Review Article

The targets and side effects of CAR-T therapy in the treatment of gastric cancer: a literature review

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Background and Objective: Gastric cancer is a most common malignant tumor in the world today. The latest method of chimeric antigen receptor (CAR)-T cell therapy brings a promising future for these patients. However, the method also brought a series of negative effects while improving patients' survival since many side effects were produced in the process of CAR-T therapy. In order to make a deep understanding of CAR-T therapy in the gastric cancer, we prepared the review on the side effects and specific targets for gastric immunity therapy. Today, T cells are widely used in the treatment of tumors. The key point for this method was finding a specific antigen. In order to facilitate gastric cancer therapy research and evaluate their risk, we outline the essential targets of CAR-T in the treatment of gastric cancer and some of the most likely side effects after CAR-T treatment.

Methods: The date of the literature search is mainly in March 2021, and the keywords "gastric cancer", "target", "side effects" and other searches include clinical trials, meta-analysis, randomized controlled trials and research articles as our references. All retrieval processes are completed in PubMed and Google Scholar. The documents used must include detailed experiments, detailed expositions, etc., and most articles have been published in the past five years.

Key Content and Findings: Some potential targets for the treatment of gastric cancer, including HER2, MSLN, FOLR1, EGFR, MUC1 and so on, are mentioned in this review. On this basis, we also made some summaries of possible side effects of CAR-T therapy, including cytokine release syndrome (CRS), immune effector cell associated neurotoxicity, on- target off-tumor toxicity, tumor lysis syndrome and metabolic complications.

Conclusions: Some of these targets have shown good clinical efficacy and have even been approved for use. However, the side effects of CAR-T treatment cannot be ignored. In the follow-up research, it is very important to choose a specific target and reduce the side effects to achieve good treatment.

Keywords: Chimeric antigen receptor-T (CAR-T); gastric cancer; targets

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Introduction

Gastric cancer, as an important health problem, is the fourth most common cancer and the second leading cause of cancer death in the world (1). To date, there is still no good treatment for it. The Chimeric Antigen Receptor T-Cell Immunotherapy, a newly developed technology, reveals significant clinical efficacy for some patients with malignant tumors. This new form of adoptive T cell therapy redirects the endogenous anti-tumor activity of T cells to a predetermined tumor-associated antigen through artificial chimeric antigen receptor (CAR), thereby achieving the

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	2021.3.15
Databases and other sources searched	PubMed and Google Scholar
Search terms used (including MeSH and free text search terms and filters)	Above all, we searched literatures with main terms "gastric cancer + CAR + target". Second, each target was used as a key word such as MSLN to search for detailed target information. Again, with "specific target + gastric cancer + CAR-T" as the key word, articles with complete experimental procedures and experimental conclusions are chosen as the main references for this review. Finally, the search term was changed to "side effects + gastric cancer + CAR-T" and literatures were eligible for inclusion should met with experimental support and detailed elaboration as the description of the side effects of gastric cancer CAR-T treatment
Timeframe	Most of the cited articles are from 2017–2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Complete experimental procedures and results are necessary. Types include clinical trials, meta-analyses, randomized controlled trials, and research articles

CAR, chimeric antigen receptor.

goal of eliminating specific tumors (2). Currently, CAR-T technology has been introduced to the treatment of gastric cancer. Although CAR-T technology has many advantages (specificity, orientation, etc.) and a good curative effect on hematological tumors, the treatment for solid tumors still remains unsatisfactory (3). Unlike hematological tumors, the discrete foci and biological barriers of solid tumor cells limit the entry of T cells for immunotherapies. In addition to physical barriers, chemokines secreted by solid tumor cells are usually abnormal, which may lead to insufficient T cell recruitment and inhibition effect on T cell killing ability. This review aims to provide researchers in CAR-T therapy with some ideas for target selection and to provide some warnings about clinical problems arised from CAR-T therapy. We present the following article in accordance with the Narrative Review reporting checklist (available at https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-6/rc).

Methods

The date of the literature search was conducted in March 2021. Before preparing this review, we searched literatures with main terms "gastric cancer + CAR + target". Second, each target was used as a key word such as MSLN to search for detailed target information. Again, with "specific target + gastric cancer + CAR-T" as the key word, articles with complete experimental procedures and experimental conclusions are chosen as the main references for this review. Finally, the search term was changed to "side effects + gastric cancer + CAR-T" and literatures were eligible for inclusion should met with experimental support and detailed elaboration as the description of the side effects of gastric cancer CAR-T treatment. Through these retrieval methods, we conducted a comprehensive retrieval of the articles that needed to be cited. All retrieval processes were performed on PubMed and Google Scholar, most of which were expected to be released within five years, and their types include clinical trials, meta-analysis, randomized controlled trials, and research articles. The specific strategy was listed in the following table (*Table 1*).

Discussion

Targets for CAR-T cell therapy

HER2

The HER2 receptor is a transmembrane glycoprotein with tyrosine kinase activity, which may be overexpressed and amplified in some patients with gastric cancer. The reported data showed that the rate of HER2 overexpression in gastric cancer patients was between 9% and 23% (4,5). Its structure includes an extracellular ligand binding domain and transmembrane domain, as well as an intracellular protein tyrosine kinase domain. Trastuzumab, a first molecularly targeted drug developed for HER2, which as a monoclonal antibody was originally used to treat breast cancer and has shown a certain degree of efficacy (6). With the development of immunotherapy, HER2 receptor was used as the CAR-T target for the treatment of gastric cancer. Through the design of CAR containing CD137 and anti-

HER2 single chain antibody and the introduction of T cells, it was the first time that CART-HER2 cells showed specific, effective and long-lasting tumor killing in clinical trials against HER2-positive primary gastric cancer GC cells and gastric cancer stem cells (GCSCs) (7). The application of humanized chA21scFv-based CAR modified T cell to treat HER2 overexpression of gastric cancer become a potential approach for therapy of gastric carcinoma. The results of this trial indicated that CAR-based specificity and proactive recognition could induce the homing of T cells to tumor sites and make T cells exert anti-tumor functions. Furthermore, the transfer therapy of CAR-T cells also inhibit the occurrence of peritoneal cancer to a certain extent and prolong the patients' survival time (8).

Mesothelin (MSLN)

MSLN, a differentiation antigen, with 40-kDa molecular weight, comes from its precursor. The MSLN protein could attach to the cell membrane by linking to a 31-kDa shedding fragment (megakaryocyte enhancer factor) (9). The biological function of MSLN remains unclear, but it is highly expressed in many cancers including gastric cancer, which makes it an attractive candidate for cancer therapy (10,11). Therefore, MSLN has become a potential target for gastric cancer tissues, particularly applied in CAR-T therapy. The research on the effect of anti-MSLN CAR (M28z10) T cells on gastric cancer was conducted in mouse models and the results documented that M28z10 T cells have a strong anti-gastric cancer activity, especially M28z10 T cells in killing MSLN + GC cells *in vivo* (12). With the third-generation of CAR-T technology developed, the MSLN-CAR-T cells not only kill specific MSLN-positive cancer cells *in vitro*, but also kill MSLN-positive CDX and PDX solid tumors *in vivo* (13). It is for sure that in the very near future, along with research going deep in MSLN-CAR-T cells for gastric cancer therapy, the MSLN-CAR-T cells must be translated from bench to bedside and bring benefit for patients with gastric cancer.

FOLR1

FOLR1, a 38-kDa glycosylated phosphatidylinositol-anchored glycoprotein, as a membrane-bound protein with high affinity, can bind to folic acid and its derivatives and transport it into cells (14). Folic acid is an important component of cell metabolism. Studies indicated that a number of cancers have an elevated expression of folate receptors, which means the cancer cells possessed high metabolic rate in folic acid. The high expression of folate receptors in some cancer cells makes it a very attractive biomarker (15). Unfortunately, the single-dose activity of the combination of FOLR+ targeting antibody with early folic acid is disappointing (16). By constructing the single-chain variable region (ScFv) and the signal domain (composed of CD28 and CD3ζ) of CAR against FOLR1, the T cells expressing the CAR were produced and used to kill the FOLR1-positive gastric cancer cells. The results demonstrated that FOLR1-CAR T cells had specific recognition and effective anti-cancer activity against FOLR1-positive GC cells, indicating that FOLR1-CAR T cells are an ideal choice for the treatment of patients with FOLR1-positive GC cells (17). I believe the CAR-T therapy targeting FOLR1 will be applied in the clinical in the future.

EGFR

Epidermal growth factor receptor (EGFR) belongs to the EGFR family which includes four members and the other three receptors were: HER2/ErbB-2, HER3/ErbB-3 and HER4/ErbB-4. All four receptors consist of an enzymatically active intracellular domain and an extracellular ligand binding domain (18). The activation of the EGFR by the proto-oncogene is mainly through gene amplification or autocrine change. Usually, the EGFR is activated following binding with peptide growth factors of the EGF-family of proteins. Evidence suggests that EGFR is involved in the pathogenesis and progression of different carcinoma types. Activation of EGFR by tyrosine kinase can trigger a series of intracellular pathways, which may contribute to the transformation of cell phenotype and provide growth and survival advantage for tumor cells (19,20). Moreover, the EGFR signaling pathway can also affect the role of regulatory T cells (Treg cells) in cancer patients. The post-translational regulation of Foxp3 expression in cancer patients through AREG/EGFR/GSK-3 may lead to the degradation of Foxp3 protein in Treg cells and enhance the inhibitory function of Treg cells. All this information makes EGFR a potential therapeutic target for cancer treatment (21).

MUC1

MUC1 is a transmembrane glycoprotein, which is widely expressed in normal glandular epithelial cells of the pancreas, breast, lung, and gastrointestinal tract (22). MUC1 is a multifunctional protein that plays a role in the protection and lubrication of the epithelial surface. It is located on the surface of the cell and can be used as an environmental sensor to send a signal to the inside when a

problem occurs (23). Helicobacter pylori infection increases the level of methylation and reduces the expression of TFF2, which is related to the occurrence of gastric cancer. TFF2 is a member of the secreted protein family which consists of TFF1, TFF2 and TFF3. TFF1 is a gastric-related tumor suppressor gene, but the expression of TFF2 in gastric cancer is often silenced. However, TFF2 has an inhibitory effect on other tumors such as pancreatic ductal adenocarcinoma, prostate cancer and breast cancer. Studies have shown that in gastric cancer patients of different ages, genders, stages and grades, the methylation of MUC1 and TFF2 in gastric cancer is negatively correlated, while the expression of TFF2 is positively correlated (24). Therefore, MUC1 can be used as a potential ideal gastric cancer treatment target to some extent. And in the latest researchers, the use of MUC1-TN CAR modification can make V-γ-9V-δ-2 T cells have antigen-specific cytotoxicity, and then the introduction of IL-2 enhances the therapeutic sustainability of V-γ9V-δ-2 T cells. The study also showed that MUC1-TN CAR modified Vγ9Vδ2 T cells had obvious antigen-specific anti-tumor activity both *in vivo* and *in vitro*, and could be used as a new ready-made allogeneic immunotherapy product to overcome the limitations of current tumor immunotherapy (25).

c-Met

The original sugar gene c-MET (MET) is a member of the RTK family and is a known receptor for hepatocyte growth factor (HGF), which is encoded by the MET gene (26). The transcription level of MET gene in gastric cancer tissue is significantly higher than that in normal gastric tissue (27). The HGF/c-Met signaling pathway can be used as a target for GC molecular therapy. In the experiment designed by Chen *et al.*, T cells specifically modified with c-Met CAR not only have effective cytotoxic effects on c-Met-positive GC cells *in vitro*, but also significantly inhibit the growth of gastric cancer models *in vivo*, which was of no off-target toxicity. PD1/CD28 CSR can further enhance the anti-tumor activity of c-Met CAR-T, increase the proportion of central memory T cells, prolong the anti-tumor long-term effect, reduce the secretion of the inflammatory factor IL-6, and lower the release of cytokines (28). Therefore, the PD1/CD28 CSR modified T cells have become a cutting-edge treatment method.

CD133

CD133 is a novel membrane protein identified for the first time in humans and mice, and was originally classified as a marker for primitive hematopoietic and neural stem cells. In addition, CD133 is a marker of some human tumor-promoting cells and can be used as a biomarker for the treatment of gastric cancer (29). Cisplatin could significantly increase the relative expression of CD133 mRNA in BGC-823 cells. It is reasonable to speculate that cisplatin can induce the expression of CD133 in cancer cells or selectively enrich the existing $CD133^+$ cells. The use of humanized single-chain antibody fragments and lentiviral vectors to construct CD133 car-modified T cells combined with cisplatin for the treatment of gastric cancer indicated that anti-CD133 CAR-T cells could selectively target cisplatin-induced CD133-positive tumors *in vitro* and stem cell-like cells *in vivo* (30). Although CD133 is not widely used as a marker in clinical practice, its efficacy in an experimental environment is encouraging. The therapy of CD133 CAR-T cells combined with cisplatin also showed the potential of this marker to a certain extent.

EpCAM

Epithelial cell adhesion molecule (EpCAM) is a transmembrane glycoprotein that is abundantly expressed in normal and malignant epithelial cells. Usually, it is used as an "epithelial marker", which is involved in cell adhesion and tumor progression (cell proliferation and tumor stem cells) (31). The expression of EpCAM was found to be elevated in gastric cancer cells (32), so it is selected as a potential new target for gastric cancer therapy (33). However, because of the cell heterogeneity of gastric cancer, the application of immunotherapy in gastric cancer is going slowly (34). Recently, the study by Yanping Yang showed that EpCAM CAR T cells had strong anti-tumor activity in gastric cancer model mice. Especially, the EpCAM CAR with low affinity could eradicate a variety of solid tumors that are difficult to treat for a long time without causing serious treatment-related toxicity and bore significant penetration and accumulation in solid tumors (35) (*Table 1* search MESH: gastric cancer + CAR + target).

Challenge in research of CAR-T cell therapy

CAR-T cells transformed with the single-chain variable region (ScFv) of a tumor-associated antigen (TAA) antibody, which recognizes tumor cells and activates T cells by interaction with non-major histocompatibility complex (MHC). Only when the tumor antigen is specifically expressed on the cell membrane surface, CAR-T cells can recognize the tumor antigen and exert their killing

effects on the target cells. Although CAR-T therapy has an encouraging effect on hematological malignancies, many challenges are confronted by the application in solid tumor treatment.

Cytokine release syndrome (CRS)

CRS is a systemic inflammatory response that can be triggered by multiple factors such as infection and certain drugs. CRS patients could show a variety of symptoms, from mild flu-like symptoms (fever, fatigue, headache, rash, etc.) to severe life-threatening excessive inflammation (HLH, MAS, etc.). It is worth noting that cancer immunotherapy involving T cells will greatly increase the risk of CRS (36). For example: Compared with other B-cell malignancies in the treatment of ALL, CAR T cell therapy has a higher incidence of CRS in all patients, especially in the adult population (37,38). When CAR T cells participate in cancer treatment, they will undergo a rapid expansion process in the body, and react with the target cell with a very high frequency at a certain time point, hence in a very short time, most target cells will suffer pyroptosis. In addition, the stimulated macrophages produce IL-6 and IL-1, which lead to the occurrence of CRS through activating caspase1 (39). During treatment, it is fatal if a severe toxic side effect happens. Since CAR-T cells have higher specificity and effectiveness in targeting tumor cells, this may contribute to a stronger response and faster clinical results of CAR-T-related CRS. In some cases, the CRS could be relieved by timely administration of corticosteroid tocilizumab. The subsequent follow-up indicated that the recurrence rate and mortality rate in the CAR-T group reached 29.3% (12/41) and 34.1% (14/41), respectively (40). Currently, tocilizumab usually relieves symptoms within a few hours, and corticosteroids are used to treat severe CRS. If the two drugs were proved to be invalid, CRS would become difficult to treat. In the process of causing CRS, macrophages seem to be the main cell effector cells (41). Recent studies showed that CDK7 inhibitor THZ1 could inhibit the transcription of inflammatory genes (achieved by SEs-related inflammatory genes) and regulate macrophage-centered pathways to alleviate the inflammatory disorders caused by CAR T infusion (42). Although there are many methods to treat CRS caused by CAR-T, they all have more or less toxic side effects and ineffectiveness, which cannot guarantee a good prognosis for patients. Therefore, in-depth understanding the mechanisms of CRS pathogenesis is necessary for the development of novel CRS treatments.

Immune effector cell associated neurotoxicity

So far, due to the limitations of animal models which cannot fully simulate the human mechanism, the neurotoxicity mechanism caused by immunotherapy is still unknown (43,44). Similar to CRS, many cytokines (IL-6, IL-15, interferon-γ, IL-2, IL-8, etc.) were observed to be elevated in patients with severe ICAN. In addition, severe ICAN is also associated with increased levels of cerebrospinal fluid (CSF) protein (increased permeability of the blood-CSF barrier) (45). The symptoms of ICAN patients range from minor symptoms such as object naming, speech hesitation, headache and fatigue to more serious and fatal symptoms such as seizures, increased intracranial pressure, cerebral edema and coma (46,47). And compared with the onset of CRS, the onset time of ICANS-related symptoms has a greater change (38,48). However, most ICANs symptoms are short-lived and disappear completely within the first 3–4 weeks of treatment, but there is still a risk of recurrence (49,50).

On- target off-tumor toxicity

Because the expression of some tumor-associated antigens is not limited to tumor cells, it will lead to the risk of on-target off-tumor effects. In some kidney cancer patients who took CAR-T therapy, abnormal liver enzymes were detected in the serum because of the infiltration of CAR T cells into bile duct epithelial cells expressing CAIX. There are also examples of patients with metastatic colon cancer who received HER2-directed CAR T cell therapy who developed respiratory distress and pulmonary edema 15 minutes after cell infusion, and then progressed to multiple organ failure and death. There are many solutions to this side effect. Firstly, the expression of CAR can be restricted to those CAR T cells located in hypoxic TME (the tumor microenvironment), thereby reducing the adverse effects on non-malignant tumor tissues. The second is to introduce CARS into T cell subpopulations with more favorable anti-tumor and safety characteristics. By this way, the innate toxicity of traditional CAR T cells was reduced significantly (51).

Tumor lysis syndrome (TLS)

TLS is a metabolic disorder caused by the rapid death of tumor cells. When cancer cells die, normal intracellular components (potassium, phosphorus, and nucleic acids) will spill into the blood. If the tumor is large, the lysate and metabolite of dead tumor cells may overwhelm the metabolism homeostasis in normal man. These death cells enter the blood faster than the metabolic rate of kidneys,

which can lead to hyperkalemia and hyperphosphatemia. Usually, nucleic acid is converted into uric acid in the liver, and the vast tumor cells are lysed and need to be metabolized, which leads to hyperuricemia. In addition, too much uric acid in the kidneys can cause uric acid nephropathy and renal insufficiency. In the body, the phosphorus could bind to calcium, resulting in hypocalcemia due to the formation of calcium phosphate precipitation or crystals. These crystals may also cause renal insufficiency or AKI, which may lead to metabolic acidosis and deterioration of high potassium status (52,53).

Metabolic complications

Through a detailed analysis of the organ-specific toxicity of 60 patients with diffuse large B-cell lymphoma treated with CD19 CAR T cells and its correlation with the outcome, CD19 CAR T cells have a higher toxic load on the organs. It varies by organ system and most toxicity is controllable, rarely related to mortality (54) (*Table 1*, search MeSH: side effects + gastric cancer + CAR-T).

Conclusions

In the study of using CAR-T to treat gastric cancer, researchers can use the various targets we discussed as research objects. At the same time, the side effects reflected by the treatments we listed can be used in clinical use to make some preventive measures and are also conducive to relate research on the prognosis of the disease. Fortunately, CAR-T cell therapy has achieved remarkable success in the treatment of hematological diseases. Clinical trials targeting CD19 CAR modified autologous T cells have shown high clinical response rate in B-cell hematological malignancies which prompted FDA to approve two different CARs for the treatment of relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL) and diffuse large B-cell lymphoma. However, the same success has not been repeated in the treatment of solid tumors. Firstly, the biggest barrier is the lack of adequate tumor-specific antigens. On the other hand, many serious adverse reactions happened during or after the CAR-T treatment. Fortunately, a variety of researches have been conducted and produced many positive effects in the therapy of solid tumors. With the optimization of the therapeutic regimen, especially, the design of the optimized CAR structure, may bring opportunities to reduce toxicity. In addition, the continuous overcoming of negative effects such as combining with other therapeutic methods, we believe that CAR-T cell therapy will definitely bring new futures to patients with solid tumors.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-6/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-6/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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