REVIEW ARTICLE

Potential Antigen Targets of CAR T-cell Therapy in Gastric Cancer

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ABSTRACT

Gastric cancer, or stomach cancer, is one of the most common and deadliest forms of cancer, killing approximately 770,000 people in the world annually. The efficacies of traditional cancer therapies, such as surgical treatment, radiation therapy and chemotherapy, are limited: however, chimeric antigen receptor (CAR) T-cell immunotherapy was recently developed as a groundbreaking approach to cancer treatment, genetically modifying a patient's own T cells to express a CAR on the T cell surface in order to recognize specific tumor-associated antigens present on cancer cells. Significant efforts have been made to develop CAR T-cell therapies to treat solid tumors including gastric cancer in recent years. In this review, we summarize recent progress on CAR T-cell therapies for gastric cancer and focus on the most important targets for CAR T-cell immunotherapy in the context of gastric cancer. Finally, we discuss future directions of CAR T-cell therapies for gastric cancer. (*Int J Biomed Sci* 2023; 19 (3): 66-72)

Keywords: Gastric cancer; CAR T; Immunotherapy; Antigens; Cell therapy

INTRODUCTION

Despite a persistent decrease in the incident rate of gastric cancer (also known as stomach cancer) in past decades, gastric cancer is still the fifth most prevalent and the fourth leading cause of cancer deaths worldwide according to data from GLOBOCAN 2020, an online database produced by the International Agency for Research on Cancer (1). In 2020 alone, about 1.1 million new cases of gastric cancer were diagnosed, and approximately 770,000 patients died from gastric cancer worldwide. The incidence and mortality of gastric cancer are the highest in eastern Asia, with about 48.6% of all deaths reported from China (2). The main risk factors of gastric cancer are infection by the bacterium *H. pylori*, smoking, and alcohol consumption.

Depending on the cancer stages and the patient's health conditions, several therapeutic approaches are routinely used to treat gastric cancer. For early-stage gastric cancer, surgery is often the preferred treatment, while radiation or chemotherapy are used as a primary treatment for advanced gastric cancer. In addition, the FDA has approved several targeted therapeutic drugs including Trastuzumab to treat gastric cancer patients with human epidermal

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growth factor receptor 2 (HER2) protein overexpression and Ramucirumab to inhibit angiogenesis and reduce blood supply to the tumor by targeting the vascular endothelial growth factor (VEGF) receptor. Despite all these treatment options, the 5-year survival rate for advanced gastric cancer is still low and there is a significant unmet clinical requirement for gastric cancer patients.

Recently, immunotherapy has been emerging as a promising new type of treatment to advanced gastric cancer by taking advantage of the patient's own immune system to fight cancer. Under normal circumstances, the body's immune system detects and destroys cancer cells to prevent cancer growth. However, cancer cells could escape from immune surveillance through several strategies; for instance, some cancer cells might change their surface markers via genetic mutations to become less visible to the host immune system or gain additional immunosuppressive properties to evade the immune system (3). Immunotherapy boosts the ability of the host's immune system to identify and destroy cancer cells more effectively, and two main types of the immunotherapy are immune checkpoint inhibitors and chimeric antigen receptor T (CAR T) cell therapy.

Immune checkpoint inhibitors are drugs that block the immune checkpoints (such as PD-1 or CTLA-4) present on immune cells like T cells, allowing the immune system to recognize and attack cancer cells effectively (3). For details of immune checkpoint inhibitor-based immunotherapy for gastric cancer, readers may refer to previously published articles (4-6).

In contrast, CAR T-cell therapy involves engineering a patient's own T cells to express a specific CAR which can recognize and target a specific antigen on the surface of cancer cells when the engineered CAR T-cells are infused into the patient (Figure 1). CAR T-cell therapy has shown remarkable success in treating certain types of blood cancers, such as leukemia and lymphoma (7). In recent years, tremendous progress has been made in the study of CAR T -cell immunotherapy for the treatment of gastric cancer. In this article, we review CAR T-cell therapy clinical history, its recent advances and future direction of CAR T-cell therapy for the treatment of advanced gastric cancer.

CLINICAL APPLICATION OF CAR T-CELL THERAPY

Although the concept of CAR T-cells for cancer treatment can be traced back to 1989 (8), no clinical trial results of CAR T-cell immunotherapy to treat cancer had been reported till 2011. The initial clinical trial of CAR-T cells targeting CD19, an antigen expressed on B cells, showed remarkable efficacy in a patient with refractory chronic lymphocytic leukemia (CLL), who had been in remission for 10 months following treatment at the time of publication (9). Following this success, more CAR T-cell clinical trials have been conducted: the FDA has approved four CAR T-cell therapies so far to treat specific types of lymphomas and leukemias by targeting antigen CD19, and two CAR T-cell therapies to treat multiple myeloma by targeting B-cell maturation antigen (BCMA) (Table 1) (10). Studies have shown that CD19-targeting CAR T-cell therapy generated complete response rates of 40–54%, 67%, 69–74% and 71–81% in patients with relapsed and/or refractory B cell lymphomas (11, 12), mantle cell lymphoma (13), indolent B non-Hodgkin lymphoma (14), and B cell acute lymphoblastic leukemia (15, 16), respectively. In addition, BCMA-targeting CAR T-cell therapies have shown 73–98% overall response rates in patients with relapsed and/or refractory multiple myeloma (14, 17, 18). At present, CAR T-cell therapy is a standard treatment for patients with refractory or relapsed hematological cancers including B-cell acute lymphoblastic leukemia, large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and multiple myeloma.

In contrast to hematological cancers, clinical application of CAR T-cell therapy for solid cancer including gastric cancer has been hampered by several factors such as appropriate tumor antigen selection, the complex immu-

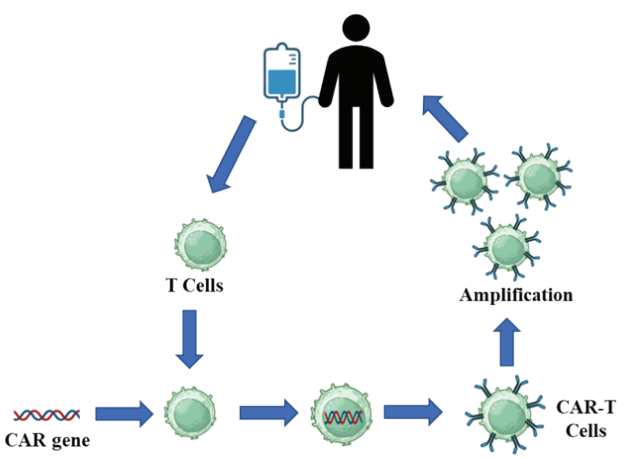

Figure 1. Mechanism of the Car T-cell Therapy. Patient's T cells are collected and are transduced with a CAR gene. The engineered Car-T cells are then amplified and infused into the patient to recognize and kill malignant cells.

nosuppressive tumor microenvironment, and the limited persistence of the CAR-T cells (19). Nevertheless, many innovative strategies have been developed to improve CAR T-cell efficacy for solid tumors including gastric cancer in recent years.

THERAPEUTIC TARGETS IN GASTRIC CANCER

Choosing the right antigen to target is essential to the success of CAR T-cell therapy for gastric cancer, and the ideal antigen should be specific to cancer cells to minimize side effects against healthy cells. To date, several potential antigens have been investigated in CAR T-cell therapy for advanced gastric cancer, including human epidermal growth factor receptor 2 (HER2), mucin 1 (MUC1), carcinoembryonic antigen (CEA), epithelial cell adhesion molecule (EpCAM), the second isoform of claudine 18 protein (CLDN 18.2), mesothelin (MSLN), natural killer group 2 member D (NKG2D), and folate receptor 1 (FOLR1).

HER2

The membrane tyrosine kinase HER2 (also known as ErbB2) is a member of the epidermal growth factor receptor (EGFR) family (20). Members of the HER family act as signal transducers within the cell that regulate cell growth, survival, proliferation, and differentiation (20). HER2 is overexpressed in multiple types of cancer including breast cancer, colorectal cancer, ovarian cancer, and about 4-53% of gastric and gastroesophageal cancers (20-25). Trastuzumab is an antibody approved by the FDA in 2010 to treat HER2-positive metastatic gastric cancer: however, many gastric cancer patients with overexpressed HER2 tumors develop resistance to Trastuzumab (26, 27). To overcome Trastuzumab resistance, the second HER-2 targeted antibody, Pertuzumab, was developed. Though Pertuzumab has shown significant improvement to treat the patients with advanced HER2 positive breast cancer, clinical trials of Pertuzumab in combination with Trastuzumab and chemotherapy did not display significant improvement in

Table 1. FDA-Approved Car-T Therapies for Gastric Cancer Treatment

Target Antigen	Study Phase	Status	Study Organization	Clinical Trials Number
HER2	I	Recruiting	Baylor College of Medicine, USA	NCT03740256
HER2	I	Recruiting	Shanghai PerHum Therapeutics Co., Ltd., China	NCT04511871
MUC1	II	Unknown	PersonGen BioTherapeutics, Suzhou, China	NCT02617134
MUC1	I	Recruiting	Poseida Therapeutics, USA	NCT05239143
CEA	I	Recruiting	Chongqing Precision Biotech Co., Ltd, China	NCT05415475
CEA	I	Recruiting	Weijia Fang, MD, Zhejiang University, China	NCT05396300
CEA	II	Recruiting	Chongqing Precision Biotech Co., Ltd, China	NCT04348643
CEA	I	Completed	Roger Williams Medical Center, USA	NCT02850536
CEA	I	Completed	Roger Williams Medical Center, USA	NCT02416466
CEA	I	Recruiting	Beijing Immunochina Medical Science & Technology Co., Ltd., China	NCT05275062
CEA	I	Unknown	Southwest Hospital, China	NCT02349724
EpCAM	I	Unknown	Jian-Kun Hu, West China Hospital, China	NCT03563326
EpCAM	II	Unknown	Sinobioway Cell Therapy Co., Ltd., China	NCT02725125
EpCAM	I	Recruiting	Wei Wang, Sichuan University, China	NCT02915445
EpCAM	I	Recruiting	Weijia Fang, MD, Zhejiang University, China	NCT05028933
EpCAM	I/II	Unknown	First Affiliated Hospital of Chengdu Medical College, China	NCT03013712
CLDN	I	Recruiting	Shanghai Longyao Biotechnology Inc., Ltd., China	NCT04977193
MSLN	II	Unknown	Shenzhen BinDeBio Ltd., China	NCT03941626
NKG2D	I	Unknown	CytoMed Therapeutics Pte Ltd., Singapore	NCT04107142

the treatment of HER2 positive gastric cancer patients compared to the placebo (28). In contrast, CAR T-cell therapies targeting HER2 could be a promising alternative therapy to treat gastric cancer. Preclinical studies have shown that HER2-targeting CAR-T cells can effectively recognize and eliminate HER2-positive gastric cancer cells *in vitro* and *in vivo* animal models (29-32). Two Phase 1 clinical trials of CAR T-cell therapies targeting HER2-positive solid tumors including gastric cancer are ongoing, one conducted at Baylor St. Luke's Medical Center, Texas, United States (NCT03740256) and the other at Zhongshan Hospital Affiliated to Fudan University Shanghai, Shanghai, China (CCT303-406) (Table 1).

MUC1

MUC1 is a transmembrane protein belonging to the mucin family (33). It has a heavily glycosylated extracellular domain, protecting the underlying epithelia from desiccation, pH changes, pollutants, and microbes (34). The overexpression of MUC1 can increase drug resistance during cancer therapy by reducing intracellular drug uptake. It's also involved in intracellular signaling pathways that increase rates of metastasis and the invasiveness of cancers (33). MUC1 is overexpressed in several types of cancer, making it a potential target for CAR T-cell therapy. Several studies have shown that CAR-T cells targeting MUC1 resulted in cancer regression.

Preclinical studies have demonstrated the feasibility and potential effectiveness of CAR T-cell therapy for MUC1-positive solid tumors by showing that MUC1-targeting CAR-T cells can recognize and eliminate MUC1-expressing cancer cells both *in vitro* and *in vivo* (35-37). Two clinical trials of CAR T-cell therapy targeting MUC1 for gastric cancer have been initiated. One was conducted by PersonGen BioTherapeutics (Suzhou) Co., Ltd in China without any reported result (NCT02617134), and the other trial is currently actively recruiting patients in four locations in the United States (NCT05239143) (Table 1).

CEA

Carcinoembryonic antigen (CEA) is a glycoprotein, and its overexpression is associated with certain types of cancer including colorectal cancer, lung cancer, pancreatic cancer and gastric cancer (38, 39). CAR T-cell therapy has been studied as a potential treatment targeting CEA-positive cancer cells in preclinical studies. Zhang et. al reported a CAR T-cell therapy targeting CEA displaying both safety and efficacy in 10 patients with colorectal cancer (38). Seven of the treated patients with progressive cancer in the previous treatments were stable after CAR T-cell therapy (40). Currently, there are five clinical trials ongoing in China of CAR T-cell therapy for CEA-positive solid tumors including gastric cancer, and two recently completed clinical trials in the United States without published results (Table 1).

EpCAM

EpCAM, also known as CD326, is a protein that is overexpressed in many types of cancer including gastric cancer while displaying limited expression on healthy tissues (41). It plays an important role in gastric tumorigenesis and metastasis and has become a promising target for CAR T-cell therapy (42). Zhang *et al* reported that EpCAM CAR-T cells effectively elicited lytic cytotoxicity to target cancer cells in vitro, and significantly delayed the growth and formation of colorectal tumors in mouse xenograft models without systemic toxicity (43). This study demonstrated the antitumor efficacy and safety of EpCAM CAR-T cells against solid tumors in preclinical studies, supporting clinical trials of EpCAM CAR T-cell therapy for solid tumors including gastric cancer. Sinobioway Cell Therapy Co., Ltd in China initiated a multicenter clinical trial to treat patients with relapsed or refractory gastric cancer with the EpCAM-targeted CAR-T cells, and no data of this study has been reported yet (NCT02725125). To date, an additional four clinical trials of EpCAM-targeted CAR T-cell therapy for gastric cancer are underway (Table 1).

CLDN 18.2

CLDN 18.2 is expressed on the plasma membrane of differentiated epithelial cells of gastric mucosa under normal conditions. Recent studies have shown that CLDN 18.2 is frequently overexpressed during the occurrence and growth of a variety of primary malignant tumors, including bronchial cancer, non-small-cell cancer of the lungs, cancer of the breast, colon, cancer of the liver, and gastric cancer. 70% of primary gastric adenocarcinomas and their metastases express CLDN 18.2 (44). In 2019, Jiang *et al* developed CLDN18.2-specific CAR-T cells which persisted well in vivo and infiltrated efficiently into tumor tissues (45). The CLDN18.2-specific CAR-T cells potently suppressed gastric tumor growth in a mouse xenograft model, and partially or completely eliminated CLDN18.2-positive gastric cancer in the patient-derived tumor xenograft mouse model (45). Therefore, CLDN18.2-specific CAR-T cells could be a promising treatment strategy for gastric cancer and other CLDN18.2-positive tumors. CAR T-cell therapies target-

ing CLDN 18.2 in the treatment of gastric cancer are now undergoing clinical trials. The application of CT041, a type of anti-CLDN18.2 CAR-T cell, has recently received FDA authorization, and an objective response rate of 33% was found in phase I clinical trials (46).

Another phase I clinical trial has recently been started in Jiangsu, China to assess the safety and effectiveness of LY011 Cell Injection (Targeting CLDN 18.2 Chimeric Antigen Receptor T Cells) in the treatment of advanced gastric cancer (NCT04977193) (Table 1).

MSLN

Mesothelin (MSLN) is a cell surface protein overexpressed in some types of cancer including gastric cancer, mesothelioma, non-small cell lung cancer, pancreatic cancer and ovarian cancer, but has a highly restricted expression in normal adult tissues, thus serving as an excellent target for CAR T-cell therapy (47).

In a preclinical study, Zhang showed that MSLN-CAR-T cells could specifically kill MSLN-positive cancer cells and release cytokines in vitro and decreased the growth of MSLN-positive tumors in multiple mouse xenograft models of ovarian, breast, and colorectal cancer and gastric cancer (48). Moreover, Molloy *et al* demonstrated that MSLN-CAR-T cells can recognize and induce MSLN-expressing tumor cell lysis in vitro, and they are well tolerated in monkeys (49). Phase I clinical trials in patients with MSLN-expressing malignancies including gastric cancer are ongoing (NCT03872206 and NCT03941626) (Table 1).

NKG2D

Natural Killer group 2 member D (NKG2D) is a C-type lectin-like activating receptor expressed on the surface of natural killer cells and some T cells, recognizing and binding to specific ligands expressed on the surface of target cells such as MHC class I chain-related molecules (50,51). Although NKG2D ligands (NKG2DLs) are uncommon on the surface of normal cells, they are overexpressed in response to stressors such as infection or transformation (49-51). The expression of NKG2D can also be increased by chemotherapy and radiation, making it a suitable target for CAR T-cell immunotherapy (52). In a preclinical study, Weiss et. al showed that radiation, the typical course of treatment for glioblastoma, increased the concentration of NKG2D ligands; and, NKG2D CAR T-cell therapy achieved undetectable glioblastoma mass in MRI scans of mouse xenograft models (50). The status of a phase I clinical trial of NKG2D-CAR T-cell therapy has been reported (NCT04107142).

FOLR1

FOLR1, also known as folate receptor α, is a glycosylphosphatidylinositol-related protein that plays a critical role in cellular uptake of folate in the body. Its expression is low in healthy cells, but very high in many cancers including ovarian, breast, colorectal, kidney, lung, and gastric cancer (53, 54). In addition, FOLR1 is involved in cancer cell proliferation and cellular signaling of oncogenesis. These features make FOLR1 a good target for CAR T-cell therapy. Kim *et al* demonstrated that FOLR1 targeted CAR-T cells recognized FOLR1-positive gastric cancer cells and induced secretion of various cytokines and caused cancer cell death (55). Although currently no clinical studies of the FOLR1 targeted CAR-T cells in gastric cancer have been reported, FOLR1-targeting CAR-T cells in ovarian cancer patients have been tested, with results showing great efficacy and safety in the treatment of ovarian cancer.

DISCUSSION & CONCLUSION

Six CAR T-cell treatments for the treatment of blood malignancies, such as lymphomas, leukemia, and multiple myeloma, have received FDA approval to date. Despite significant advances, the application of CAR T-cell therapies in solid tumors like gastric cancer is more challenging as solid tumors have a complex microenvironment, making it difficult to find tumor-specific antigens. In this article, we have summarized the most important antigens for CAR T-cell therapies that are being investigated for gastric cancer. All those antigens are highly expressed in gastric cancer cells with very low expression in healthy cells, rendering them excellent targets for CAR T-cell therapy. Cumulative preclinical studies strongly support the effectiveness of CAR T-cell therapies in the treatment of gastric cancer, and multiple early clinical trials have shown promising results of CAR T-cell therapies in gastric cancer. To fully realize the potential of CAR T-cell therapies to treat gastric cancer patients, future research must focus on improved safety profiles and persistence/durability of the CAR T-cell therapy. CAR T-cell therapies could cause severe side effects such as cytokine release syndrome and neurotoxicity; thus, the engineering of CAR-T cells with better safety profiles and reducing the potential for adverse reactions is a major future research area. In addition, CAR-T cells could lose their effectiveness over time as the cancer evolves and suppresses the immune response, so engineering CAR-T cells with prolonged persistence and durability could lead to better long-term outcomes. Finally, all

current CAR T-cell therapies are personalized by using a patient's own T cells, which is time consuming and expensive. One approach to reduce the time and cost associated with therapy production is to develop" off-the-shelf" CAR T-cell products, where T cells from healthy donors are modified and used to treat multiple patients. As more research and clinical trials in the CAR T-cell therapy have been taken, we believe that safer, affordable and longer durability of CAR T-cell immunotherapies for solid tumors, particularly gastric cancer, will soon be developed in the near future.

CONFLICT OF INTEREST

The authors disclose no conflict of interest.

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