

Advances Of Chimeric Antigen Receptor T Cell Therapy In Ovarian Cancer

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Wenyang Yan¹
Hongmei Hu²
Biao Tang¹ 

¹Department of Gynecology, Wangjiang Hospital, Sichuan University, Chengdu, Sichuan Province, People's Republic of China; ²Department of Gynecology, Sichuan Maternal and Child Health Hospital, Chengdu, Sichuan Province, People's Republic of China

Abstract: Ovarian cancer, as a common gynecological tumor, is currently recognized as the most lethal gynecological malignancy. In addition to conventional treatment methods such as surgery, radiotherapy and chemotherapy, adoptive immunotherapy represented by modified immune cells also shows good curative effects and is becoming an important method in the treatment of ovarian cancer. Studies have shown that most cancer cells can avoid the recognition of the immune system, thus limiting the anticancer effect of immunotherapy. Chimeric antigen receptor T (CAR-T) cell technology has emerged and has good targeting, killing, proliferation and persistence. A large number of clinical trials also have shown that this technology has achieved great success in improving the quality of life and prolonging the survival time of patients with malignant hematological tumors. CAR-T cell technology has become a research hotspot for immunotherapy. This article mainly reviews various CAR-T cell treatments and their specific mechanisms in the field of ovarian cancer treatment to provide new ideas for the treatment of ovarian cancer.

Keywords: immunotherapy, T cell, ovarian cancer, chimeric antigen receptor, tumor antigens

Introduction

Ovarian cancer is one of the most lethal gynecological malignant tumors. In the United States, about 22,530 new ovarian cancer patients are diagnosed each year, resulting in about 13,980 deaths.¹ Patients diagnosed with stage III or IV ovarian cancer have a 5-year survival rate of less than 25%, even after aggressive surgical resection and first-line chemotherapy drugs. Although more than 80% of the patients diagnosed had significant remission in the early stage of treatment, most of them relapsed and eventually developed anti-chemotherapeutic diseases. At the same time, because of the occult onset of ovarian cancer and the nonspecificity of screening tools and clinical manifestations, the early detection rate of ovarian cancer is very low. The fact that patients show obvious symptoms only when the cancer has spread to the pelvic cavity is also one of the reasons for the high mortality rate of ovarian cancer.² The standard treatment for ovarian cancer is surgical operation; where necessary, a combination of platinum- and taxane-based chemotherapy should be used.³ Recent clinical trials have shown that the overall survival rate and quality of life of ovarian cancer patients were not significantly improved after bevacizumab was used as conventional chemotherapy. Therefore, new therapeutic strategies need to be explored urgently.

In recent years, T cell adoptive immunotherapy, as a new strategy in cancer therapy, has been developing rapidly.⁴ Meanwhile, T cell transplantation experiments in ovarian cancer patients have shown that it has significant therapeutic effects.

Correspondence: Biao Tang
Department of Gynecology, Sichuan Maternal and Child Health Hospital, No. 290 Shayan West Second Street, Jinyang Road, Chengdu City, Sichuan Province 610041, People's Republic of China
Tel +86 28 8546 3088
Email 286546430@qq.com

Chimeric antigen receptor T (CAR-T) cell therapy, as a representative of adoptive T cell immunotherapy, plays an important role in cancer treatment and is currently the focus of researchers. CAR-T cell immunotherapy mainly uses gene-editing technology to modify the patient's autologous T cells to express chimeric antigen receptors and then mediates the direct killing of cancer cells by cytotoxic T cells.⁵ Previous studies have confirmed that CAR-T cell therapy has a significant effect on a variety of solid tumors and hematological malignancies,^{6,7} and early results in ovarian cancer have also shown a good effect; however, it is undeniable that this therapy also has certain toxic and side effects.^{6,7} In this review, we will review the molecular biological basis, antigen modification targets, preparation and clinical application of CAR-T cell therapy in ovarian cancer.

Current Status Of Ovarian Cancer

Globally, ovarian cancer is one of the most common gynecological malignancies, accounting for the seventh leading cause of death in women. Currently, the initial treatment for ovarian cancer patients can be divided into three stages: surgical treatment to remove the tumor as much as possible, first-line platinum-based adjuvant chemotherapy after surgery to eliminate incomplete microsurgery, and second-line drug maintenance therapy to delay the progress and recurrence of tumors as much as possible.^{8,9} Early stage ovarian cancer is difficult to diagnose due to the lack of clinical symptoms, and patients do not have the awareness of the need for regular physical examination so diagnosis often occurs at an advanced tumor stage. However, advanced ovarian cancer relies on traditional treatment methods with low curative effects and high recurrence rates, which can easily cause serious toxic and side effects, such as gastrointestinal reactions, hematopoietic suppression or impaired liver and kidney functions. Overall, the current treatment for ovarian cancer patients is not ideal.

Currently, the treatment methods for advanced ovarian cancer mainly include operation, radiotherapy and chemotherapy, but these methods cannot effectively control the recurrence and progression of cancer, so it is urgent to find new, safe and effective treatment methods.^{10,11}

Effect Of Ovarian Cancer On The Host Immune System

The destruction of patients' immune systems by tumors is a multistep cooperative process. Intervention or regulation

of key target molecules can trigger the rejection reaction of patients' immune systems to tumors. A meta-analysis of 1815 ovarian cancer patients in 10 independent studies showed that the lack of lymphocyte infiltration was significantly associated with poor prognosis of cancer.¹² According to the study,¹³ stimulating the host to initiate the immune response against tumors requires the following points: 1) a sufficient amount of effector T cells must be produced in the body to effectively recognize tumor antigens; 2) these cells can identify, present and infiltrate tumor tissue; 3) they can overcome the inhibition of the tumor microenvironment on the immune network; 4) they can directly identify tumor antigens and kill tumor cells; and 5) they can maintain the activity of antitumor T cells for a long time.¹⁴

Application Of Chimeric Antigen Receptor-Modified T Cell Therapy In Tumor

Despite the rapid development of medical research and the emergence of new technologies, the treatment of cancer remains a significant problem. Conventional therapies such as surgery, radiotherapy and chemotherapy can show some short-term efficacy, but they are usually accompanied by severe toxicity and side effects.¹⁵ In addition, several years of clinical epidemiological studies have shown that although these measures can increase the rate of remission of the tumor, in the long term, they have not significantly prolonged the survival of the cancer patient. Approximately 30–80% of cancer patients will inevitably experience recurrence in the later period of treatment and even have problems of tolerance to various chemotherapeutic drugs or radiotoxicity, which makes it difficult to treat cancer.^{16,17}

Adoptive immunocyte therapy has become the main tumor treatment method except for surgery, radiotherapy and chemotherapy, mainly including tumor infiltrating lymphocytes (TILs), T cell receptor (TCR) modified -T cells (TCR-T) and CAR-T. CAR-T cell therapy, as a representative means of tumor cell therapy, has the advantages of high specificity, not being limited by MHC,¹⁸ long-term efficacy after infusion, and good prognosis of patients. At present, CAR-T cells have been shown to have a good therapeutic effect on hematologic cancer^{19,20} and is expected to become a key approach for humans to conquer malignant tumors.^{21,22} CAR-T cells are a combination of single-chain variable fragment (scFv) that recognize

tumor-associated antigens and activation motifs of T cells. They are created by gene transduction and have the ability to specifically recognize and kill tumor cells.²³ The design principle of CAR-T cells is to select high affinity antibodies against tumor-specific antigens, fuse the coding sequence of the heavy chain and light chain variable region with the CD8 transmembrane region or immunoglobulin transmembrane sequence (Figure 1), a T cell activator molecule (such as CD28 or 4-1BB), and the intracellular domain of the T cell receptor complex (such as CD3) coding sequence, and construct a chimeric antigen receptor molecule, and then transfect it into T cells cultured in vitro. In recent years, the treatment of malignant hematological tumors represented by CD19-CAR-T has achieved good results,¹³ especially the second generation of CART-19 targeting CD19 antigen, which has shown unprecedented clinical efficacy in recurrent and refractory acute lymphoblastic leukemia, chronic lymphoblastic leukemia and Hodgkin's lymphoma.²⁴⁻²⁷ The results of early clinical trials of CAR-T cell therapy for cancer make it attractive to apply. In 2013, Science listed adoptive cellular immune therapy (ACT) as one of the major medical progresses of the year. On July 1, 2014, CD19-CAR-T cell therapy, namely, CTL019, designed by

the University of Pennsylvania, obtained the breakthrough designation of FDA in the United States.²⁸ In 2017, CTL019 (Novartis) and KTE-C19 (Kite Pharma) for recurrent or refractory acute lymphoblastic leukemia in children and young adults and KTE-C19 for non-Hodgkin's lymphoma were put into clinical use.^{29,30} Although the curative effect of CAR-T cell therapy on solid tumors is poor compared with that in blood tumors, previous studies have confirmed that CAR-T cell therapy also shows good curative effects in the treatment of ovarian cancer. This paper mainly summarizes the specific preparation methods of CAR-T cell therapy in ovarian cancer and discusses the clinical application and treatment prospects of CAR-T cell therapy in ovarian cancer.

Preparation Of Chimeric Antigen Receptors

The preparation process of CAR-T cells is summarized as the following four steps: 1) Separation: collection of mononuclear cells from the patient's peripheral blood by leukocyte separation;³¹ 2) Modification: using CD3/CD28 magnetic beads to activate T cells, and then high affinity CARs of specific tumor antigens are transduced into activated T cells so that activated T cells can stably express

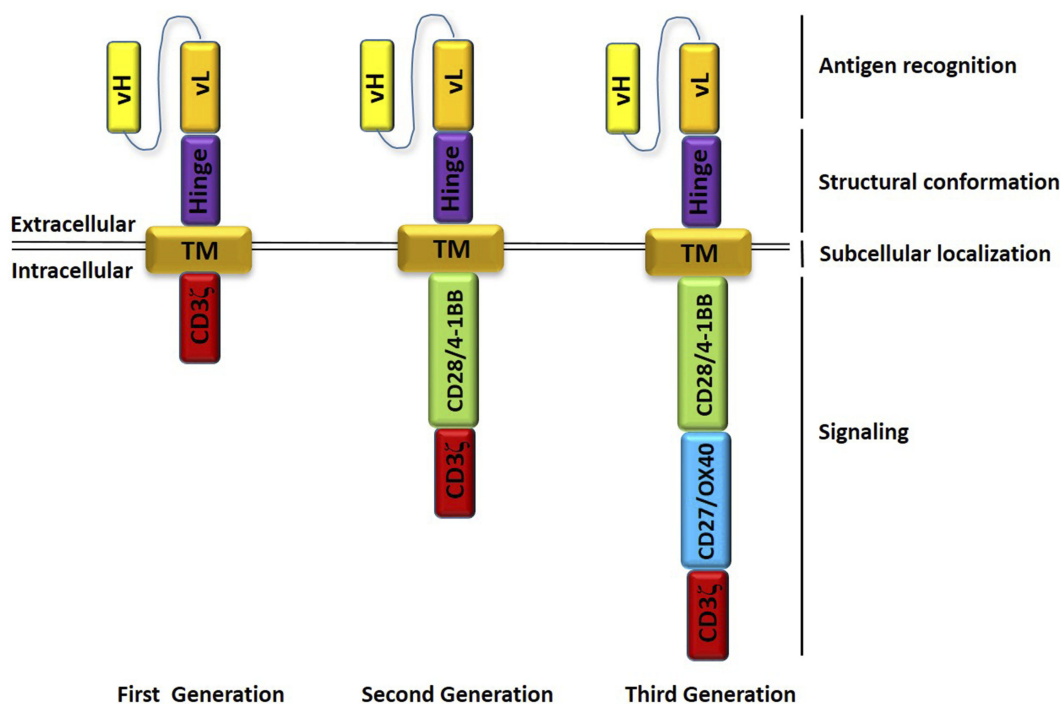


Figure 1 Chimeric antigen receptors (CARs) design. Antigen recognition domain derived from single chain variable fragment; Hinge domain; Transmembrane domain (TM) providing anchorage to plasma membrane; signaling domains responsible of T-cell activation. First generation of CARs contain a CD3 ζ -derived signaling module. Second generation of CARs contain also a costimulatory domain (CD28/4-1BB). Third generation of CARs contain two costimulatory domains (CD28/4-1BB and CD27/OX40).

CARs that can specifically recognize tumor antigens;³¹ 3) Amplification: expansion of modified T cells in vitro to achieve the desired number; and 4) Retransfusion: the expanded CAR-T cells are transfused back to the pre-treated patients to observe their proliferation and ability to kill cancer cells, as well as possible toxic and side effects such as tumor lysis reaction and cytokine storm and to comprehensively evaluate their therapeutic effect on cancer.

Antigen Targets

The surface antigens targeted by CARs are mainly proteins and glycolipids.³² In CAR-T cell therapy for ovarian cancer, the most common target antigens include MUC16, mesothelin, HER2 and FR α (folate receptor-alpha).

MUC16

MUC16 is usually expressed in the cornea, respiratory tract and reproductive epithelium, mainly to protect the epithelium from external pathogen invasion.³³ Once the expression of MUC16 is abnormally increased, it helps cancer cells in the affected tissue escape the body's immune surveillance.³⁴ Overexpression of MUC16 was always found in ovarian, pancreatic, cervical and lung cancer.^{35,36} More than 80% of ovarian cancer is characterized by overexpression of MUC16, and the high expression of MUC16 and CA-125 is an important indicator for the early diagnosis of ovarian cancer.³⁷

Studies have shown that MUC16-CAR-T cells have specific killing effects on MUC16+ ovarian cancer cells in vitro. Intravenous or intraperitoneal injection of MUC16-CAR-T cells can delay the progression of ovarian cancer or completely clarify the tumors in mouse tumor-bearing models.³⁸ These studies also confirmed the research value of MUC16 as a potential target for the treatment of a class of ovarian cancer cells.

Mesothelin

Mesothelin, a group of glycoproteins anchored on the plasma membrane through the phosphatidylinositol region (GPI),³⁹ is normally expressed in pleura, peritoneum, pericardium and mesothelial cells. Mesothelin is highly expressed in 30% of tumors, such as pancreatic cancer, ovarian cancer, mesothelioma, lung adenocarcinoma, cholangiocarcinoma, gastric cancer, colon cancer and endometrial cancer. Because mesothelin is often expressed on the surface of human normal tissues and its nonspecific toxicity is lower,^{40,41} researchers have designed a variety

of therapeutic methods targeting mesothelin antigens, such as antitoxins, antibody-based therapy, cancer vaccines and adoptive T cell therapy. Preclinical and clinical experiments have shown good antitumor effects, thus showing that mesothelin is a potential target.⁴²

Studies have shown that mesothelin is a promising and potential specific target in immunotherapy. Encouraging results have been achieved in the experimental phase of mesothelin-based CAR-T cell research, and clinical trials have been approved for a variety of tumors. Preclinical studies of mesothelin-based CAR-T cells in subcutaneous or in situ mouse models of mesothelioma, ovarian cancer and lung cancer transplantation were also carried out.^{40,41,43-45} Recently, a second-generation mesothelin-based CAR-T cell (SS1-4-BBCAR) clinical trial at the University of Pennsylvania was carried out. Four patients with pancreatic cancer and mesothelioma did not observe serious adverse reactions, such as cytokine release syndrome,⁴⁶ pleurisy and pericarditis. These trials all showed that mesothelin is a safe and feasible target for treatment by CAR-T cells.⁴¹

HER2

Human epidermal growth factor receptor 2 (HER2/neu), also known as HER2 or ERBB2, is a proto-oncogene and plays an important role in the pathogenesis and clinical process of various tumors. In vitro and animal experiments have clearly shown that gene amplification and protein overexpression of HER2/neu play a key role in tumorigenic transformation and development of tumors.⁴⁷ Subsequent studies have shown that HER2/neu gene amplification and overexpression are associated with other tumors, such as ovarian cancer,⁴⁸ gastric cancer,⁴⁹ colorectal cancer,⁵⁰ salivary adenocarcinoma⁵¹ and non-small-cell lung cancer,⁵² while protein expression in normal tissues is negative or very low. Overexpressed HER2/neu proteins make tumors more aggressive and are independent risk factors for poor prognosis in these cancer patients.⁵³ Research on monoclonal antibodies targeting HER2 is increasing, and the development and application of trastuzumab (Herceptin) also shows a trend of transition from traditional nonspecific chemotherapy to molecular targeting in cancer therapy. However, trastuzumab is expensive and may cause side effects, including cardiotoxicity and corneal ulcers, so its clinical application is limited. At present, HER2-specific CAR-T cell therapy has shown good therapeutic potential in the preclinical stage. However, HER2-CAR-T cell treatment in ovarian cancer is still in the clinical experimental stage.

Folate Receptor- α (FR α)

Folate receptor- α , as a carbonyl phosphatidylinositol anchoring protein, is highly expressed in epithelial tumors but lowly expressed in normal tissues.⁵⁴ Studies have shown that in ovarian cancer, the overexpression of FR α is significantly correlated with tumor malignancy and prognosis.⁵⁵ Therefore, FR α is also a potential target for CAR-T cell therapy of ovarian cancer.

At present, it has been reported that FR α showed good antitumor effects in *in vitro* experiments, but due to the limited homing efficiency of CAR-T cells entering the tumor, the question of how to direct them to provide a good therapeutic effect in clinical trials still needs to be further explored. Kershaw, et al⁵⁶ first reported the application of CAR-T cells in FR α ovarian cancer, but no remission manifestations, such as tumor load reduction, were observed in this study. The results showed that a large number of CAR-T cells could be detected in the peripheral circulation of patients 2 days after infusion, followed by a sharp decrease in CAR-T cells, and almost no CAR-T cells could be detected 1 month after infusion. It was concluded that although a high dose of FR α -CAR-T cells is safe, its short life time in the human body and its inability to amplify are the main reasons for the failure of the clinical trial.⁵⁶ Song, et al studied the coupling of the FR α -specific site scFv (MOv19) with the T cell receptor CD3 ζ chain signaling module alone (MOv19- ζ) or in combination with the CD137 (4-1BB) costimulatory motif in tandem (MOv19-BB ζ).⁷ In the coculture process of FR α (+) ovarian cancer cells, MOv19- ζ and MOv19-BB ζ can increase the secretion of various inflammatory factors, such as IFN- γ , IL-2, TNF- α and IL-4.⁷ In addition, in animal models of FR α (+) intraperitoneal, subcutaneous, and lung metastases, MOv19-BB ζ CAR-T cells also demonstrated good therapeutic effects. Modified CAR-T cells can not only proliferate steadily *in vivo* but also accumulate specifically in tumor tissues to enhance the antitumor effect.

Limitations Of CAR-T Cell Therapy

Although CAR-T cell therapy has shown good therapeutic potential in hematological tumors, it still needs to be further optimized in solid tumors for the following reasons: 1) off-target effects; 2) complex composition of tumor tissues and lack of ideal target antigens; 3) immunosuppressive effects of tumor microenvironment;¹¹ 4) efficiency of CAR-T cells reaching the tumor site is

difficult to guarantee; and 5) cytokine release syndrome induction.

To overcome the off-target effects, researchers constructed double-targeted CAR-T cells. Two different kinds of CAR were modified on T cells to recognize different tumor surface antigen targets, one of which was responsible for the transmission of killing signals and the other for the transmission of costimulatory signals. Only when two different kinds of CAR bind to the corresponding target on the surface of the tumor at the same time can CAR-T cells be fully activated and produce effective anti-tumor effects.⁵⁷ A double-targeted strategy can not only avoid the off-target effects of CAR-T cell therapy but also overcome immune escape and enhance anticancer activity.

Different tumors have various tumor microenvironment (TME), which can be divided into two categories: hot tumors and cold tumors. "Hot tumors" (inflamed) are associated with better prognosis and response to antitumor immunotherapy than "cold tumors" (noninflamed). Because of the immunosuppressive cells in the tumor microenvironment (TME), including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), the anti-tumor immune function of ovarian cancer patients is greatly attenuated.⁵⁸ Thus, patients have the poorest outcomes after receiving immunotherapy. This may be limitations of CAR-T cell therapy in ovarian cancer, but it can be hope to reprogramming tumor from an immunologically cold, or T cell excluded, to an inflamed tumor.⁵⁹

The occurrence of cytokine release syndrome is mainly due to the overactivation of CAR-T cells and lack of effective control, which means that the regulation of CAR-T cells is particularly important. Currently, there are two main methods: 1) introduce suicide genes to modify T cells to remove overactivated T cells to achieve a balance between CAR-T cell therapy toxicity and antitumor activity. Recently, researchers have developed suicide gene systems for CAR-T cells, such as HSV-TK, iCasp9 and CD20, to control adverse reactions caused by CAR-T cells in treatment.⁶⁰ 2) Construction of CAR-T cells carrying negative regulatory receptors, which can reduce the activity of overactivated T cells when recognizing the corresponding ligands on the surface of tumors. Wu et al divided CAR-T cells into two parts: the extracellular antigen binding domain (scFv) and the intracellular signal region (ITAM), the receptors of which can reversibly bind small molecular particles such as kanamycin.⁶¹ The activation of T cells requires the binding of tumor surface antigens and

small molecule particles to the corresponding receptors so that the activation time and intensity of CAR-T cells can be regulated by increasing or decreasing the concentration of molecule particles without affecting the anticancer activity.

Conclusion

CAR-T cell therapy has made a breakthrough in the treatment of hematologic tumors, which has great potential value in the field of tumor research. However, the treatment of solid tumors is not mature enough to achieve the desired results. To enhance the anticancer activity of CAR-T cells and avoid the related toxicity of treatment, it has become a research hotspot in this field to find suitable tumor surface antigens, overcome the microenvironment of tumor immunosuppression, optimize the combination of costimulatory molecules, construct the fourth generation of CAR, design suicide genes, and reduce adverse reactions after reinfusion.

Abbreviations

CAR-T, Chimeric antigen receptor T; TILs, tumor infiltrating lymphocytes; scFv, single-chain variable fragment; ACT, adoptive cellular immune therapy; FR α , folate receptor-alpha; HER2, human epidermal growth factor receptor 2; TAAs, tumor-associated antigens.

Disclosure

The authors report no conflicts of interest in this work.

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