Advances in adoptive cellular therapy for colorectal cancer: a narrative review

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Background and Objective: In recent years, adoptive cell therapy (ACT) has shown great potential in antitumor treatment. To significantly improve the clinical efficacy of ACT against solid tumors, we may need to carefully study the latest developments in ACT. As one of the most common malignancies, colorectal cancer (CRC) is a major risk to human health and has become a significant burden on global healthcare systems. This article reviews the recent advances in the treatment of CRC with ACT.

Methods: We searched PubMed for articles related to ACT for CRC published as of August 31, 2022, and retrieved relevant clinical trial information on the National Institutes of Health ClinicalTrials.gov website. Based on search results, comprehensive and systematic review is made.

Key Content and Findings: This article provides an overview of the research progress of ACT for CRC, including chimeric antigen receptor (CAR) T-cell therapy, T-cell receptor (TCR)-engineered T-cell therapy, and tumor-infiltrating lymphocyte (TIL) therapy. Common tumor-associated antigens (TAAs) in clinical trials of CAR-T cell therapy for CRC are described.

Conclusions: Despite many obstacles, ACT shows great promise in treating CRC. Therefore, more basic experimental studies and clinical trials are warranted to further clarify the effectiveness and safety of ACT.

Keywords: Adoptive cellular therapy; colorectal cancer (CRC); clinical trials

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Introduction

Colorectal cancer (CRC) is a major global public health problem. As the third most common malignancy and the second most deadly cancer, CRC poses serious threats to human health (1). Despite the dramatic advances in diagnostic techniques and treatment strategies in recent decades, the therapeutic effectiveness and prognosis of CRC remain suboptimal. Therefore, new therapeutic strategies for CRC to improve survival are urgently required.

Immune checkpoint inhibitors (ICIs), such as cytotoxic-T-lymphocyte-associated antigen 4 (anti-CTLA-4) and anti-programmed cell death-1 (PD-1) antibodies, when used in combination with surgery, radiotherapy, and/or chemotherapy, can achieve better clinical outcomes in patients with CRC. However, these drugs are only approved for the treatment of tumors with mismatch repair deficiency or high microsatellite instability (2,3).

Although ICI has brought about significant changes in the treatment of many solid tumor malignancies, its efficacy depends critically on the presence of sufficient tumor-

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Table 1 The search strategy summary

Items	Specification
Date of search	August 31, 2022
Databases and other sources searched	PubMed and ClinicalTrials.gov
Search terms used	"Colorectal cancer", "adoptive cellular immunotherapy (ACT)", "CAR-T", "TCR-T", "TIL"
Time frame	1982–2022
Inclusion and exclusion criteria	Content related to search keywords were included in the analysis
Selection process	All the authors jointly discussed and selected the studies to obtain the consensus of the review
Any additional considerations	None

CAR, chimeric antigen receptor; TCR-T, T cell receptor-engineered T cell; TIL, tumor-infiltrating lymphocyte.

specific lymphocytes, and adoptive cell therapy (ACT) is rapidly evolving to fill this gap (4). ACT is a highly personalized cancer therapy, in which the immune cells are isolated from tumor patients, expanded and modified in vitro, and then infused back into the patient, so that these cells can specifically recognize tumor cells and induce autologous immune responses to kill tumor cells (5). ACT works in ways that traditional small-molecule drugs and biologics cannot, representing a major advance in biotechnology that has great potential (6). Unlike ICIs that block T-cell suppressor receptors, ACT exhibits antitumor activity by isolated expansion of large numbers of T cells, which may allow bypassing certain suppressive immunomodulatory factors. In addition, some forms of ACT require genetic modification or redesign of T cells, which can help improve T cell specificity. ACT is often combined with lymphocyte-depleting chemotherapy, and lymphocyte-depleting chemotherapy pretreatment may eliminate certain T cell suppressive mechanisms and help improve T cell proliferation and persistence (7).

Unfortunately, the development of ACT in solid tumors faces important limitations imposed by the availability and quality of immune cells isolated from the donor. Because ACT requires the generation of tumor-specific lymphocytes for each patient, it can only be performed in a small number of specialized treatment centers, which is technically and economically challenging (8). Secondly, the identification of specific tumor antigens is crucial for the design and execution of ACT (9). In addition, ACT exhibits high efficiency accompanied by high toxicity, especially with the risk of cytokine release syndrome (CRS). The inefficiency of tumor-specific lymphocyte transport to the tumor site likewise poses a barrier to the clinical application of ACT in the context of solid tumors (10). This article provides an overview of the research progress of ACT for CRC, including chimeric antigen receptor (CAR) T-cell therapy, T-cell receptor (TCR)-engineered T-cell therapy, and tumor-infiltrating lymphocyte (TIL) therapy. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6196/rc).

Methods

Information used to write this paper was collected from the sources listed in *Table 1*.

CAR-T cell therapy

CAR-T cell therapy has been the most rapidly developed and widely applied branch of anticancer cellular immunotherapy. It rapidly changed the landscape of hematological malignancy treatment and already accounts for more than half of the cell therapies currently under development or in the market (11). The US Food and Drug Administration (FDA) has approved treatments of CAR-T cells targeting CD19 [including Kymriah (tisagenlecleucel), Yescarta (axicabtagene ciloleucel), Tecartus (brexucabtagene autoleucel), and Breyanzi (lisocabtagene maraleucel)], as well as those targeting B-cell maturation antigen (BCMA) [including Abecma (idecabtagene vicleucel) and Carvykti (ciltacabtagene autoleucel)], which are expected to play key roles in tumor treatment (12).

During CAR-T cell therapy, T lymphocytes are isolated from the patients' own peripheral blood and expanded *in vitro*; subsequently, CARs are expressed on the cell surface through the use of a plasmid vector or messenger RNA (mRNA) or by viral vector transduction, which enables

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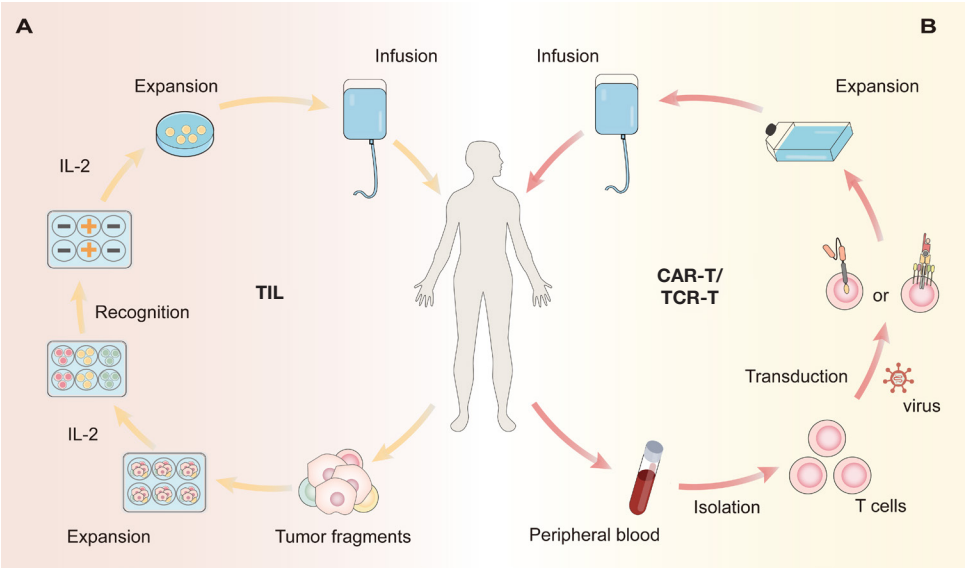

Figure 1 Production processes of TILs, CAR-T cells and T cell receptor-engineered T cells. (A) TILs are isolated from surgically removed tumor tissue, which is followed by *in vitro* expansion using IL-2 and the screening of tumor-specific TILs; after further expansion, the cells are infused back into the patient. (B) T lymphocytes are isolated from a patient's peripheral blood and then expanded, which is followed by genetic modification to make them express CAR or TCR; after extensive amplification and quality control, the cells are infused back into the patient, thereby exerting an antitumor effect. CAR, chimeric antigen receptor; IL-2, interleukin 2; TCR-T, T cell receptor-engineered T cell; TIL, tumor-infiltrating lymphocyte.

the human immune system to recognize tumor antigens and respond accordingly (13-16) (*Figure 1*). CAR-T cell therapy does not rely on the participation of major histocompatibility complex (MHC), thus avoiding the T-cell dysfunction caused by MHC downregulation on the tumor surface (17-19).

Structure of CAR-T cells

CARs are synthetic fusion proteins consisting of 4 domains: extracellular antigen binding domain, hinge region, transmembrane (TM) domain, and intracellular signaling domain (*Figure 2*) (20-24). The extracellular domain is an extracellular tumor antigen-binding region, composed of single-chain fragment variable (scFv) derived from the heavy chain variable region (VH) and light chain variable region (VL) of antibodies. The hinge region (or spacer region) is composed of immunoglobin G (IgG)4 and CD8 molecules and connects the extracellular antigen-binding domain and the TM domain. CAR is anchored to the cell membrane via the TM domain and the hinge region. The intracellular signaling domain consists of CD3ζ and many costimulatory molecules, which initiate antigen-specific immune responses and directly affect the effect of CARs in activating T cells (25).

As our understanding of T-cell activation and tumor microenvironment (TME) improves, the structures of CARs are becoming more complex (*Figure 3*) (26-29). The intracellular signaling domains of the first-generation CARs had no costimulatory molecules and include only CD3ζ, which is fused with the extracellular single-chain antibody scFv to modify and activate T cells (30). However, after the specific antigens recognize tumor cells, the proliferative capacity, persistence, and cytotoxicity of the first-generation CARs becomes suboptimal. Therefore, costimulatory molecules [e.g., CD28, 4-1BB (CD137), inducible T cell costimulator (ICOS), and CD278] that enhance the T-cell response were added to the second-generation CARs to increase cell persistence (22). The third-generation CARs include CD3ζ and 2 costimulatory domains (i.e., CD28/ICOS and 4-1BB/OX-40/CD27), which further enhances their ability to combat tumor cells (31,32). The fourth-generation CARs contain nuclear factor of activated T cells (NFAT) domain, which can induce a large number of cytokines [e.g., interleukin (IL)-12 and IL-15] and increase the survival rate of CAR-T cells in the immunosuppressive

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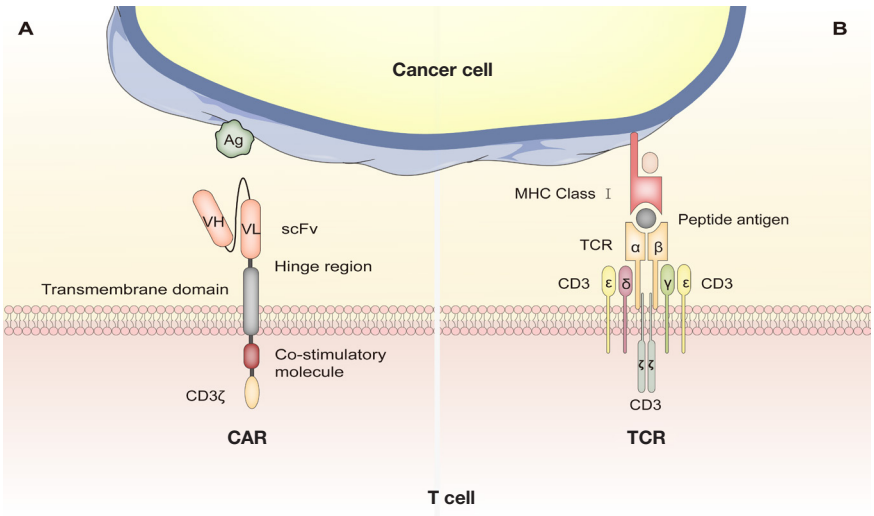

Figure 2 Structures of CAR and TCR. (A) CARs consist of 4 domains: extracellular antigen-binding domain, hinge region, transmembrane domain, and intracellular signaling domain. The extracellular scFv domain binds to tumor-associated antigens on the surface of tumor cells. The intracellular signaling domain consists of CD3ζ and many co-stimulatory molecules, which initiate antigen-specific immune responses. (B) TCR is a heterodimer with α and β subunits that recognizes antigenic peptides presented by MHC class I molecules. It forms complexes with multiple CD3 signaling subunits (CD3εγ, CD3εδ, and CD3ζζ) to activate T cells. CAR, chimeric antigen receptor; TCR, T cell receptor; scFv, single-chain variable fragment; MHC, major histocompatibility complex; Ag, antigen; VH, heavy chain variable region; VL, light chain variable region.

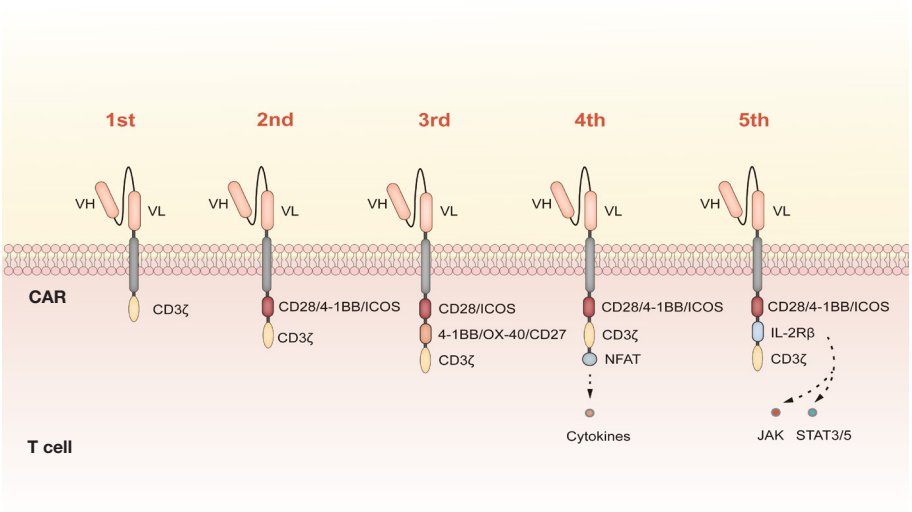

Figure 3 Structures of different generations of CAR-T cells. The 5 generations of CARs developed thus far have specific intracellular domains. The first-generation CARs only have a CD3ζ-derived signaling module. The second-generation CARs contain additions of costimulatory domains, including CD28, 4-1BB (CD137), or ICOS (CD278). The third-generation CARs include CD3ζ and 2 costimulatory domains (e.g., CD28/ICOS and 4-1BB/OX-40/CD27). The fourth-generation CARs contain NFAT domain, which can induce cytokines such as IL-12. The fifth-generation CARs include the addition of IL-2Rβ to the second generation of CARs to drive JAK-STAT signaling. CAR, chimeric antigen receptor; IL, interleukin; VH, heavy chain variable region; VL, light chain variable region; ICOS, inducible T cell costimulatory; NFAT, nuclear factor of activated T cells; JAK, Janus kinases; STAT-3/5, signal transducer and activator of transcription 3/5.

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TME (33-35). The safety and efficacy of the fifth-generation CARs, which are distinguished by the addition of IL-2Rβ to the second-generation CARs, are still being tested. The IL-2Rβ fragments can induce the production of Janus kinases (JAKs) as well as signal transducer and activator of transcription 3/5 (STAT-3/5) via mRNA transcription (36).

Basic research on CAR-T cell therapy for solid tumors is being driven forward, but CAR-T cell therapy for solid tumors like CRC is not as successful as in hematologic malignancies and faces a variety of challenges. Although the reasons for this are unclear, it is likely that multiple factors limit the efficacy of CAR-T cells in solid tumors, such as low tumor tissue infiltration, lack of tumor-specific antigens (TSAs), the presence of an immunosuppressive TME, and the development of toxic side effects (37,38). The choice of target antigens is a major determinant of the safety and efficacy of CAR-T cell therapy. Since most solid tumors are of epithelial origin, the presence of TSAs is rare (39). CAR-T cells must recognize the correct tumor-associated antigens (TAAs), however, the targets currently used for anti-CRC CAR-T cell therapy are usually co-expressed in normal cells and have generally low specificity. CAR-T cells targeting nonspecific surface antigens can generate cross-reactivity, leading to normal cell death and severe toxicity (40,41).

Therapeutic targets of CAR-T cell therapy in CRC

CAR-T cell therapy has shown great potential in the personalized immunotherapy of tumors. Many relevant studies are being conducted in patients with solid tumors. Various strategies have been proposed to further improve the efficacy and safety of CAR-T cell therapy. Among them, target selection is a crucial step. Ideally, TSAs are more suitable as antigenic targets for CAR-T cells to achieve specificity to ensure clinical safety, however, they are rarely present in most solid tumors of epithelial origin (39). Therefore, the targets identified by CAR-T cells in solid tumors have always been TAAs. However, the targets currently used for anti-CRC CAR-T cell therapy are usually co-expressed in normal cells and generally have low specificity. CAR-T cells targeting nonspecific surface antigens can generate cross-reactivity, leading to normal cell death and severe toxicity (39). For CAR-T cell-mediated tumor cell recognition and killing, finding suitable tumor antigens to improve the clinical applicability and safety of CAR-T cell therapy while maintaining the antitumor activity of CAR-T cells is a major challenge. Here, we summarize the possible targets of CAR-T cell therapy for CRC and the recent studies (42-52) (*Table 2*).

Carcinoembryonic antigen (CEA)

CEA, an autoantigen membrane-binding protein that belongs to the immunoglobulin family, is currently the most commonly used marker for CRC. CEA can be detected in the early stages of human embryos and fetuses. In normal adult tissues, CEA is expressed only at low levels on the apical surface of glandular epithelia in the gastrointestinal tract, making it a promising target for CAR-T cell therapy (53-55). CEA is overexpressed in many tumors including colon cancer, pancreatic cancer, gastric cancer, lung cancer, and ovarian cancer (55,56).

The first clinical trial on CAR-T cell therapy for CRC (NCT02349724) began in 2014. Five escalating dose levels (DLs) (1×10^5 to 1×10^8/CAR$^+$/kg cells) of CAR-T cells were applied in 10 patients with CRC who had previously received treatments but experienced progressive disease (PD). Of these patients, 7 patients achieved stable disease (SD) after treatment, and 2 patients maintained SD for more than 30 weeks. In addition, serum CEA levels decreased significantly in most patients, and the tumor lesions shrank in 2 patients. Furthermore, CEA CAR-T cell therapy was well tolerated in CEA$^+$ CRC patients even in high doses, and no serious treatment-related adverse events were reported. Therefore, CAR-T cell therapy is considerably effective and safe for patients with CEA$^+$ CRC (47).

The natural killer group 2 member D (NKG2D)

The NKG2D receptor is a C-type lectin-like activating receptor mainly expressed in natural killer (NK) cells, γδ T cells, CD8$^+$ T cells, and a subset of CD4$^+$ T cells (57). It activates immune cells through TM adaptor DNAX-activating protein 10 (DAP10), thus triggering cell proliferation, proinflammatory cytokine [e.g., interferon γ (IFN-γ) and IL-2] production, and cytotoxic effects (58). The KG2D receptor recognizes a broad and structurally diverse range of ligands. In particular, human NKG2D recognizes MHC class I polypeptide-related sequence A and B as well as family of 6 cytomegalovirus UL16-binding proteins (ULBP1-6) (57,59). Generally, these ligands are highly expressed in response to stressors (e.g., infection and oncogenic transformation) but are at low levels in normal tissues (57,58,60). NKG2DL is expressed in a variety of tumors, including ovarian cancer, colon cancer, cervical cancer, breast cancer, lung cancer, hepatocellular carcinoma, kidney cancer, prostate cancer, pancreatic cancer, head

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Table 2 The relevant studies and possible therapeutic targets of CAR-T cell therapy for colorectal cancer

Target	NCT number	Disease type	N	Phase	Status	First posted	Last update posted	Ref.
CEA	NCT02349724	Colorectal cancer	75	I	Unknown status	2015-01-29	2017-04-25	(47)
	NCT02416466	Liver metastases	8	I	Completed	2015-04-15	2019-03-26	NA
	NCT02850536	Liver metastases	5	I	Completed	2016-08-01	2021-10-21	(48)
	NCT02959151	Colorectal cancer metastatic	20	I/II	Unknown status	2016-11-08	2016-11-08	NA
	NCT04348643	Colorectal cancer	40	I/II	Recruiting	2020-04-16	2020-09-01	NA
	NCT04513431	Stage III colorectal cancer/colorectal cancer liver metastasis	18	eI	Not yet recruiting	2020-08-14	2020-08-14	NA
	NCT05240950	Colorectal cancer liver metastasis	18	I	Recruiting	2022-02-15	2022-03-11	NA
	NCT05396300	Colorectal cancer	60	I	Recruiting	2022-05-31	2022-06-02	NA
	NCT05415475	Colorectal cancer	36	I	Recruiting	2022-06-13	2022-07-22	NA
NKG2D	NCT03018405	Colorectal cancer	146	I/II	Unknown status	2017-01-12	2019-09-19	(49)
	NCT03310008	Colon cancer liver metastasis	36	I	Active, not recruiting	2017-10-16	2020-06-16	NA
	NCT03370198	Colon cancer liver metastasis	1	I	Active, not recruiting	2017-12-12	2020-06-18	NA
	NCT03692429	Unresectable metastatic colorectal cancer	49	I	Recruiting	2018-10-02	2020-11-20	(50)
	NCT04107142	Colorectal cancer	10	I	Unknown status	2019-09-27	2019-09-27	NA
	NCT04550663	Colorectal cancer	10	I	Not yet recruiting	2020-09-16	2020-09-23	NA
	NCT05248048	Refractory metastatic colorectal cancer	9	eI	Recruiting	2022-02-21	2022-02-21	NA
EGFR	NCT03152435	EGFR-positive colorectal cancer	20	I/II	Unknown status	2017-05-15	2017-08-16	NA
	NCT03542799	Metastatic colorectal cancer	20	I	Unknown status	2018-05-31	2018-05-31	NA
GUCY2C	NCT05287165	Colorectal cancer	19	eI	Recruiting	2022-03-18	2022-03-18	NA
	NCT05319314	Colorectal cancer	30	I	Recruiting	2022-04-08	2022-08-05	NA
HER2	NCT03740256	Colorectal cancer	45	I	Recruiting	2018-11-14	2022-08-29	(51)
CD133	NCT02541370	Colorectal cancer	20	I/II	Completed	2015-09-04	2019-12-17	(52)
MUC1	NCT02617134	Colorectal carcinoma	20	I/II	Unknown status	2015-11-30	2016-12-06	NA
	NCT05239143	Colorectal cancer	100	I	Recruiting	2022-02-14	2022-07-25	NA
EpCAM	NCT03013712	Colon cancer	60	I/II	Unknown status	2017-01-06	2017-01-06	NA
	NCT05028933	Colorectal cancer	48	I	Recruiting	2021-08-31	2022-01-13	NA
C-Met	NCT03638206	Colorectal cancer	73	I/II	Recruiting	2018-08-20	2019-12-11	NA
MSLN	NCT04503980	Colorectal cancer	10	eI	Recruiting	2020-08-07	2020-08-07	NA
	NCT05089266	Colorectal cancer	30	I	Not yet recruiting	2021-10-22	2021-10-22	NA
B7-H3	NCT05190185	Colorectal cancer	18	I	Recruiting	2022-01-13	2022-01-13	NA

CEA, carcinoembryonic antigen; eI, early phase 1; NKG2D, natural killer group 2D; EGFR, epidermal growth factor receptor; GUCY2C, guanylyl cyclase C; HER2, human epidermal growth factor receptor 2; CD133, prominin-1; MUC1, mucin 1; EpCAM, epithelial cell adhesion molecule; c-Met, cellular mesenchymal-epithelial transition factor; MSLN, mesothelin; B7-H3, B7 homolog 3; NA, not applicable. CAR, chimeric antigen receptor.

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and neck cancer, leukemia, lymphoma, multiple myeloma, melanoma, glioma, osteosarcoma, and neuroblastoma (59).

CAR-T cell therapy targeting NKG2D has shown CRC cell-specific cytotoxicity and thus could significantly suppress tumor growth and extend the overall survival in mouse models. One study reported human NKG2D-positive lymphocyte infiltration found in the tumor sections of NKG2D CAR-T cell-treated mice; NKG2D CAR-T cells showed excellent immunotherapeutic activity, although gradual weight loss was also observed in the mice (60). The clinical trial (NCT03018405) to investigate the safety and clinical activity of NKG2D-based CAR-T cells retrovirally modified (NKR-2) in the treatment of 7 refractory tumors (including CRC) demonstrated that NKR-2 exerted long-term antitumor activity against multiple tumors, with maximum efficacy observed after multiple NKR-2 administrations (49).

Epidermal growth factor receptor (EGFR)

EGFR, also known as human epidermal growth factor receptor 1 (HER1), is a TM glycoprotein a member of the erbB family of tyrosine kinase receptors. It binds to ligands to activate dimerization, triggering cell proliferation, survival, and differentiation (61). EGFR is also a driver of tumorigenesis. Recent research has shown that EGFR has emerging functions that are related to autophagy and metabolism, which can be induced by cellular and environmental stress and be activated in cancer cells to provide them with a survival advantage and resistance to therapy (62). This receptor is often overexpressed and/or mutated in most solid tumors, including those of glioblastoma, non–small cell lung cancer, and cancers of the colorectum, breast, kidney, ovary, head and neck, and brain (61,62).

A phase I (NCT03542799) and II trial (NCT03152435) have been designed to explore the maximum tolerated dose (MTD), safety, and feasibility of EGFR-IL-12-CAR-T cells and EGFR-CAR-T cells in patients with CRC metastasis. The MTD escalation trial is expected to include 9 patients, whereas the phase II trial is expected to include 11 patients. The safe doses of these trials will be applied in the clinical efficacy study.

Guanylyl cyclase C

Guanylyl cyclase C (GUCY2C or GCC), a member of the membrane-bound guanylyl cyclase family, is expressed only on the apical surface of intestinal epithelial cells from the duodenum to rectum and in a subset of hypothalamic neurons (63,64). GUCY2C is overexpressed in nearly 95% of those with CRC [including metastatic CRC (mCRC)] as well as in those with pancreatic, gastric, or esophageal cancer (63).

In mouse models of human CRC treated with CAR-T cells, the tumors shrank significantly, and mice in the CAR-T cell group survived longer than did those in the control group, with no side effects being observed, Therefore, human GUCY2C-targeted CAR-T cells may be developed for the treatment of GUCY2C-expressing mCRC (64).

Human epidermal growth factor receptor 2 (HER2)

HER2 is an oncogene encoding the TM glycoprotein receptor with intracellular tyrosine kinase activity (65,66). In the human body, HER2 is found in the epithelial structures of the respiratory and digestive systems and in the ependymal cells in brain ventricles (67). HER2 is overexpressed in esophageal adenocarcinoma as well as in breast, gastric, lung, pancreatic, and CRCs (68,69). The mutation frequency of HER2 is higher in microsatellite instability-high/hypermutated (MSI-H) CRC than in microsatellite-stable (MSS) CRC (70,71).

In mouse models of CRC, HER2-specific CAR-T cells selectively killed HER2-positive tumor cells; compared with the control group, adoptive transfer of HER2-specific CAR-T cells resulted in the regression or even elimination of the CRC xenograft, protection against tumor relapse, and significant survival advantage (72). In one trial (NCT03740256), HER2-specific CAR-T cells were used to treat patients with a variety of solid tumors (including CRC); along with the intratumoral injection of the oncolytic adenovirus CAdVEC, the safety and efficacy of CAR-T cell therapy were also investigated (51).

CD133

CD133 (also known as AC133/prominin-1), a pentaspan membrane glycoprotein located in membrane protrusions, is expressed by cancer stem cells (CSCs) derived from various epithelial cells. It is the most commonly used cell surface antigen for detecting and isolating CSCs from various solid tumors, including brain, colon, pancreas, prostate, lung, and liver cancers (73). In CRC, CD133 expression was found to be associated with chemotherapy resistance and a high metastasis and recurrence rate (74,75).

In one study (NCT02541370), CD133-CAR-T cells (CART-133) were infused into patients with CD133-positive metastatic pancreatic cancer, hepatocellular carcinoma, or

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CRC, yielding significant efficacy and tolerable toxicities. In addition, repeated cell infusions provided a longer period of disease stability, especially in patients who achieved tumor shrinkage after the first cell infusion (52).

Mucin 1 (MUC1)

MUC1 is a highly glycosylated TM protein that forms a mucosal barrier on the apical surface of most glandular epithelial cells, thus playing an important protective role and mediating signaling. MUC1 with abnormal glycosylation is a well-recognized TSA on epithelial cell tumors (76). MUC-1 is overexpressed in colorectal, lung, pancreatic, prostate, ovarian, lung, breast, and prostate cancers (77).

A phase I/II clinical trial (NCT02617134) was initiated in 2015 with the aim to evaluate the safety and efficacy of MUC1-CAR-T cell immunotherapy in patients with relapsed or refractory solid tumors (including malignant glioma, CRC, and gastric cancer).

Epithelial cell adhesion molecule

Epithelial cell adhesion molecule (EpCAM or CD326) is a type I TM glycoprotein that is expressed in the tissues of most healthy adults, mainly in the basolateral membrane of normal epithelial cells (78,79). Under normal circumstances, EpCAM is involved in cell-to-cell adhesion and regulates the differentiation of progenitor cells and embryonic stem cells; however, its overexpression is associated with increased cell proliferation, migration, and invasion as well as tumor metastasis (79,80). Although EpCAM is overexpressed in a variety of epithelial tumors, it is only associated with poor prognosis in certain cancer types (e.g., colorectal, breast, prostate, gallbladder, ovarian, bladder, pancreatic, and adenoid cystic cancers) (81). In CRC, EpCAM is overexpressed in more than 90% of cancer cells and plays a key role in the development and progression of tumors (80).

In the xenograft mouse models of CRC, it was reported that EpCAM-CAR-T cells could kill the target cells in an EpCAM-dependent manner and secrete tumor necrosis factor α (TNF-α) and IFN-γ, significantly delaying tumor growth and formation and showing excellent safety (82).

Cellular mesenchymal-epithelial transition factor

Cellular mesenchymal-epithelial transition factor (c-Met), also known as hepatocyte growth factor receptor (HGFR), is a receptor tyrosine kinase (RTK) (83). C-Met is expressed on epithelial cells, endothelial cells, neurons, hepatocytes, and hematopoietic cells (84) and is associated with cell proliferation and motility, tissue regeneration, wound healing, epithelial-mesenchymal transformation, and angiogenesis (85). C-Met is overexpressed in a variety of solid tumors including gastric, colorectal, pancreatic, lung, head and neck, ovarian, kidney, prostate, and breast cancers (86). More specifically, C-Met is overexpressed in 30–70% of CRC cases and is associated with tumor progression and metastasis (85).

In a phase I/II trial (NCT03638206), involving a variety of malignancies including colorectal, liver, ovarian, and kidney cancers, multitargeted genetically modified CAR-T cells/T cell receptor-engineered T cells (TCR-Ts), including 10 different tumor-specific antibodies, were used. Among them, C-Met was used as a target for colorectal, liver, ovarian, and kidney cancers.

Mesothelin (MSLN)

MSLN is a cell surface-bound, glycosylphosphatidylinositol (GPI)-anchored protein, whose normal expression is restricted to the mesothelial cells of the pleura, pericardium, peritoneum, and tunica vaginalis (87). MSLN is highly expressed in malignant pleural mesothelioma, ovarian cancer, breast cancer, pancreatic cancer, lung adenocarcinoma, and other malignancies.

Positive MSLN expression is found in 60% of patients with CRC, and its clinicopathological features and prognosis have not been fully elucidated. Although the biological function and molecular mechanism of MSLN in the pathogenesis of CRC remain unclear, MSN may become an important target for antitumor therapy (88).

B7 homolog 3

B7 homolog 3 (B7-H3 or CD276), a member of the B7/CD28 family, plays a key role in the T-cell-mediated immune response (89,90). B7-H3 can inhibit the activation and proliferation of T cells, reduce the secretion of cytokines (e.g., IL-2 and IFN-γ), and promote the immune escape of tumor cells (91). B7-H3 is highly expressed in malignant tumors including CRC, prostate cancer, breast cancer, and melanoma and is closely related to the tumor-node-metastasis (TNM) stage, cancer metastasis, and poor prognosis of patients (92,93).

B7-H3 may promote epithelial-mesenchymal transition (EMT) in CRC cells by activating the PI3K-Akt pathway to upregulate Smad1 expression (92). Therefore, B7-H3 is expected to be a target in CRC immunotherapy, and a relevant study (NCT05190185) is underway.

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Tumor-associated glycoprotein 72 (TAG-72)

TAG-72, a high-molecular-weight glycoprotein, is not expressed in most normal tissues except the secretory endometrium and fetal tissues. TAG-72 is mainly expressed in ovarian, colon, gastric, esophageal, pancreatic, breast, and lung cancers and is associated with poor prognosis. TAG-72 is highly expressed in 80% of CRCs and in 43% of sera samples from CRC patients (94,95).

In the C-9701 and C-9702 trials, Tag-72 was used as a tumor target for CAR-T therapy. In these two studies, 14 patients with mCRC were enrolled in C-9701 and 9 in C-9702. The difference between the two trials was that CART72 (CAR-T cells targeting Tag-72) was infused back into patients by intravenous infusion (C-9701) or via direct hepatic artery infusion (C-9702) in escalating doses, which was followed by a short course of IFN-α to upregulate TAG-72 expression. No significant treatment-related toxicity was observed in either trial. Detectable, but mostly short-term (≤14 weeks) persistence of CART72 cells was observed in blood. Trafficking to tumor tissues was confirmed in a tumor biopsy from 1 of 3 patients (96).

CAR-T cell therapies in China

As one of the major forces in CAR-T therapy research, China contributes about 33% of the global clinical trials and plays an integral role in CAR-T therapy innovation strategies (97). Two CAR-T products have been launched in China, and several CAR-T products are already on the verge of commercialization, potentially benefiting a wide range of cancer patients in China and globally. However, challenges remain in the development and optimization of new targets, functional enhancement, precise regulation, synthetic biology, and universal CAR-T cell therapy design (98). Chinese researchers are committed to enhancing the clinical efficacy and safety of cell therapies through strategies such as optimization of CAR structure, cocktail therapy, combined application of CAR-T with hematopoietic stem cell transplantation (HSCT), development of more efficient universal CAR-T (UCAR-T) cell therapy, and induced pluripotent stem cells (iPSCs)-derived cell therapy (97).

TCR-T therapy

The concept of TCR therapy actually predates the creation of CARs, and the relevant *in vitro* and animal experiments began very early. In 1986, Dembić *et al.* successfully transduced MHC-restricted *TCR*α and *TCR*β genes in mouse T cells, redefining the specificity of T cells. This was the origin of the current TCR-T cell therapy (99,100). In January 2022, tebentafusp (tebentafusp-tebn; Kimmtrak), a bispecific gp100 peptide-human leukocyte antigen (HLA)-A*02:01-directed TCR CD3 T cell engager received its first approval by the US FDA for the treatment of HLA-A*02:01-positive adults with unresectable or metastatic uveal melanoma (101). As the world's first approved TCR-T cell therapy for solid tumors, tebentafusp is a milestone for the application of T-cell therapy in the treatment of solid tumors.

TCR-engineered T-cell therapy uses genetic engineering technology to introduce antigen-specific TCR gene sequences into patients' own T cells and mediates the specific recognition of tumor antigens by T cells through the expressed receptors, thereby exerting antitumor activities (32) (*Figure 1*).

TCR is a heterodimer composed of 2 highly variable peptide chains linked by disulfide bonds (*Figure 2*). The majority of T cells express an αβ TCR (TCR2) composed of alpha (α) and beta (β) chains (95%), and a smaller subset of T cells express a γδ TCR (TCR1) with gamma (γ) and delta (δ) chains (102). Each peptide chain is composed of a variable (V) region, constant (C) region, TM domain, and cytosolic region. The V region of the α and β peptide chains possess 3 hypervariable regions known as complementarity determining regions (CDR1, CDR2, and CDR3), which recognize polypeptide fragments presented by MHC class I molecules (103). Since αβ TCR itself does not have an intracellular signaling component, it requires the formation of complexes (TCR-CD3 complexes) with multiple CD3 signaling subunits (CD3εγ, CD3εδ, and CD3ζζ) for signal transduction to activate T cells (104).

Compared with CAR-T cells that recognize specific antigens on the surface of tumor cells, TCR-T cells have a wider range of target antigens. In fact, TCR-T can recognize any antigen presented by MHC molecules, regardless of whether it is located inside a cell or on the cell surface or whether it is a novel antigen produced after tumor cell mutation (105). Such antigens may include melanoma antigen recognized by T cells 1 (MART-1), gp100, CEA, New York esophageal squamous cell carcinoma-1 (NY-ESO-1), melanoma-associated antigen A3 (MAGE-A3), melanoma-associated antigen A4 (MAGE-A4), HER2, and CD19 (106). Due to their high specificities and strong immunogenicities, neoantigens (neoAgs) have been considered the ideal targets for

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Table 3 Studies on TCR-T therapy for colorectal cancer

NCT number	Target	Disease type	N	Phase	Status	First posted	Last update posted
NCT01212887	CEA	Colorectal cancer	14	I	Terminated	2010-10-01	2012-02-28
NCT01723306	CEA	Colorectal cancer	48	II	Suspended	2012-11-07	2016-06-14
NCT03431311	TGFβRII	Colorectal cancer	1	I/II	Terminated	2018-02-13	2019-06-13
NCT03638206	C-Met	Colorectal cancer	73	I/II	Recruiting	2018-08-20	2019-12-11
NCT03970382	Neo-antigen	Colorectal cancer	21	I	Suspended	2019-05-31	2022-02-08
NCT05124743	Neo-antigen	Colorectal cancer	2,000	I/II	Recruiting	2021-11-18	2022-07-28
NCT05194735	Neo-antigen	Colorectal cancer	180	I/II	Recruiting	2022-01-18	2022-07-28
NCT05292859	Neo-antigen	Colorectal cancer	180	I/II	Not yet recruiting	2022-03-23	2022-07-28
NCT05451849	MSLN	Colorectal cancer	115	I/II	Recruiting	2022-07-11	2022-08-22

CEA, carcinoembryonic antigen; TGFβRII, transforming growth factor-beta receptor type II; c-Met, cellular mesenchymal-epithelial transition factor; MSLN, mesothelin; TCR-T, T cell receptor-engineered T cell.

antitumor immunotherapy (107).

Several clinical studies have been validated the effectiveness of TCR-T cell therapy as a therapeutic intervention. In 2006, Morgan *et al.* first reported the treatment of 15 melanoma patients with MART-1 TCR-engineered T cells, and 2 patients achieved complete response (108). However, the research and development in TCR-T cells have also suffered several setbacks. In 2009, in the clinical trials (NCI-07-C-0174 and NCI-07-C-0175) for treating metastatic melanomas with TCR-T cells, objective response was seen in 30% and 19% of patients receiving anti-MART-1 or anti-gp100 TCR-T cell therapy, respectively. However, patients exhibited destruction of normal melanocytes in the skin, eye, and ear, which led to uveitis and hearing loss (109). In 2013, in the clinical trial (NCT01273181) of anti-MAGE-A3 TCR-T cell therapy, 5 patients experienced clinical regression of their cancers; however, 1 to 2 days after infusion, 3 patients experienced mental status changes, and 2 patients lapsed into comas and subsequently died (110). In 2011, Robbins *et al.* demonstrated for the first time the clinical efficacy of NY-ESO-1-targeting TCR-T cells in treating patients with metastatic melanoma or synovial sarcoma (111). Similarly, Rapoport *et al.* reported in 2015 that NY-ESO-1-targeting TCR-T cells achieved a complete response rate of 70% in 20 patients with advanced multiple myeloma without significant side effects (112).

For CRC, the first reported TCR-T cell therapy targeted the CEA antigen. In 2011, Parkhurst *et al.* constructed CEA-targeting TCR-T cells to treat 3 patients with mCRC with high CEA expression refractory to standard treatments. Although these TCR-T cells showed certain antitumor abilities, 2 patients developed PD 5–6 months after treatment, and no therapeutic response was observed in the remaining patient. All patients developed severe colitis, suggesting TCR-T cells attacked normal intestinal cells. Therefore, the trial was suspended. This trial demonstrated the feasibility of TCR-T cell therapy in metastatic colon cancer but also emphasized the toxicities of TCR-T cells and the limitations of using CEA as a target for cancer immunotherapy (113).

In summary, TCR-T cell therapy has shown good potential in both preclinical and clinical studies (8,35,102,107,114-116). However, clinical trials evaluating TCR-T for CRC are still in their early phases, and the safety and efficacy of these therapies still face many challenges (43). According to the US ClinicalTrials.gov website, clinical trials on the application of TCR-T in CRC patients include NCT03638206, NCT05124743, NCT05194735, NCT05292859, and NCT05451849 (*Table 3*). With the development of tumor immunology and the availability of more breakthrough technologies, it is believed that TCR-T cell therapy will exert a more important role in the treatment of solid tumors.

TILs

TILs are isolated from tissues adjacent to the tumor by tissue biopsy or surgery. After *in vitro* expansion using IL-2, they are implanted back into the patients to induce a robust

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Table 4 Studies on TIL-T for colorectal cancer

NCT number	Disease type	N	Phase	Status	First posted	Last update posted
NCT01174121	Metastatic colorectal cancer	332	II	Recruiting	2010-08-03	2022-09-08
NCT03610490	Metastatic colorectal adenocarcinoma	27	II	Active, not recruiting	2018-08-01	2021-11-10
NCT03904537	Colorectal cancer stage III	20	I/II	Unknown status	2019-04-05	2019-04-05
NCT03935893	Colorectal cancer	10	II	Recruiting	2019-05-02	2022-07-22
NCT04426669	Colorectal cancer	20	I/II	Recruiting	2020-06-11	2021-08-23
NCT04842812	Colorectal cancer	40	I	Recruiting	2021-04-13	2021-04-13

NCT, National Clinical Trial; TIL, tumor-infiltrating lymphocyte.

immune-mediated antitumor response (32) (*Figure 1*).

In 1982, Eberlein *et al.* were first to isolate TILs from a series of mouse tumor models (117). With the combination of cyclophosphamide, TIL, and IL-2, 100% of mice bearing MC-38 colon adenocarcinoma were cured of advanced hepatic metastases, and up to 50% of mice were cured of advanced pulmonary metastases, which paved the way for the application of TIL in the treatment of advanced tumors in humans (118).

The earliest clinical applications of TIL date back to 1988, when Rosenberg *et al.* were first to demonstrate the efficacy of TILs in treating metastatic melanoma in human body. After treatment with TIL cells + IL-2 + cyclophosphamide in patients with metastatic melanoma, the objective regression of the cancer was observed in 60% of patients who had not previously been treated with IL-2 and in 40% of patients in whom previous therapy with IL-2 had failed (119).

In more recent studies, TIL therapy has shown impressive results in patients with metastatic melanoma (120-123). Lifileucel (LN-144), a commercial autologous TIL product for patients with advanced melanoma whose conditions progress after PD-1/programmed death ligand 1 (PD-L1) treatment, has entered phase II clinical trial and is expected to be the first FDA-approved TIL therapy. In the phase II clinical trial C-144-01 (NCT02360579) that evaluated LN-144 combined with IL-2 for the treatment of metastatic melanoma the disease control rate (DCR) reached 80% and the objective response rate (ORR) was 36% (124).

In addition to melanoma, TIL therapy has also achieved good responses in other solid tumors, including ovarian cancer (125), CRC (126), cervical cancer (127,128), breast cancer (129), kidney cancer (130), and non-small cell lung cancer (131,132).

TIL therapy requires that patients have preexisting tumor-reactive lymphocytes that can be expanded *ex vivo*. However, in many patients with tumors, especially those with tumors other than melanoma, it is difficult to identify these tumor-reactive lymphocytes (108). Therefore, for gastrointestinal tumors, the main challenge to the development of TIL therapy may not be the *in vitro* expansion of bulk TILs but rather the ability to select and enrich tumor-reactive T cells (133).

This is reflected in a case report on CRC. In an ongoing phase II trial (NCT01174121), a patient with mCRC experienced objective regression of multiple lung metastases without significant side effects after infusion of HLA-C*08:02-restricted TILs specifically targeting KRAS G12D. However, 1 of these lesions had progressed on evaluation 9 months after therapy. The lesion was resected and found to have lost the chromosome 6 haplotype encoding the HLA-C*08:02 class I MHC molecule. Such a loss impaired the tumor recognition ability of KRAS G12D-specific T cells, which in turn led to immune escape (126). Among all the efforts to improve the effectiveness of TIL therapy, the identification of tumor-specific T cells in peripheral blood is a barrier to overcome (134).

To date, TIL cell therapy has shown encouraging results in many studies (7,135-138). As of August 2022, there are 6 clinical trials being conducted on the feasibility and safety of TIL cells for CRC treatment, whose details are available on the ClinicalTrials.gov website (NCT01174121, NCT03610490, NCT03904537, NCT03935893, NCT04426669, and NCT04842812; *Table 4*).

Conclusions

ACT, especially CAR-T cell therapy, is evolving rapidly and is becoming the most promising treatment strategy

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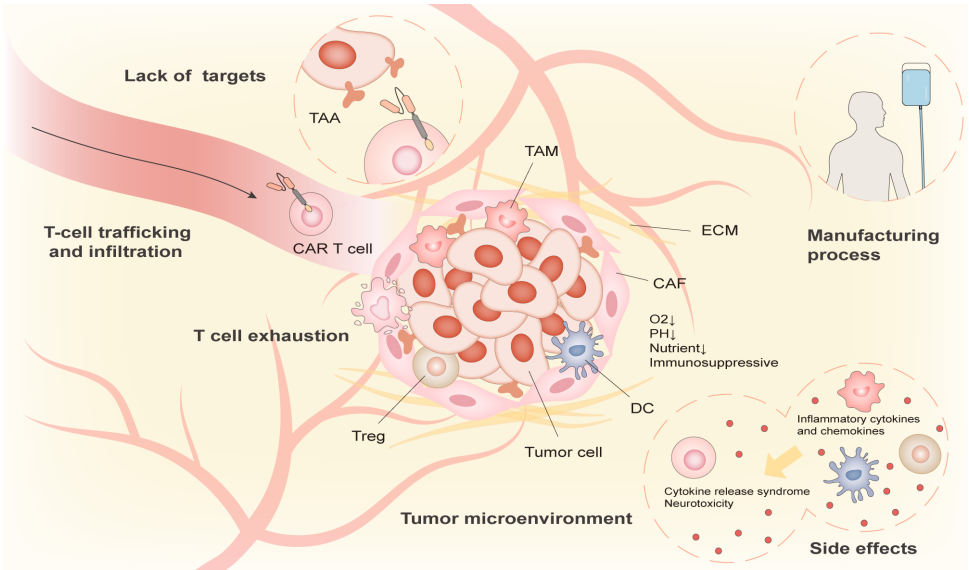

Figure 4 Challenges faced by adoptive cell therapy. The application of adoptive cell therapy in solid tumors faces various challenges, such as the migration and infiltration of T cells, target selection, immunosuppressive tumor microenvironment, toxicities, manufacturing costs, T cell exhaustion, and technical limitations. CAR, chimeric antigen receptor; TAM, tumor-associated macrophages; ECM, extracellular matrix; CAF, cancer-associated fibroblast; DC, dendritic cell; Treg, regulatory T cell; TAA, tumor-associated antigen.

for various cancers. However, the use of ACT in CRC still faces several challenges (*Figure 4*) (7,37,38,104,106,139). Different from the homogeneous environments of hematologic malignancies, solid tumors are surrounded by rich fibers and ground substances, which hinders the migration and infiltration of T cells to the tumor site (31,140). The TME of a solid tumor is hypoxic, acidic, nutrient-starved, and immunosuppressive, within which the survival, proliferation, and differentiation of effector T cells are impaired, thus rendering it difficult to achieve the ideal tumor-killing effect (141-143). Choosing the right target is critical to killing tumor cells (39-41). However, the number of targets identified with sufficient safety and efficacy is still limited. Despite its tumor cell-killing ability, adoptive T-cell transfer also has toxicities including CRS, targeted and nontargeted toxicities, and neurotoxicities (144,145). In addition, the high-cost and labor-intensive manufacturing processes further restricts the wider application of ACT (146,147). T-cell proliferation and persistence are important limiting factors in the clinical efficacy of ACT (140). T cell exhaustion is a state of hypofunction characterized by progressive loss of T-cell effector function and self-renewal capacity and is associated with reduced efficacy in ICI and ACT(148). Exhausted CAR-T cells with impaired proliferative capacity and persistence are not effective in killing malignant tumors and usually result in treatment failure (149). T cell exhaustion in ACT therapy may be alleviated by increasing the ratio of CAR-T cells to tumor cells, optimizing T-cell culture conditions, optimizing CAR architecture for signaling, mitigating metabolic exhaustion, and engineering transcriptional programmes (148).

The design of TCR may have some advantages over other cellular immunotherapy drugs, which makes it more promising in the clinical treatment of CRC. First, TCR-T cells have a broader range of targets to identify and target intracellular tumor neoAgs in solid tumors lacking specific surface tumor markers, allowing for more precise targeting of tumor cells (102). Second, since TCRs have evolved to efficiently detect and amplify antigenic signals, these receptors respond to epitope densities much smaller than required for CAR signaling (150). In addition, TCR-T cell therapy may result in decreased release of cytokines, which can lead to a low risk of CRS (115). Compared with CAR-T cells, TCR-T penetrates more easily into solid tumors, while CAR-T usually adheres to the outside of the tumor and does not penetrate easily to the inside (4).

From basic research to clinical trials, more advances in the use of ACT in solid tumors have been made, and more strategies have been thereby developed to further optimize the specificity and safety of ACT. In the near future, the

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use of ACT therapy alone or in combination with other treatments is expected to make breakthroughs in CRC treatment and improve the survivals and prognosis of patients with CRC.

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Footnote

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