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Challenges and prospects of CAR-T cell therapy in colorectal cancer (CRC)

Yanan Lv

The Affiliated Middle School of Huazhong University of Science and Technology, Wuhan, Hubei, 430000, China

ABSTRACT
Colorectal cancer (CRC), also known as "colorectal cancer", includes colon cancer and rectal cancer, and refers to malignant tumors that occur in the mucosal epithelium and glands of the colon and rectum. The incidence and mortality of CRC are at the forefront of digestive system malignancies. The early symptoms of patients are not obvious. As the disease progresses, there will be changes in bowel habits, changes in stool shape, abdominal pain or abdominal discomfort. Since CRC is harmful to human health, effective treatment methods are needed. From the current research status, Chimeric antigen receptor T cell therapy (CAR-T cell therapy), as a new type of precise targeted treatment of tumor cells, can play an anti-tumor role in the treatment of CRC. Therefore, this article analyzes the main targets of CAR-T cell therapy for CRC, and then combines the challenges faced by CAR-T cell therapy for CRC to further explore the prospects of CAR-T cell therapy for CRC, aiming to deepen the understanding of CAR-T cell therapy and provide some valuable references for the clinical treatment of CRC patients.

KEYWORDS
CAR-T cell therapy; colorectal cancer (CRC); challenges; prospects

1 Introduction

Colorectal cancer (CRC), as a malignant tumor, has many risk factors, including genetic factors, environmental factors, and chronic intestinal disease factors. In recent years, with the changes in the dietary habits and dietary structure of the Chinese people, coupled with the influence of the aging population, the incidence and mortality of CRC have shown an increasing trend year by year. It is worth noting that CRC has an insidious onset, and patients usually have no typical symptoms in the early stages, or only show positive fecal occult blood. As the disease progresses, a series of typical symptoms will occur, such as changes in bowel habits, changes in stool shape, abdominal pain or abdominal discomfort, abdominal masses, intestinal obstruction, etc. In addition, relevant studies have shown that CAR-T cell therapy can play a certain role in the treatment of CRC, such as targeted killing of cancer cells, improving the patient's immune response, and thus prolonging the patient's survival [1]. Of course, from the current situation, since CAR-T cell therapy is in the clinical trial stage in the treatment of CRC, it still faces some challenging problems, such as difficulty in target selection and susceptibility to inhibition by the tumor microenvironment. In order to effectively respond to challenging problems, give full play to the role of CAR-T cell therapy, and improve the clinical treatment effect of CRC patients, it is necessary for this article to conduct an in-depth review and analysis on the topic of "Challenges and Prospects of the Application of CAR-T Cell Therapy in Colorectal Cancer (CRC)".

2 Analysis of the main targets of CAR-T cell therapy for CRC

2.1 Guanylate cyclase C (GCC)

GCC is a variant of transmembrane receptors present in intestinal epithelial cells, belonging to the guanylate cyclase family. After the ligand binds to GCC, it can catalyze guanosine triphosphate (GTP) to convert it into cyclic guanosine monophosphate (cGMP), further activating the downstream cGMP-related signaling pathway. In addition, the GCC-cGMP signaling axis can effectively maintain the normal balance of intracellular and extracellular ion concentrations, body fluids and electrolytes, thereby effectively maintaining normal intestinal function. If the GCC-cGMP signaling axis is out of balance, the disease of colorectal cancer patients will progress. In addition, GCC belongs to a class of proteins expressed in approximately 70% to 80% of colorectal cancer metastases. For normal tissues, GCC is only expressed on the inner surface of the intestine. Its cells are tightly connected to form a cyclic isolation relationship with the system, making it difficult for T cells to come into close contact with it, so GCC has a high degree of targeting.

Associated clinical research has revealed that the amalgamation of CAR-T cells aimed at GCC and leukocyte differentiation antigen (CD19), namely "GCC19CART" therapy, can have a good therapeutic effect on patients with metastatic colorectal cancer who have received multiple lines of standard treatment [2]. Clinical trials have shown that some patients have adverse reactions to GCC19CART therapy, but some patients' tumors have significantly shrunk [3].

Correspondence: crissy0419@outlook.com

Typically, CAR-T cell therapy focusing on GCC can attain a level of effectiveness in treating colorectal cancer patients clinically, with good safety and tolerability. From the perspective of patients' side effects, there are mainly diarrhea, cytokine release syndrome (CRS), etc., but the side effects are generally mild or moderate, and can be effectively controlled by taking appropriate drugs. This indicates that the GCC target serves as a benchmark for employing CAR-T cell therapy in the treatment of CRC patients.

2.2 Carcinoembryonic antigen (CEA)

CEA represents a wide-ranging marker for tumors. Within regular tissue cells, a minor quantity of CEA is present on the cell membranes of cells in the digestive tract, with its expression directed towards the intracellular cavity, which can prevent it from being identified by CAR-T cells targeting CEA. However, based on related malignant tumor diseases, such as common lung cancer, pancreatic cancer, and colorectal cancer, CEA expression is significantly increased, especially in patients with CRC disease, the CEA positivity rate is >80%. According to the current research status, CEA may have a specific function in tumor formation and progression, yet the exact mode of action remains somewhat ambiguous [4]. However, considering its high expression characteristics in tumor cells, CEA can be used as one of the important targets in CAR-T cell therapy.

Combined with clinical studies, it has been found that CAR-T cell therapy targeting CEA can have a certain therapeutic effect in patients with colorectal cancer. After treatment with CAR-T cell therapy, the condition of some patients with advanced CRC has stabilized, and the serum CEA levels of most patients have been significantly reduced [5]. From the perspective of safety and tolerability, under high-dose conditions, the human body has a high tolerance to CEA CAR-T cells. Some patients may experience adverse reactions, such as liver damage, lymphocytopenia, fever, etc., but they are all under control.

In general, CEA, as one of the main targets of CAR-T cell therapy for the treatment of CRC patients, has some obvious advantages, namely: First, high expression rate. Based on CRC patients, the high expression rate of CEA can enable CAR-T cell therapy to accurately identify tumor cells and further effectively attack tumor cells. Second, good specificity. Even if CEA is expressed in small amounts in normal tissue cells, because its expression is directed toward the intracellular cavity, CAR-T cell therapy targeting CEA is based on symptomatic tissues, and the side effects are relatively low. Therefore, in the process of CAR-T cell therapy for the treatment of CRC, CEA can be considered as an effective target.

2.3 Other targets

CRC patients are treated with CAR-T cell therapy. In terms of target selection, in addition to the above two major targets of GCC and CEA, there are other targets, such as mesothelin (MSLN), transmembrane protein (EGFR), etc. Among them, MSLN belongs to a class of cell surface glycoproteins encoded by the MSLN gene, which is anchored on the cell surface by glycosylphosphatidylinositol and is abnormally expressed in colorectal cancer tumor tissue. In patients with CRC, it can be used as a major therapeutic target because it can cause tumor proliferation and clearing. On the basis of designing CAR-T cells targeting MSLN, the specificity of CRC cells can be accurately identified and an effective attack can be formed. EGFR, as a transmembrane protein, belongs to the tyrosine kinase receptor family. Based on CRC patients, EGFR can be highly expressed and can be used as a biomarker for the prognosis of metastatic CRC. When EGFR is highly expressed, it can promote tumor cell proliferation, invasion and metastasis. When the EGFR signaling pathway is abnormally activated, it will promote the occurrence and development of CRC. CRC patients receive CAR-T cell therapy, and use EGFR as a target. By modifying T cells, they can further specifically identify CRC cells with high EGFR expression, and then activate their immune killing mechanism, so that the patient's tumor volume can be reduced to a certain extent.。

CAR-T cell therapy offers a promising approach for treating colorectal cancer (CRC), with multiple targets currently under investigation in clinical trials. While it demonstrates potential for targeted treatment, several challenges remain that require further exploration and innovation to fully realize its therapeutic benefits.

3 Evaluating the hurdles of CAR-T cell therapy in colorectal cancer (CRC) treatment

3.1 Tumor microenvironment suppression issues

Research indicates that the tumor microenvironment (TME) in CRC patients contains various immunosuppressive cells and cytokines, which can suppress the function and proliferation of CAR-T cells, ultimately diminishing the effectiveness of CAR-T cell therapy [6]. For instance, when CAR-T cell therapy targeting CEA is applied to CRC, the acidic and immunosuppressive conditions within the solid tumor can hinder the infiltration and expansion of CAR-T cells in tumor tissues. Similarly, other therapeutic targets like MSLN and EGFR also face significant challenges due to the

immunosuppressive nature of the TME.

In general, the CRC tumor microenvironment is highly complex and contains many immunosuppressive factors, which will affect the infiltration, survival, and functional effects of CAR-T cells, thereby affecting the efficacy and safety of CAR-T cell therapy for CRC patients. Therefore, effective measures need to be taken to solve the problem of tumor microenvironment suppression.

3.2 Difficulty in target selection

Although there are many targets for CAR-T cell therapy to treat CRC, in addition to the above-mentioned GCC, CEA, MSLN, and EGFR targets, there are also activated natural killer group 2 member D ligand (NKG2DL), human epidermal growth factor receptor-2 (HER-2), etc., Each target has the potential to contribute to the treatment of CRC; however, the selection of an optimal target is complicated by the influence of various factors, posing significant challenges in the process.

Tumor heterogeneity factors: CRC is highly heterogeneous. In other words, there may be cancer cells with different characteristics in the same tumor, and different cancer cells may express different antigens or antigen levels. In this case, If CAR-T cell therapy is applied to treat CRC and a single target is chosen, it will not cover the heterogeneous cancer cells, which will lead to tumor escape or recurrence.

The scarcity of tumor-specific antigens (TSAs) is due to the fact that there are relatively few TSAs and more tumor-associated antigens (TAAs) in colorectal cancer. As TSAs are specifically expressed in tumor cells, they can accurately target tumor cells and reduce off-target effects during CAR-T cell therapy for CRC. However, insufficient TSA in CRC will limit the target selection of CAR-T cell therapy.

Tumor-associated antigen (TAA) off-target risk factors. TAAs are expressed to a certain extent in normal tissues. TAA-based CAR-T cell therapy carries the risk of off-target effects, leading to unintended damage when CAR-T cells attack not only tumor cells but also healthy tissues expressing the target antigen, they may also attack normal tissues expressing the same antigens, thereby causing adverse reactions in CRC patients. Research has demonstrated that EGFR is frequently overexpressed in colorectal cancer (CRC), but it is also expressed to a certain extent in normal tissues. Therefore, CAR-T cell therapy using EGFR as a target may cause off-target risks [7].

3.3 Side effects and safety issues

CAR-T cell therapy can produce certain therapeutic effects in the treatment of CRC, and there are many targets to choose from, but it will also cause a series of side effects and safety issues in CRC patients. In terms of side effects, they mainly include CRS, neurotoxicity, infection risk, blood system changes, etc. In terms of safety, the main reasons are the specificity of CAR-T cell therapy and the risk of T-cell malignancy. When CRC patients receive CAR-T cell therapy for treatment, toxic side effects may occur, such as systemic inflammatory response caused by CRS, headache, confusion, and epileptic seizures caused by neurotoxicity, and bacterial, viral, and fungal infections caused by infection risks. Improper treatment will affect the overall efficacy and safety of the patient and threaten his or her life [8]. Therefore, when using CAR-T cell therapy to treat CRC patients, it is equally crucial to thoroughly consider and address potential side effects and safety concerns associated with the treatment.

4 Analysis of the prospects of CAR-T cell therapy for CRC

4.1 Optimizing treatment techniques to overcome tumor microenvironmental inhibition

Over the past few years, as medical technology has continued to advance and develop, relying on new technologies such as gene editing and cell culture, CAR-T cell therapy can be more sophisticated and efficient in design and preparation. On this basis, the targeting ability and safety of CAR-T cells can be improved, thereby achieving the effect of improving clinical treatment efficacy. Therefore, from the perspective of the prospects of CAR-T cell therapy for CRC, it is necessary to focus on the optimization of treatment technology, such as optimizing the structure and function of CAR-T cells to enhance their adaptability in the tumor microenvironment, thereby effectively counteracting the suppression of CAR-T cell function caused by the CRC microenvironment. For example, optimizing and transforming CAR-T cell technology can effectively respond to immunosuppressive molecules [9-10]. In the future, with the continuous development of medical technology, genetic engineering technology can be used to transform CAR-T cells, enhance their ability to express antibodies or receptors for immunosuppressive molecules, and neutralize the inhibitory effects of immunosuppressive molecules, further promoting the improvement of CAR-T cell anti-tumor ability.

4.2 Develop personalized treatment plans and screen scientific cell targets

As mentioned above, CRC is highly heterogeneous, and different patients have certain differences in tumor genotype, phenotype, and treatment response. Therefore, from the perspective of the prospects of CAR-T cell therapy for CRC, it is necessary to focus on the formulation of personalized treatment plans. For example, by analyzing the gene sequencing and immunohistochemistry of tumor tissues of CRC patients in detail, the CAR-T cell targets and treatment plans suitable for patients can be scientifically screened out to further improve the clinical treatment's efficacy and safety. In addition, in order to meet the needs of multi-target treatment of CRC and overcome the constraints of single-target CAR-T cell therapy, it is necessary for clinical medical researchers to devote themselves to the development and research of dual-target or multi-target CAR-T cell therapy in the future. For example, some scholars have proposed that the anti-tumor effect of CAR-T cell therapy targeting CEA and HER2 may be more advantageous and can reduce the occurrence of off-target effects. This research conclusion can be used as a reference point for the formulation of personalized treatment plans. Combined with the specific condition and clinical manifestations of CRC patients, scientific cell targets can be screened out to achieve personalized and targeted treatment, thereby improving the clinical therapeutic impact and safety of targeted treatment of CAR-T cell therapy.

4.3 Using combined treatment options to improve the safety of clinical treatment

Since the side effects of CAR-T cell therapy for targeted treatment of CRC will affect the overall efficacy and safety of patients, the research, development and utilization of combined treatment plans should be emphasized in the future. CAR-T cell therapy can be combined with chemotherapy, radiotherapy, targeted therapy and Synergistic targeting of co-inhibitory immune checkpoints through combinatorial blockade strategies could recalibrate the tumor-immune interface, thereby enhancing treatment responsiveness and reducing immune-related toxicities in CRC therapeutics. For example, CAR-T cell therapy can be combined with chemotherapy to use the effect of chemotherapy drugs to kill tumor cells, reduce tumor load, and further promote CAR-T cell infiltration and reproduction; at the same time, chemotherapy treatment methods can be used to promote the improvement of tumor microenvironment and improve the efficacy of CAR-T cell therapy. From the current situation, there are relatively few clinical trials on the combination of CAR-T cell therapy and chemotherapy for the treatment of CRC patients. However, from a theoretical perspective, its feasibility is high and needs further exploration [11-12]. In addition, in order to reduce the efficacy and safety of CAR-T cell therapy for CRC patients, local delivery of CAR-T cells can be explored in the future to effectively prevent and control the occurrence of systemic and psychological side effects in patients; through the development of new immunomodulators, Pharmacodynamic optimization of CAR-T constructs through dual-affinity tuning and microenvironment-responsive regulation could achieve therapeutic index expansion in solid tumors, balancing enhanced tumor clearance capacity with controlled cytokine release syndrome.

5 Conclusion

In summary, there are many targets that can be selected for CAR-T cell therapy in the treatment of CRC patients, including GCC, CEA, MSLN, EGFR, etc. Different targets can play different therapeutic mechanisms, such as reducing tumor size, prolonging patient survival, etc. However, there are still some challenging problems in the clinical treatment process, which are mainly reflected in tumor microenvironment inhibition, difficulty in target selection, side effects and safety issues. Therefore, from the perspective of the prospects of CAR-T cell therapy for CRC, in the future, we need to focus on optimizing CRC treatment technology, formulating personalized treatment plans, and using combined treatment plans, etc., in order to overcome tumor microenvironment inhibition, screen out scientific cell targets, reduce side effects, improve clinical treatment safety, and further enhance the therapeutic potential of CAR-T cell therapy in CRC is constrained by tumor heterogeneity., promote the improvement of patients' condition and prolong their survival.

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