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Review
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Engineered T Cell Receptor for Cancer Immunotherapy

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Abstract

Among the therapeutic strategies in cancer immunotherapy—such as immune-modulating antibodies, cancer vaccines, or adoptive T cell transfer—T cells have been an attractive target due to their cytotoxicity toward tumor cells and the tumor antigen-specific binding of their receptors. Leveraging the unique properties of T cells, chimeric antigen receptor-T cells and T cell receptor (TCR)-T cells were developed through genetic modification of their receptors, enhancing the specificity and effectiveness of T cell therapy. Adoptive cell transfer of chimeric antigen receptor-T cells has been successful for the treatment of hematological malignancies. To expand T cell therapy to solid tumors, T cells are modified to express defined TCR targeting tumor associated antigen, which is called TCR-T therapy. This review discusses anti-tumor T cell therapies, with a focus on engineered TCR-T cell therapy. We outline the characteristics of TCR-T cell therapy and its clinical application to non-hematological malignancies.

Key Words: Cancer immunotherapy, CAR-T cell, TCR-T cell, Solid tumor

INTRODUCTION

Cancer immunotherapy has been an area of interest since its inception. Immunotherapy, especially adoptive cell transfer (ACT), began with tumor infiltrating lymphocytes (TIL), which were first clinically effective in the 1980s (Rosenberg *et al*., 1986). TIL-based therapy is a method of isolating T cells with anti-cancer effects that have infiltrated the tumor microenvironment (TME), multiplying them *ex vivo*, and then injecting them back into the patient for a stronger anti-cancer effect (Lin *et al*., 2020). To improve selectivity and effectiveness against cancer cells, chimeric antigen receptor (CAR)-T and T cell receptor (TCR)-T cell therapies are evolved from TIL therapy to introduce genetically modified receptors (Weber *et al*., 2020). Both are genetically engineered to express receptors that allow them to specifically bind to targeted cancer cells. This creates a powerful weapon to treat cancer while minimizing the impact on normal cells. Briefly, the genetically engineered receptors are transplanted *in vitro* into the patient's T cells via viral vectors such as lentiviruses or retroviruses, or by using non-viral method such as the clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9 system. After the T cells expressing the recombinant receptor are allowed to proliferate, they can be infused back into the patient to treat the cancer (Restifo *et al*., 2012). The injected CAR-T and TCR-T cells track and migrate to the cancer cells, recognize antigens of the cancer cells, and eradicate them (Fig. 1). While both CAR and TCR-T cell therapies bear engineered receptors, CAR recognizes tumor surface antigens whereas TCR is able to bind peptide antigens derived from surface and intracellular of the tumor cells in the context of major histocompatibility complex (MHC). The intrinsic difference between CAR and TCR results in a potentially wider application of TCR-T cell therapy to solid tumors. Eradicated cancer cells shed neoantigens into their surroundings, which are recognized by antigen presenting cells (APCs) and induce an intrinsic T cell-mediated immune response. This process is known as cross-priming and enables effective cancer eradication. Currently, CD19-targeted CAR-T cell therapy has been approved by the United States Food and Drug Administration (FDA) for the first time as a treatment for B cell acute lymphoblastic leukemia (ALL) in 2017, and many trials are underway to apply it to solid cancers as well as blood cancers (June and Sadelain, 2018). With the notion that a restricted usage of currently available CAR-T cell therapy within blood cancers, this review focuses on TCR-T therapy and emphasizes its clinical application to solid tumors.

FEATURES OF TCR-T CELL THERAPY

Antigen recognition of TCR-T cells

TCR-T cells recognize internal antigens loaded on the

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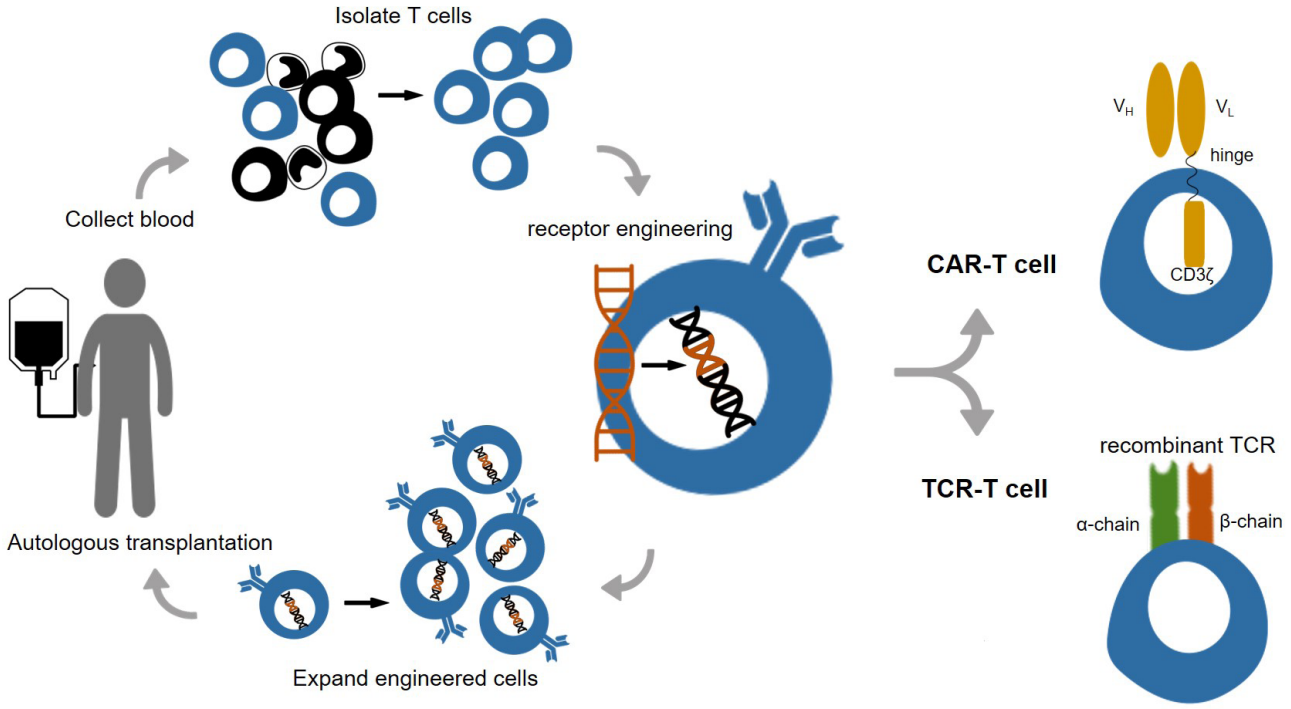

Fig. 1. Generation of T cells with engineered T cell receptor for cancer immunotherapy. T cells are isolated from patients' peripheral blood and T cell receptor (TCR) is edited to recognize tumor-specific antigen. Engineered T cells are classified to either chimeric antigen receptor (CAR)-T cell or recombinant TCR-T cell depending on the design of the receptor introduced to T cells. CARs are comprised of variable region of antibody linked to the signaling domain of CD3 molecule, and generally recognize surface antigen of tumor cells. On the other hand, recombinant TCR is modified to be able to interact with intracellular tumor antigen. After expansion *in vitro*, these T cells are reinfused into the patients, which lead to destruction of tumor cells mediated by engineered T cells.

MHC molecules of cancer cells. The intrinsic TCR works by recognizing the MHC-antigen complex structure expressed by APCs, resulting in T cell activation. Therefore, TCR-T cells are somewhat limited by the need to recognize not only cancer-specific antigens but also MHC molecules expressed by cancer cells. But this limitation is also a feature that can increase specificity and reduce off-target side effects. In addition, TCRs have a lower affinity for MHC complexes but a higher sensitivity than CARs, which means that fewer antigens are required to trigger a sufficient signal (Salter *et al*., 2021).

Targeted Antigens

Due to the different structural characteristics of the receptors expressed, CAR-T and TCR-T cells recognize different classes of antigens. CAR-T cells can only recognize the tertiary structure of antigens expressed on the surface of the cancer cell because the variable region that recognizes the antigen is derived from the antibody (Weiner *et al*., 2012). Therefore, they can be effective against cancers that express specific cell surface antigens. Transmembrane proteins make up a small percentage of the total protein pool, which may limit the antigens that CAR-T cells can recognize, but they have the potential to recognize not only proteins but also glycoproteins and glycolipids (Chandran and Klebanoff, 2019). In contrast, TCR-T cells can recognize MHC-loaded internal antigens of cancer cells. This has the advantage of recognizing types of cancer cells that do not express surface-specific antigens. Antigens recognized by TCR-T cells include tumor associated antigens (TAAs), cancer germline antigens (CGAs), and tumor specific antigens (TSAs) (Shafer *et al*., 2022).

TAAs are antigens expressed on both cancer and normal cells. TAAs are divided into differentiation antigens, which are expressed on cells of the same origin, and overexpressed antigens, which are expressed much more on cancer cells. TAAs are more likely to exhibit on-target off-tumor toxicity because they are also expressed on normal cells. CGAs are antigens whose expression is suppressed in normal cells because they are germline cells but are fully expressed in cancer cells. TSAs are antigens that are expressed only in cancer cells, from genes that are not present in normal cells. Most viral cancers are examples of TSAs, so they are also called viral antigens or neoantigens (Fig. 2). To reduce on-target off-tumor toxicity, current TCR-T cell research is focused on CGAs and TSAs (Ecsedi *et al*., 2021).

TCRs are designed to recognize cancer antigens that are not expressed on the cell surface, which enable TCR-T cell therapy to be used for treatment of all types of cancers. MHC restrictions are one of the defining features of TCR-T cells. Recognizing MHC-loaded antigens may provide greater sensitivity to the antigen, but it is somewhat limited for general use because it requires information about the MHC molecules expressed by the target cancer cell in addition to information about the antigen specific to that cell. TCRs use the signal transduction pathway through the T cell's endogenous CD3 complex to amplify the signal, so it can be activated at low antigen density, potentially providing higher antigen recognition capacity than CAR-T cells (Rudolph *et al*., 2006). In addition, the risk of cytokine release syndrome (CRS) is less than that

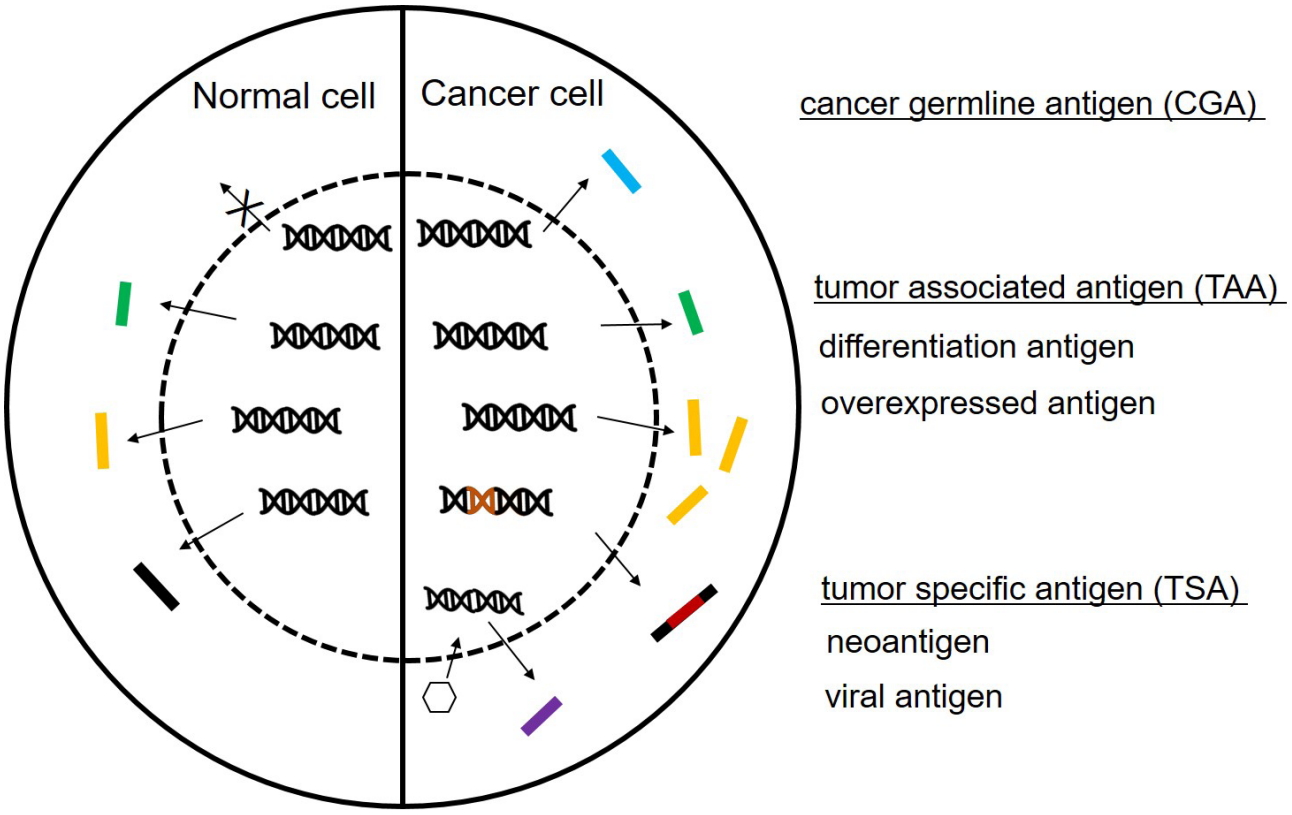

Fig. 2. Antigens recognized by TCR-T cells. Cancer germline antigens (CGAs) are from proteins expressed only in germ cells but their expression is suppressed on normal cells. On the other hand, tumor associated antigens (TAAs) are expressed on normal and cancer cells, which include differentiation antigens and overexpressed antigens. Differentiation antigens are expressed on the cancer cells and are limited to normal cells from the same tissue origin. Overexpressed antigens are highly presented on cancer cells compared to normal cells. Neoantigens and viral antigens are categorized in tumor-specific antigens (TSAs) as both are not exist in normal cells. Neoantigens arise from somatic mutations in cancer cells, and viral antigens are generated from viral oncogenes.

of CAR-T cells due to autoregulation of the TCR-CD3 complex (Sun *et al*., 2021).

APPLICATION OF TCR-T CELL THERAPY

Regarding the clinical use of the receptor-engineered T cell therapy, the major barrier of CAR-T cell therapy is that its treatment is currently limited to certain tumor types such as hematologic malignancies expressing cell surface antigens. To expand the application of CAR-T cell therapy, surface targets from different solid tumors are being explored in both *in vitro* studies and clinical trials (Marofi *et al*., 2021). On the other hand, TCR-T cells, which can recognize intracellular antigens, have broader windows of tumor antigens to be targeted for cancer treatment. Accordingly, repertoire of TCRs specific to tumor antigens are more diverse than CARs. In addition, TCR-based therapy is potentially more effective and safer by recognition of tumor-exclusive neoantigen generated by tumor cell-specific mutation. Structural features of TCR also endow an advantage of using TCR-T therapy. TCRs are comprised of multiple subunits with signaling motifs and possess co-stimulatory receptors, which enables TCR to elicit sensitive T cell response to a single neoantigen peptide-MHC complex.

Regarding target antigens, the ideal tumor antigen for TCR-T therapy should be exclusively present in tumor cells. Although it is tough procedure to select neoantigen and corresponding MHC among diverse peptides, various *in vitro* screenings and prediction methods have been developed. Currently, TCR-T cell therapy has mainly explored tumor-associated antigens (TAAs) that are over-expressed in certain types of cancers and are shared among individuals. For instance, TCR-T cells have developed to recognize peptides from melanoma-associated antigen (MAGE) or New York Esophageal Squamous Cell Carcinoma-1 (NY-ESO-1) that is prevalent in melanoma and non-small cell lung cancer (NSCLC). NY-ESO-1 TCR-T cells have demonstrated anti-cancer efficacy in myeloma, melanoma, and synovial sarcoma (Rapoport *et al*., 2015; Robbins *et al*., 2015; Ramachandran *et al*., 2019). Since an initial clinical study in melanoma in early 2000s, TCR-T cell therapy has been evaluated in various solid tumors such as NSCLC, pancreatic cancer, HPV-associated epithelial cancer, lung cancer, and synovial sarcoma. Number of clinical studies of TCR-T cells targeting various tumor antigens have shown promising results (Table 1). Nonetheless, TCR-T cell clinical studies require careful interpretation regarding the balance between efficacy and toxicity. This is due to the small number of patients recruited for these studies, with most clinical trials being in phase 1 and only a limited number in phase 2 thus far.

Table 1. Clinical studies of the engineered TCR-T cells in solid tumors

Target	HLA Allele	Tumor type	No. Patients	Efficacy (ORR, %)	Phase	Reference
E6	HLA-A*0201	HPV-associated epithelial cancer	12	16.67	I/II	Doran *et al*., 2019
E7	HLA-A*0201	HPV-associated epithelial cancer	12	50	I	Nagarsheth *et al*., 2021
KRAS G12D	HLA-C*0802	Pancreatic cancer	1	-	II	Leidner *et al*., 2022
MAGE-A4	HLA-A*02	Synovial cell sarcoma	16	43.75	I	Hong *et al*., 2023
MAGE-A10	HLA-A*0201 or *0206	Non-small cell lung cancer	11	9.09	I	Blumenschein *et al*., 2022
MART-1	HLA-A*0201	Melanoma	15	13.3	-	Morgan *et al*., 2006
NY-ESO-1	HLA-A*0201	Melanoma	11	45.4	-	Phan and Rosenberg, 2013
NY-ESO-1	HLA-A2	Lung adenocarcinoma	4	25	I	Xia *et al*., 2018
NY-ESO-1	HLA-A*0201	Synovial cell sarcoma	6	66.67	-	Robbins *et al*., 2011
NY-ESO-1	HLA-A*0201 or *0206	Synovial cell sarcoma	42	35.71	I/II	Ramachandran *et al*., 2019

HLA, Human Leukocyte Antigen; ORR, Objective Response Rate; HPV, Human Papilloma Virus; MAGE, Melanoma-Associated Antigen; MART-1, Melanoma Antigen Recognized by T cells-1; NY-ESO-1, New York Esophageal Squamous Cell Carcinoma-1.

Melanoma

Malignant melanoma is suitable cancer for the application of engineered TCR-T cell-based strategies due to its highly immunogenic nature. Melanoma Antigen Recognized by T cells-1 (MART-1) is expressed in up to 80-95% of melanomas, while New York Esophageal Squamous Cell Carcinoma-1 (NY-ESO-1) and Melanoma-Associated Antigen (MAGE)-A3 are present in around 52% and 62% of these cancers, respectively. Given the high frequency of TAAs expression in melanoma, TCR-T cell therapy has been extensively investigated as a potential treatment option for this disease (Yarza *et al*., 2023).

Robbins *et al*. (2011) organized a clinical study involving patients with metastatic melanoma expressing NY-ESO-1. Anti-NY-ESO-1 TCR-modified peripheral blood lymphocytes were used along with high-dose IL-2 after lymphodepletion. In this study, tumor response was observed in 5 out of 11 melanoma patients. Among the 11 patients included in the report, two patients achieved a complete response (CR), while 3 patients showed partial responses (PR) (Phan and Rosenberg, 2013). Clinical trials are currently investigating the effectiveness of TCR-T cell therapy in the treatment of melanoma. Although clinical trials targeting MART-1, NY-ESO-1, and MAGE-A3 have been completed (with clinical trial numbers NCT00910650, NCT01967823, and NCT02111850 respectively), results have yet to be reported. Now a clinical trial is underway (NCT04729543) to examine the potential of TCR-T cells to treat melanoma that express MAGE-C2.

Pancreatic cancer

The majority of pancreatic cancer cases (about 9 out of 10) starts in the exocrine cells that line the ducts in the pancreas. However, pancreatic ductal adenocarcinoma is one of the most lethal cancers in humans and resistant to current immunotherapies, possibly due to the low mutational burden of this cancer. This low mutational burden results in a scarcity of neoantigen-reactive tumor-infiltrating lymphocytes, which further contributes to the resistance. To overcome this challenge, T cells that have been genetically modified to express allogenic TCRs can be utilized in adoptive cell therapy, targeting "hotspot" mutations that are commonly found in pancreatic cancer.

Lately, Leidner *et al*. (2022), conducted a clinical trial (NCT03935893), in which a single infusion of genetically-modified autologous T cells was administered to a patient with metastatic pancreatic cancer that had lung lesions. These T cells have been edited to express two allogenic HLA-C*0802-restricted TCRs targeting mutant KRAS G12D expressed by the tumor. Six months after the T cell infusion, the patient experienced a reduction in metastases that had spread to the lung, with an overall response of 72%, according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Furthermore, they have treated another patient with pancreatic cancer by utilizing autologous T cells that were modified to express the HLA-C*0802-restricted KRAS G12D-reactive TCRs. Nevertheless, the infusion product for this patient was produced with the different *in vitro* growth conditions, and additional immune modulation with tocilizumab was not included in the preconditioning chemotherapy regimen. After the T cell infusion, the patient experienced a grade 3 CRS and a grade 2 immune effector cell-associated neurotoxic event. The radiographic imaging conducted a month after the infusion indicated a slight regression of the patient's lung metastases and stable liver lesions. However, despite of the high levels of T-cell persistence in the blood, the patient showed progressive disease and died six months following the therapy. Taken together, these results offer an optimistic novel cellular immunotherapy strategy for treating pancreatic cancer (Leidner *et al*., 2022).

Currently, clinical trials continue exploring the efficacy of TCR-T cell therapy for pancreatic cancer. Several trials (NCT03136298, NCT03190941, NCT03745326) are underway to examine the potential of TCR-T cells in dealing with pancreatic cancer that expresses either KRAS G12V or KRAS G12D.

Human Papilloma Virus (HPV)-associated epithelial cancer

Several studies have been dedicated to investigate the potential of TCR-T cells targeting the E6 and E7 antigens of HPVs as a therapy for HPV-associated cancer. In HPV-associated cancer cells, E6 and E7 are only viral genes that are consistently maintained and expressed (Hoppe-Seyler *et al*., 2018). In 2018, Jin *et al*. (2018) reported a pre-clinical trial in which they discovered an HPV-16 E7-specific, HLA-A*02:01-restricted TCR-T cell. They extracted this TCR from a biopsy of the uterine cervix of a woman with cervical intraepithelial

neoplasia. When human T cells were transduced with this TCR, they exhibited recognition and destruction of cervical and oropharyngeal cancer cell lines associated with HPV-16. Moreover, the T cells led to regression of HPV-16 cervical cancer tumors in a mouse model. These finding demonstrate the therapeutic potential of TCR-T cell therapy in the treatment of HPV-associated epithelial cancers (Jin *et al*., 2018).

A phase 1 clinical trial (NCT02858310) was conducted for the treatment of HPV-associated epithelial cancer, where T cells were modified to express a TCR targeting the HPV-16 E7 antigen. In this study, 6 out of 12 patients showed tumor regression and objective clinical responses, which included 4 out of 8 patients with anti-PD-1 resistant disease. Besides, some patients experienced significant reduction in size of large tumors and complete disappearance of most tumors (Nagarsheth *et al*., 2021). A phase I/II clinical was also performed to examine efficacy of the HPV-16 E7-specific TCR-T cells in HPV-associated epithelial cancer. Among 12 patients treated with TCR-T cells, two patients in the highest-dose cohort showed objective tumor responses. One patients with three lung metastases had complete regression of one tumor and partial regression of two tumors (Doran *et al*., 2019).

Non-small cell lung cancer

Lung cancer accounts for the highest number of cancer-related deaths globally, and approximately 84% of lung cancer cases are classified as non-small cell lung cancer (NSCLC). In addition, squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma are subtypes of non-small cell lung cancer. There has been some progress in engineered TCR-T cell therapy for NSCLC, and TCR-T cells targeting MAGE-A10 and NY-ESO-1 have demonstrated promise.

According to Schultz-Thater *et al*. (2011), the prevalence of MAGE-A10 protein expression in lung cancers is notably high. It was reported that more than 50% of tumor cells in over 34% of squamous cell carcinoma and 12, 15, and 13% of adenocarcinoma, large, and small cell carcinoma, respectively, express MAGE-A10 protein (Schultz-Thater *et al*., 2011). In 2021, Blumenschein *et al*. (2022) reported a phase I clinical trial where they utilized T cells that express a TCR targeting MAGE-A10 to treat NSCLC. Autologous T cells have been generated to express an affinity enhanced TCR that recognize a complex of HLA-A*0201 or HLA-A*0206 and the GLYDGMEHL peptide derived from MAGE-A10 Cancer/Testis Antigen (CTA). Out of the 11 patients who received treatment, one exhibited a partial response. According to RECIST V.1.1, this patient's tumor was reduced by 25% after the initial infusion. After eight weeks from the second infusion of the TCR-T cells, the patient attained a confirmed partial response compared to the baseline measurement taken before the first infusion (Blumenschein *et al*., 2022). Additionally, a phase I clinical study was conducted to treat lung adenocarcinoma, where TCR-T cells were engineered to recognize the NY-ESO-1:157-165 epitope in the context of HLA-A2. One of the 4 treated patients showed a partial response without any apparent toxicity. Specifically, patient 2 exhibited a partial response that lasted for 4 months post-treatment. In particular, on day 42 after the initial T cell infusion, a CT scan indicated a decrease in the size of the primary lung tumor and liver metastases. To enhance the treatment's effectiveness, the patient was given a second TCR-T cell infusion about a month later. However, when evaluated around two months (on day 138) following the second infusion, the patient's condition had worsened (Xia *et al*., 2018).

Ovarian cancer

Given the understanding that ovarian cancer cells overexpress mesothelin, TCR-T cells have been developed and utilized in preclinical research to specifically target this antigen (Schoutrop *et al*., 2021). In a preclinical study, Anderson *et al*. (2019) assessed the ability of CD8 TCR-T cells targeting mesothelin to infiltrate into tumors and to effectively control tumor growth by using ovarian tumor mouse model. They also examined the efficacy of engineered human CD8 T cells, designed to target mesothelin, in their ability to kill HLA-A2^{+} High Grade Serous Ovarian Cancer (HGSOC) cell lines. These T cells engineered with mesothelin-specific TCRs effectively infiltrated the tumor in mice, but experienced a decline in function over time and were unable to maintain persistence. However, when the mice with advanced-stage disease at the start of treatment were given repeated doses of TCR-T cells, their functional activity was preserved, resulting in significant prolonging of their survival. Human CD8 TCR-T cells, specifically designed to target mesothelin, demonstrated tumoricidal activity against of HGSOC lines (Anderson *et al*., 2019).

Sarcoma

At present, clinical trials are actively assessing the efficacy of TCR-T cell therapy for the management of sarcoma. In particular, the NY-ESO-1 CTA , present in 80% of synovial cell sarcoma patients, represents a promising target for engineered T cell therapy. Robbins *et al*. (2011) conducted a clinical trial to assess the capability of adoptively transferred autologous T cells, transduced with a TCR targeted against NY-ESO-1, in inducing tumor regression among patients with synovial cell sarcoma. In this clinical trial, patients with tumors expressing NY-ESO-1 received autologous TCR-transduced T cells in conjunction with IL-2 following preparative chemotherapy. Objective clinical responses were observed in 4 out of 6 patients with synovial sarcoma. These patients demonstrated partial responses, with one lasting for 18 months. These observations suggest that utilizing TCR-based gene therapies targeting NY-ESO-1 presents a novel and effective therapeutic strategy for individuals diagnosed with synovial cell sarcoma (Robbins *et al*., 2011). Additional clinical study was also carried out, focusing on the immunological mechanisms involved in the response and resistance of patients with synovial sarcoma who were treated with NY-ESO-1 SPEAR T-cells. The NY-ESO-1 SPEAR T-cell is a gene-modified autologous T cell that expresses NY-ESO-1^{C259}, a T-cell receptor with enhanced affinity. This TCR specifically targets the NY-ESO-1 peptide SLLMWITQC, which is restricted to HLA-A*02. Among the 42 patients included in the report, one patient achieved a complete response (CR), while 14 patients showed partial responses (PR). These findings provide the initial evidence of successful infiltration of solid tumors by SPEAR T cells, which possess the ability to eliminate tumor cells (Ramachandran *et al*., 2019). Hong *et al*. (2023) performed a phase 1 clinical trial to evaluate the safety, clinical activity, and translational effects of afami-cel in patients with MAGE-A4-expressing solid tumors, including synovial sarcoma. Afami-cel, also known as amitresgene autoleucel, is a specifically modified autologous T cell that targets the MAGE-A4. As a result, the objective response rate (ORR) was 24% (9/38), with a specific ORR

of 44% (7/16) for synovial sarcoma and 9% (2/22) for other cancer types, encompassing partial responses. The observed ORR of 24% in the overall patient population was primarily attributed to the clinical activity observed in synovial sarcoma. In contrast, responses were limited in non-sarcoma cancers. Despite the limited number of patients with synovial sarcoma, the observed ORR of 44% is superior to the historically low ORR associated with conventional standard-of-care treatments, such as pazopanib and trabectedin, used in post-first-line metastatic setting. These findings suggest that afami-cel could hold promise as therapeutic option for patients with metastatic synovial sarcoma (Hong *et al*., 2023).

Challenges in engineered TCR-based therapies

These promising T cell-based ACTs face several challenges. First, the process of manipulating T cells is expensive and complex. It is also difficult to meet Good manufacturing practice (GMP) standards for mass production and distribution (Shafer *et al*., 2022). Efforts to overcome this challenge include strategies such as changing the existing T cell engineering methods from viral methods such as retroviral vectors to non-viral methods such as RNA electroporation and CRISPR-Cas9 (Zhao *et al*., 2006,Roth *et al*., 2018).

The crucial task is to identify suitable antigens that are specific to cancer cells and possess adequate antigenic density, which determines the effectiveness of CAR-T or TCR-T cell therapies tailored to each type of cancer. To find an effective target antigen, such as CD19 in B cell ALL, which has been approved by the FDA, many trials are underway in several areas to screen for antigens specifically expressed in cancer cells and confirm that they are appropriate targets (Mailankody *et al*., 2022; Majzner *et al*., 2022; Ishihara *et al*., 2023).

It is also important to ensure that the T cells infused into the patient are maintained with sufficient anti-cancer activity. As one way to improve survival/expansion and activity of transferred cells *in vivo*, various CAR-T constructs has been generated to incorporate additional intracellular costimulatory domains. Another way is to manipulate homeostatic cytokines that affect T cell persistence, such as IL-7 and IL-15, to make them last longer (Hoyos *et al*., 2010, Shum *et al*., 2017).

When it comes to fighting solid tumors, the biggest hurdle for infused T cells is the immunosuppressive TME. TME forms around cancer cells to help them grow, including myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and tumor associated macrophages (TAMs), which neutralize immune cells that infiltrate the cancer cells (Ma *et al*., 2019). This is the main reason why TCR-based cell therapies for solid cancers are difficult. The ability to get past these TMEs and reach the cancer cells without being neutralized is required.

CONCLUSIONS

Within a few decades, T cell-based immunotherapy has become a promising therapeutic strategy for treatment of cancer. Moreover, it has been evolved fast to improve the specificity of T cells against tumor antigens. In particular, approaches utilizing a homologous population of T cells bearing tumor antigen-specific receptor, such as TCR-T cells, are currently under intensive exploration. Although TCR-T cell therapy has its intrinsic advantage and limitation, it has presented successful clinical outcomes in several solid tumors. With endeavor to overcome challenges continued, application of TCR-T cell therapy would be extended to various solid cancer indications. Furthermore, advances in identification of patient-specific tumor antigen, engineering of receptor and large scale manufacturing will facilitate the development of innovative personalized T cell therapies.

CONFLICT OF INTEREST

The authors reports no conflicts of interest related to this work.

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