



MiniReview

Human Epidermal Growth Factor Receptor 2 Targeting Specific T Cells Immunotherapy for Gastric Cancer

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Abstract

The current traditional treatment methods have no apparent advantages in further improving the survival rate of gastric cancer patients. With the rapid development of molecular biology and gene editing technology, a new type of antitumor treatment model - human epidermal growth factor receptor 2 (HER-2), targets chimeric antigen receptor T (CAR-T) cells. Immunotherapy has shown great potential and therapeutic prospects. CAR-T cell immunotherapy has made significant progress in the treatment of solid tumors. However, due to the high heterogeneity of gastric cancer and the complex tumor microenvironment, the immune escape of tumors is caused, and the treatment of gastric cancer still faces many challenges. This article reviews the research progress of HER-2 targeting CAR-T cell immunotherapy for gastric cancer and hopes that it will become a safe and effective treatment for gastric cancer.

Keywords: gastric cancer, immunotherapy, targeted therapy, HER-2, CAR-T

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1 INTRODUCTION

The morbidity and mortality of malignant tumors have always been high. Although the traditional treatment methods have made significant progress, the long-term survival rate of patients still needs to improve, and the curative effect still needs to be ideal^[1,2]. In recent years, with the introduction of the “immune editing” theory and the rapid development of molecular biology and

genetic engineering technology, a new antitumor therapy model has shown great potential and prospects, namely, modifying T cells with chimeric antigen receptors. Chimeric antigen receptor T (CAR-T) cell is the representative adoptive immune cell therapy^[3].

Human epidermal growth factor receptor 2 (HER-2) is a tyrosine kinase receptor and is a member of the

epidermal growth factor receptor (EGFR) family^[4,5]. Studies have found that HER-2 is overexpressed in various solid tumors such as stomach, colon, and ovarian cancer. Long-term preclinical studies and clinical trials have shown that CAR-T cells are effective and safe in treating tumors^[6,7]. However, due to the high heterogeneity of solid tumors and the complex tumor microenvironment, the immune escape of tumors is still valid when treating solid tumors. Face many challenges. This article reviews HER-2 targeting CAR-T cells immunotherapy for gastric cancer. HER-2 targeting CAR-T cells immunotherapy is expected to become a safe and effective treatment for solid tumors.

2 STRUCTURE, PRINCIPLE AND DEVELOPMENT PROCESS

The body's immune response to tumors involves a variety of immune cells and their secreted products, such as natural killer cells, natural killer T cells, and tumor necrosis factor-related apoptosis-inducing ligands and γ -interferon and so on^[8]. Tumor cells can evade the surveillance of the body's immune system by changing the surrounding environment to form a physical or immune barrier. The mechanism is related to tumor antigen mutations, immunosuppressive factors such as interleukin (IL)-10 production, and the central tissues on the tumor surface. Compatibility complex [(major histocompatibility complex (MHC)) molecules and costimulatory molecules (CM) decreased expression and so on^[9-11].

2.1 The Structure of HER-2 Targeting CAR

The HER-2 targeted CAR is a synthetic receptor composed of an extracellular antigen binding domain, a transmembrane domain, and an intracellular signal transduction domain. The extracellular antigen binding region is composed of the single chain variable fragment (scFv) and hinge region composed of the variable light chain and variable heavy chain of the HER-2 monoclonal antibody and is responsible for recognizing and binding to the surface of tumor cells^[12] - tumor-associated antigen (TAA). The scFv determines the specificity of the CAR antigen, expresses a variety of targeted antigens on the surface of tumor cells, and binds to the target protein in an MHC-independent and non-restrictive manner^[13].

The transmembrane region plays a role in signal transduction downstream after binding to the antigen. However, it is still being determined whether there is any influence on the structure and biochemistry of CAR^[14,15]. The intracellular signal transduction region comprises immunoreceptor tyrosine-based activation motifs (ITAMs) and CM and plays a crucial role in T cell activation, proliferation, persistence and cytotoxicity.

2.2 Principle and Development History

CAR-T cells are CD8⁺ T lymphocytes activated by

antigen-presenting cells, that is, cytotoxic T cells, to exert antitumor effects. Tumor cells escape immune recognition by down-regulating the expression of MHC, limiting the tumor-killing effect of T cells in the body. CAR-T cells have been developed for 20 years and are divided into four generations according to the structure of intracellular signal transduction regions. Gross was equivalent to combining scFv monoclonal antibodies with ITAMs (usually CD3 and Fc ϵ R1 γ) 1989 to prevent antigen recognition from MHC restrictions and successfully constructed the first-generation CAR^[16].

According to the dual signal theory of T cell activation, based on the first generation CAR containing only ITAMs, the second and third generations have increased CM (commonly used CD28, CD134, CD137 and DAP10), which enhances the proliferation ability of T cells and lasts forever: sex and antitumor activity^[17,18]. The third-generation CD28-CD134-CD3 with double CM has a more vital ability to release cytokines than the second-generation CD28-CD3 with single CM. In the 4th generation, a carrier expressing CAR has been added. By producing and releasing a large number of cytokines, it activates the body's innate immune response and further enhances the antitumor effect^[19].

3 PROGRESS OF HER-2 TARGETING CAR-T CELLS IN THE TREATMENT OF GASTRIC CANCER

Currently, the immunotherapy methods or medications for gastric cancer include non-specific immune enhancers, tumor vaccines, immune cell adoptive therapy, monoclonal antibodies and so on^[20]. As a "new star" in immunotherapy, adoptive immune cell therapy has gradually received attention in treating advanced gastric cancer. The HER-2 signaling pathway is a crucial target for adoptive immune cell therapy to treat solid tumors^[21]. Although the targeted drugs targeting HER-2 include trastuzumab, pertuzumab, lapatinib, etc., and these targeted drugs have also carried out gastric cancer-related clinical trials, only trust Rizumab is approved by the FDA for first-line treatment of patients with advanced gastric cancer.

As trastuzumab has officially become the first-line drug for treating advanced gastric cancer, to improve the efficacy further and reduce drug resistance, HER-2 targeting CAR-T cells for treating gastric cancer has also become a research hotspot^[22]. Ye et al.^[23] used the constructed CD137-CD3 anti-HER-2 CAR for the first time to treat gastric cancer after transfecting T cells with a lentiviral vector. They found that HER-2 targeting CAR-T cells can not only specifically recognize and effectively kill HER-2⁺ *in vitro* gastric cancer cells and also showed effective and long-lasting antitumor activity on HER-2⁺ gastric cancer tissue xenotransplanted in mice. This indicates that HER-2 targeting CAR-T cells

may be suitable for treating HER-2⁺ advanced gastric cancer patients, but its toxicity and immunogenicity still need to be verified in future trials^[24]. Zhang et al.^[25] and other studies have found that reducing the affinity of CAR-T cells can effectively improve their killing specificity, reduce “off-target effects”, and significantly improve the safety of HER-2 targeting CAR-T cell immunotherapy.

Future research focuses on improving the antitumor activity of HER-2 targeting CAR-T cells by enhancing their proliferation, functional effects, and durability. Chen et al.^[26] found that the second-generation HER-2, which is composed of FRP5, CD28 and CD3 with high affinity for HER-2 monoclonal antibody, targets CAR-T cells and can specifically recognize and kill HER-2⁺ glioblastoma (GBM) cells. However, it is not effective against HER-2-GBM cells^[27]. HER-2-specific T cells can effectively kill HER-2⁺ osteosarcoma cells. Oh et al.^[28] successfully constructed a new type of humanized ChA21-28zCAR-T cells that can transduce CD4⁺ and CD8⁺ T cells (including the ChA21 single-chain variable region and the intracellular signal transduction region containing CD28 and CD3), which can not only recognize and kill the isolated HER-2⁺ ovarian cancer cells, the growth of xenotransplanted SKBR3 tumors in mice was also significantly inhibited. The above studies all provide ideas for improving the HER-2 targeting CAR-T cell immunotherapy project for gastric cancer^[29].

4 ADVERSE REACTIONS AND COUNTERMEASURES

HER-2 targeting CAR-T cell immunity is a promising new tumor treatment method with specific safety issues. Firstly, while the second and third-generation CAR-T cells containing CM proliferate in large quantities in the body, they will release a variety of cytokines such as TNF- α , IFN- γ , IL-1 β , IL-2, IL-6, IL-8, and IL-10 enter the blood, causing inflammatory reactions, and even renal dysfunction, respiratory distress and multiple organ failure. Secondly, HER-2 as a target is found in human lungs, gastrointestinal tract, breast, and epithelial cells^[30,31]. There is a low level of expression in normal tissue cells, which leads to HER-2 targeting CAR-T cells to specifically kill tumors while damaging normal tissue cells. This toxic adverse reaction is mainly due to “off-target effects” and cytokine release syndrome (CRS) and was further confirmed by the patient’s serum analysis and autopsy results.

The American Recombinant DNA Advisory Committee summarized CAR-T cell therapy’s toxic and adverse effects and believes in designing safer CAR-T cells, optimizing cell purification and expansion methods, pre-injecting immunosuppressants, and following strict dose escalation during reinfusion. The program can reduce

CRS-related adverse events. Research by Arcangeli et al.^[32] found that applying suicide genes such as Caspase-9 and other “safety switches” to CAR-T cells can quickly eliminate over-activated CAR-T cells in the body, reduce the occurrence of “off-target effects”, and greatly increase their safety. Prospects CAR-T cells have made amazing progress as a new adoptive immunotherapy method, bringing hope to curing solid tumors^[33]. Much basic research, preclinical trials, and clinical research have made HER-2 an increasingly important therapeutic target for CAR treatment. Although the efficacy of HER-2 targeting CAR-T cell therapy for gastric cancer is supported by many studies, it still requires large-scale, multi-center, and high-quality clinical randomized trial results and evidence-based evidence before it is used as a mainstream strategy in clinical practice support^[34].

Due to gastric cancer heterogeneity, tumor micro-environment immunosuppression, and antigen migration, single-target EGFR-targeted CAR-T cell immunotherapy has not yet achieved the desired effect. Future research on HER-2 targeting CAR-T cells may focus on the following aspects: (1) Upgrade structural design and improve curative effect by improving its antitumor activity and migration ability and constructing CAR-T with multi-target antigens; (2) Explore more effective T cell subsets, reduce tumor immune escape by transforming T cells; (3) Eliminate tumor microenvironment, especially the immunosuppressive transmembrane protein ligands PD-L1 and PD-L2 inhibition, by enhancing the proliferation of HER-2 targeting CAR-T cells and the release of cytokines to enhance the antitumor effect; (4) Adjust and optimize the treatment plan to minimize the adverse reactions caused by CAR-T cells.

5 CONCLUSION

With the continuous deepening of research and the continuous development of genetic engineering technology, HER-2 targeting CAR-T cells will become a safe and effective treatment for gastric cancer and other solid tumors in the future.

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Conflicts of Interest

The authors declared no conflict of interest.

Author Contribution

Chen W designed this study and wrote the article. Huang S, Fan X and Gao Y revised the paper for important intellectual content. All authors made a substantial, direct and intellectual contribution to this research, and approved the manuscript for publication.

Abbreviation List

CAR-T, Chimeric antigen receptor T
EGFR, Epidermal growth factor receptor
GBM, Glioblastoma
HER-2, Human epidermal growth factor receptor 2
ITAMs, Immunoreceptor tyrosine-based activation motifs
ScFv, Single chain variable fragment

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