Breast Cancer: Challenges and Opportunities

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Abstract

Triple- negative Breast cancer (TNBS) is highly aggressive and heterogeneous disease with limited treatment options. That lacks expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor2 [HER2]. The absence of these targets limits the effectiveness of conventional hormonal and targeted therapies, resulting in poor prognosis and high recurrence rates. CAR-T cell therapy has emerged as promising immunotherapeutic strategy, offering novel approach for selective targeting and eradication of TNBC cells. This review explores the current advancements in CAR-T therapy, focusing on key target antigens such as MUC1, EGFR, and folate receptor alpha [FRα], which have demonstrated encouraging preclinical efficacy. Despite significant potential, several challenges hinder clinical translation, including tumor antigen heterogeneity, immunosuppressive tumor microenvironment, and risks of off- targeted toxicity. Overall, CAR-T cell therapy represents a transformative and promising approach for improving the management and survival outcomes of patients with TNBC.

Keywords: Triple-negative breast cancer, CAR-T cell therapy, MUC1, EGFR, Folate receptor alpha (FRα), Tumor microenvironment.

INTRODUCTION

Globally, breast cancer is the most prevalent cancer in women. According to WHO Breast Cancer is a complex and multifaceted disease that affects millions of women worldwide. It is estimated that in 2022 alone, over 43,000 women will lose their lives to breast cancer [1]. The active proliferation of breast tissue's epithelial cells, which results in the development of malignant cells in the breast's ductal or lobular compartment, is the molecular mechanism that causes breast cancer to arise [2]. Three established criteria for classifying breast cancer and assessing a breast tumor's aggressive potential are histologic grade, disease stage, and expression of classic hormone and growth factor receptors. Invading cancers account for the remaining 75% to 80% of all breast cancer diagnoses and penetrate the myoepithelial cell layer and basement membrane to invade locally into the surrounding breast stroma, while in situ cancers make up 20% to 25% of breast cancers and stay contained within the site of origin [3]. To assess the aggressive potential and progression of a breast tumor, breast cancers are further categorized based on their histologic grade and stage, respectively. Furthermore, IHC expression of classic hormone and growth factor receptors, such as the estrogen receptor (ER), progesterone receptor (PR), and HER2, as well as their proliferative index in terms of Ki-67 expression, are used to classify breast cancers into four molecular subtypes.

PR+, HER2−, Ki-67 < 14%), or Luminal B (ER+ and/or PR+, HER2+ or HER2−, Ki-67 > 14%) breast cancer subtypes [4,5]. It is estimated that between 70 and 80 percent of newly discovered breast cancers are hormone receptor-positive [6]. The etiology of BC is significantly influenced by steroid hormones, such as progesterone and estrogen, and their corresponding receptors, which are involved in many physiological processes. Progesterone has a significant impact on the health and illness of women [7]. According to earlier research that only looked at PR, postmenopausal women who have high levels of circulating progesterone are 16% more likely to develop breast cancer [8]. Furthermore, compared to breast tumors that were ER+/PR+ or ER+/PR, tumors with ER-/PR+ status were more common in younger patients (those under 49) and had worse outcome [9].

It may be treated with tyrosine kinase inhibitors, antibody–drug conjugates, or HER2-targeting monoclonal antibodies, as well as endocrine therapies such as selective estrogen receptor modulators, aromatase inhibitors, or ER degraders [10]. Although these three subtypes are linked to positive clinical outcomes because they respond well to targeted therapies, a significant subset of the fourth subtype of breast cancer, known as triple-negative breast cancer (TNBC), which tests negative for ER, PR, and HER2 overexpression, has a poor prognosis because there are no targeted treatment options available for this patient population [11,12]. One of the traits of TNBC is a high mutational burden. TNBCs actually have a higher percentage of mutations that contribute to their aggressive phenotype, including phosphatidylinositol 3-kinase catalytic alpha polypeptide (PIK3CA; 8.60%–23.28%), tumor protein 53 (TP53; 74.51%–82.80%), and the breast cancer type I susceptibility gene (BRCA-1; 1.96%–21.55%). TNBC is now recognized as an immunogenic malignancy due to recent evidence of the immune system's interaction with the disease's progression. Microsatellite instability, cytotoxic CD8+ and regulatory FOXP3+ tumor-infiltrating lymphocytes, a high tumor mutational burden, a lack of mismatch repair, and the expression of immune checkpoint molecules like programmed death-ligand 1 (PD-L1) are all examples of factors that make TNBC immunogenic [13,14]. The main treatment for TNBC is chemotherapy (anthracycline + taxane); however, treatment resistance and long-term recurrence still need to be addressed [15]. The last ten years have seen a significant increase in interest in adoptive cell therapy, especially chimeric antigen receptor-modified T-cell (CAR-T) therapy. Peripheral blood mononuclear cells (PBMCs) are obtained from patients (in the case of autologous CAR-T therapy) or third-party healthy donors (in the case of allogeneic CAR-T therapy) to initiate the CAR-T generation process [16]. T lymphocytes are separated from the population of the isolated PBMCs. To express a synthetic chimeric antigen receptor (CAR) on their surface, these T cells go through activation and genetic manipulation processes, typically involving retroviruses. Three crucial parts make up a CAR construct. An endodomain, a transmembrane domain, and an extracellular domain [17]. CARs' ectodomain is made from a tumor antigen-specific portion of a monoclonal antibody (mAb), such as a single variable domain on a heavy chain (VHH) or single-chain fragment variable (scFv).

Both hinge and transmembrane domains have been shown to have notable effects on CAR expression and signaling in recent years [18]. Between the ectodomain and the transmembrane domain, this targeting domain is connected to a flexible spacer known as a hinge [19]. The type of transmembrane domain (as opposed to hinge) has a significant influence on the stability and rate of CAR expression on T cells. Through the regulation of CAR surface expression, the CAR transmembrane domain can regulate the magnitude of CAR signaling [20,21]. For solid tumors, CAR T cell immunotherapy is still difficult because there are no particular targetable cell surface antigens. A tumor target antigen should ideally be very specific to tumor cells and barely noticeable in healthy tissues. Mucin1 glycoprotein (MUC1) has been suggested as one of the favorable targets for engineering CAR T cells [22]. When inserted into T cells, synthetic receptors known as chimeric antigen receptors (CARs) might redirect T cells to identify a tumor-specific antigen, activate them to become cytolytic, and ultimately lyse the tumor cells [23]. The CAR T cell strategy creates a fusion molecule for tumor cell lysis by combining an extracellular single chain variable fragment (scFv) from an antibody that recognizes a tumor surface antigen, a transmembrane domain, and a T cell intracellular signaling domain. Because solid tumors lack specific targetable cell surface antigens, CAR T cell immunotherapy is still difficult to use for solid tumors, despite its success in treating hematologic malignancies [24].

The ideal tumor target antigen should be very specific to tumor cells and barely noticeable in healthy tissues. One of the promising targets for CAR T cell engineering has been proposed to be the mucin1glycoprotein (MUC1). The transmembrane protein mucin 1 (MUC1) is highly glycosylated; however, tumor cells differ from normal cells in that their glycosylation levels are abnormally low. The hydroxyl (-OH) group of serine (S) or threonine (T) is joined to an O-glycosidic-linked N-acetylgalactosamine (GalNAc) to form the Thomsen-nouvelle (Tn) antigen [25]. One tumor-specific antigen (TSA) that has demonstrated encouraging diagnostic and therapeutic potential in adenocarcinomas is the Tn glycoform of MUC1 (TnMUC1). All of the glandular epithelial cells that make up our major organs, including the breast, normally express MUC1, a transmembrane mucin protein that is naturally highly glycosylated. The variable number tandem repeats (VNTR) region is located in the large extracellular domain of MUC1. Proline, serine,and threonine residues make up the majority of the 20 amino acid sequence that is repeated 25-125 times in the VNTR region. O-glycans can attach to the enriched serine and threonine residues and undergo extensive O-linked glycosylation because they act as a scaffold [26]. In over 90% of cases of breast cancer, MUC1 is abnormally glycosylated and overexpressed. In addition to acting as a tumor neoantigen for the highly specific targeted immunotherapeutic monoclonal antibody TAB004 that does not recognize normal epithelia, this tumor-associated MUC1 is a marker of an aggressive phenotype. TAB004 targets 95% of all malignant tissues, including TNBC, indicating that tMUC1 is expressed in these tissues. TAB004 only accumulated in the tumor and not in any other organs when it was injected into human TNBC (HCC70) tumor-bearing mice or PyVMT. MUC1 transgenic mice, which develop spontaneous mammary gland tumors. As a result, TAB004 recognizes tMUC1 in a very specific way while avoiding normal tissue recognition [27]. In order to engineer the MUC28z fusion molecule and produce CAR T cells, we used TAB004. The scFv sequence from TAB004 is fused to CD28 and CD3ζ T cell intracellular signaling molecules to form MUC28z. MUC28z CAR T cells exhibited robust tumor cytolytic efficacy for TNBC *in vitro* and *in vivo*, along with high tumor antigen specificity. CAR-T combines the capacity of T cells to eradicate tumor cells with the specificity of an antibody to target particular antigens on tumor cells in a single fusion molecule. Indeed, patients with hematological malignancies experienced remarkable tumor regression as a result of CAR-T immunotherapy [28]. Numerous CAR-Ts, including the orphan receptor CAR-T that resembles receptor tyrosine kinase, Clinical trials for the treatment of TNBC are presently testing natural killer group 2 member D (CAR-T) and mucin-1 glycoprotein CAR-T [29,30]. Epidermal growth factor receptor (EGFR, also known as HER1) is a marker that more accurately differentiates TNBC from other subtypes of breast cancer, according to recent research [31]. Additionally, EGFR has been found to be overexpressed in 72% of patients with TNBC. EGFR overexpression was detected in 9.1% and 66.7% of all tested samples and TNBCs. EGFR is involved in angiogenesis, apoptosis, cell division, and other processes that affect the course of cancer. TNBC cell membranes exhibit high levels of EGFR expression [32]. EGFR homodimerization or heterodimerization and transphosphorylation are triggered when EGF binds to and activates EGFR, and this in turn activates downstream molecular signaling [33]. By binding to and activating STAT through the Src homology 2 domain, for instance, EGFR and JAK cause STAT to homo- and heterodimerize before being translocated into the nucleus, where it initiates the expression of downstream genes related to survival and proliferation [34]. In the current study, when EGFR-specific CAR-T cells were co-cultured with high-EGFR-expressing TNBC cells *in vitro*, they were activated and secreted more IFN-γ, IL-2, and IL-4. These cells recognized EGFR more efficiently than Con CAR-T cells [35]. Folate receptor-alpha (FRα) is expressed at low levels on the apical surface of a subset of polarized epithelial cells, such as the parotid, kidney, lung, thyroid, and breast, and at high levels in non-mucinous tumors of epithelial origin, such as ovarian, breast, and lung cancers. Due to its low coordinate expression in normal tissue and specific overexpression in some cancers, such as TNBC, FRα is a desirable target for targeted therapies. Steroid hormones, especially estrogens, can control the expression of FRα in breast cancer [36]. The direct action of the ER on the P4 promoter of FRα has been shown to down-regulate FRα expression in response to 17β-estradiol, indicating a negative correlation between ER expression and FRα. The use of folate-conjugated therapeutic compounds, which bind FRα or murine, chimeric, and humanized monoclonal antibodies (mAbs) either alone or in conjugates to deliver radionuclides, T cells, and stimulatory cytokines to malignant tissue, has made FRα an appealing candidate for targeted drug delivery [37]. Furthermore, a promising technology that is being actively studied is the transfer of T cells that have been genetically redirected with a chimeric antigen receptor (CAR) unique for FRα. In a single fusion molecule, the CAR approach combines the antigen specificity of an antibody with T cells' capacity to mediate tumor cell death. CAR-modified T cells can survive as memory cells *in vivo* and actively and precisely target their designated antigen [38]. Therefore, it's possible that CAR-modified T cells that target tumor-associated antigens

(TAAs), like FRα, will produce more robust tumor responses than monoclonal antibodies. In a murine xenograft model of human TNBC, we produced a FRα specific CAR with an intracellular CD27 co-stimulatory signaling domain and assessed the therapeutic effectiveness of T cells transduced to express this CAR. We show that human TNBC growth can be inhibited *in vivo* by FRα specific CAR T cells, and that when TNBC cells overexpress the surface FRα protein, more robust tumor regression can be achieved [39].

Table 1: Key strategies to overcome solid tumor CAR-T cell therapy challenges

S. No.	Difficulties in using CAR-T cells to treat solid tumors	Important strategies for overcoming the difficulties with solid tumor CAR-T cell therapy	TNBC mitigation technique examples.
1	Heterogeneity or lack of specificity of the target antigen	❖ AND-gate circuits, including synthetic notch and dual CARs ❖ NOT-gate circuits: CARs that inhibit ❖ OFF switches: safety switches for suicide genes	• EGFR safety switch-engineered Integrin αvβ3-CAR-T cells. • Bispecific CAR-T cells that target mesothelin and FRα.
2	Tumor microenvironment that suppresses immunity.	• T cell redirected for universal cytokine – mediated killing • Antigen targeting on various cell types • Negative receptor dominance • Cytokine receptor inverted	• Target the expression of antigens on primary TNBC tumor cells and stromal cells, such as angiogenic endothelial cells, MDSCs, CAFs, TAMS, and Tregs.
3	Immune checkpoint receptor expression	• Antibodies that block immune checkpoints • CAR-T cells that secrete antibodies	• Mesothelin-CAR-T cells with PD-1 knockout.
4	Ineffective infiltration and trafficking of the intra tumoral space.	• Chemokine receptor co-expression	• Preclinical research on TNBC that tackles this issue is lacking.
5	Insufficient perseverance	• Cytokine receptor coexpression	• The IL7 receptor is constitutively active in AXL-CAR-T cells.

Table 2: Using antigenic targets for CAR-T cell therapy in TNBC

S. No.	Target of CAR-T cells	CAR-T cell target class	Important preclinical findings for TNBC using CAR-T cell therapy
1.	AXL (uncontrolled)	Tyrosine kinase binding	AXL-CAR-T cells inhibit tumor cell growth in a TNBC xenograft mouse model and exhibit *in vitro* cytotoxicity in TNBC cells
2.	Epidermal growth factor inhibitors	Tyrosine kinase binding	*In vitro*, EGFR-CAR-T cells cause TNBC cell lysis, and *in vivo*, they prevent TNBC tumor growth
3.	Folate receptor α (FRα)	Glycosylphosphatidylinositol (GPl) linked membrane protein	In a TNBC xenograft mouse model, FRα-CAR-T cells promote tumor regression and kill TNBC cells *in vitro*
4.	Mucin 1(MUC1)	Cell surface glycoprotein	MUC1-CAR-T cells inhibit the growth of TNBC tumors *in vivo* and increase cytotoxicity in TNBC cells *in vitro*
5.	Intercellular adhesion molecule 1 (CD54	Glycoprotein at the cell surface	CAM-1-CAR-T cells mediate *in vitro* killing of TNBC cells
6.	Tumor endothelial marker -8	Glycoprotein at the cell surface	In a TNBC xenograft mouse model, TEM8-CAR-T cells exhibit antitumor activity.

CONCLUSION

For the treatment of triple negative breast negative, a subtype with few treatment options and a dismal prognosis, CAR –T therapy presents a novel and promising strategy. Strong anti -tumor activity and specificity have been demonstrated in preclinical studies that target antigens like MUC1, EGFR and FRα. These studies have produced encouraging results. For clinical success, however, significant obstacles must be addressed such as, tumor heterogeneity, restricted tumor infiltration, and possible off target toxicity.

Conflict of interest

There is no conflict of interest.

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