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Review article

The role of CD8$^+$ T-cells in colorectal cancer immunotherapy

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ABSTRACT

Immunotherapy has been an advanced and effective approach to treating various types of solid tumors in recent years, and the most successful strategy is immune checkpoint inhibitors (ICIs), which have shown beneficial effects in patients with colorectal cancer (CRC). Drug resistance to ICIs is usually associated with CD8$^+$ T-cells targeting tumor antigens; thus, CD8$^+$ T-cells play an important role in immunotherapy. Unfortunately, Under continuous antigen stimulation, tumor microenvironment(TME), hypoxia and other problems it leads to insufficient infiltration of CD8$^+$ T-cells, low efficacy and mechanism exhaustion, which have become obstacles to immunotherapy. Thus, this article describes the relationship between CRC and the immune system, focuses on the process of CD8$^+$ T-cells production, activation, transport, killing, and exhaustion, and expounds on related mechanisms leading to CD8$^+$ T-cells exhaustion. Finally, this article summarizes the latest strategies and methods in recent years, focusing on improving the infiltration, efficacy, and exhaustion of CD8$^+$ T-cells, which may help to overcome the barriers to immunotherapy.

1. Introduction

CRC is the third most common cancer in the world, after lung and breast cancer [1,2]. According to the American Cancer Society, by 2023, approximately 153,020 people will be diagnosed with CRC, and 52,550 will die from the disease, including 19,550 cases and 3750 deaths of people under the age of 50, which constitutes a major public health burden worldwide [3]. The treatment of CRC mainly includes surgery, radiotherapy, chemotherapy, and molecular targeted therapy, but the effect on patients with advanced or recurrent CRC is not good. At present, new immunotherapy has become an advanced and effective cancer treatment method due to its remarkable curative effect and few side effects, and it offers a potential treatment for advanced or recurrent metastatic colorectal cancer [4].

Immunotherapy regulates the immune response by activating the body's immune defense system or bioactive compounds to inhibit the occurrence and development of tumors [5]. Specifically, targeted immunosuppression is achieved by enhancing antitumor responses through various vectors in the immune system, including chimeric antigen receptor (CAR) T cells, ICIs, T-cell receptors (TCRs), cytokines, and vaccines. Of these, the most successful strategy is ICIs, which have shown beneficial effects in CRC patients. However, they are only applicable to "hot tumors" that are sensitive to the immune system, such as melanoma and precancerous lesions [6–8]. For "cold tumors" with poor sensitivity to immunotherapy, such as breast cancer, CRC, and lung cancer, the effect of immunotherapy is

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Abbreviations

ICIs	immune checkpoint inhibitors
CRC	colorectal cancer
TME	tumor microenvironment
CAR	chimeric antigen receptor
TCRs	T-cell receptors
TILs	tumor infiltrating lymphocytes
dMMR	mismatch repair deficiency
MSI-H	microsatellite instability-high
Th1s	T helper 1 lymphocyte subtypes
Th2s	T helper 2 lymphocyte subtypes
TGF-β	transforming growth factor-β
NKs	natural killer cells
APCs	antigen presenting cells
TAMs	tumor-associated macrophages
DCs	Dendritic cells
TNF-α	tumor necrosis factor-α
CXCL1	CXC chemokine ligand 1
Tregs	Regulatory T cells
MDSCs	myeloid suppressor cells
HSCs	hematopoietic stem cells
CLPs	common lymphoid progenitors
CXCR3	chemokine receptor 3
CXCL9	CXC chemokine ligand 9
CXCL10	CXC chemokine ligand 10
ECs	endothelial cells
IRs	inhibitory receptors
CXCR5	CXC chemokine receptor 5
VEGF	vascular endothelial growth factor
PGE2	Prostaglandin E2
COX-2	overexpression of cyclooxygenase
APOL3	apolipoprotein L3
LDHA-l	lactate dehydrogenase A
MAP	microtubule-associated protein
FMOD	Fibromodulin
SLRP	small leucine-rich repeat proteoglycan
TRIB3	Tribbles homolog 3
TiPE2	tumor necrosis factor-alpha-inducible protein-8 like-2
RCE	Rubus coreanus Miquel extract
SR	Safflower
ATT-I	Atractylodes lactone I
ChAd68	hetero-chimpanzee adenovirus
CTL	cytotoxic T-cell
Rg	Ruminococcus jawum
Bp	Bacillus
Df	Proteus fungus
m6A-N6	methyladenosine
METTL3/4	methyltransferase 3/4
MSCs	Mesenchymal stem cells

almost insignificant [9]. This is because "cold tumors" create their own TME, which resists recognition and attack by the immune system [9–12]. A large amount of research data shows that in the TME, the amount of tumor-infiltrating lymphocytes (TILs), especially $CD8^+$ T-cells, can be used to predict the survival rate of patients with advanced CRC [13,14].

$CD8^+$ T-cells directly lyse tumor cell substrates through cytotoxic mechanisms and serve as the primary immune cells in the killing process [15]. Suppose the infiltration and activity of $CD8^+$ T-cells in the center of the tumor lesion are low, and the effect of CRC immunotherapy will be limited, thereby affecting the tumor patient's prognosis and the immune response rate [15–17]. However, for patients with mismatch repair deficiency (dMMR) or microsatellite instability-high (MSI-H) CRC types, only ICIs have a modest effect [18]. Due to the lack of $CD8^+$ T-cells infiltration or the loss of $CD8^+$ T-cells function as an important mechanisms leading to ICI

resistance, this characteristic is also an essential factor for tumor progression [19]. Therefore, increasing the infiltration and activity of $CD8^+$ T-cells and improving or even reversing the exhaustion of $CD8^+$ T-cells has become the key to immunotherapy for CRC. This article reviews the complex relationship between CRC and immunotherapy, emphasizes the critical role of $CD8^+$ T-cells, and provides a new direction for immunotherapy.

2. Immunoediting and CRC

Immune editing involves the innate and adaptive immune systems and mainly includes the following three stages: elimination, balance, and escape(Fig. 1) [10]. The "elimination stage" is the active immune monitoring of tumor-associated antigen-specific lymphocytes and natural killer cells (NKs), which recognize tumor antigens expressed by tumor cells or tissue damage and growth caused by invasive tumors, stimulate the local production of chemokines at tumor sites, and recruit innate immune system components, such as antigen presenting cells (APCs), NKs and tumor-associated macrophages (TAMs) [20]. These innate immune cells stimulate the accumulation of immune cytokines (IFN-γ, IL-1, IL-6, TNF-α, and IL-12), which can then prime and activate $CD4^+$ T-cells and $CD8^+$ T-cells to identify and destroy precancerous cells. This shows that immune cells mainly select tumor cells with reduced immunogenicity [21].

The second "equilibrium phase" is when the host's immune system stops tumor growth. Even surviving tumors and their stroma formed by immune responses enter homeostasis. Therefore, in the immune response process, TILs, mainly composed of $CD8^+$ T-cells and $CD4^+$ T-cells, are closely related to the occurrence and prognosis of CRC and have become a benign marker for the prognosis of advanced CRC [22,23]. $CD8^+$ T-cells can directly kill tumor cells. $CD4^+$ T-cells include two subtypes of T helper 2 lymph nodes (Th1s) and T helper 2 lymph nodes (Th2s), which are T cells that secrete heterogeneous cytokines [24]. Although immune cells can prevent

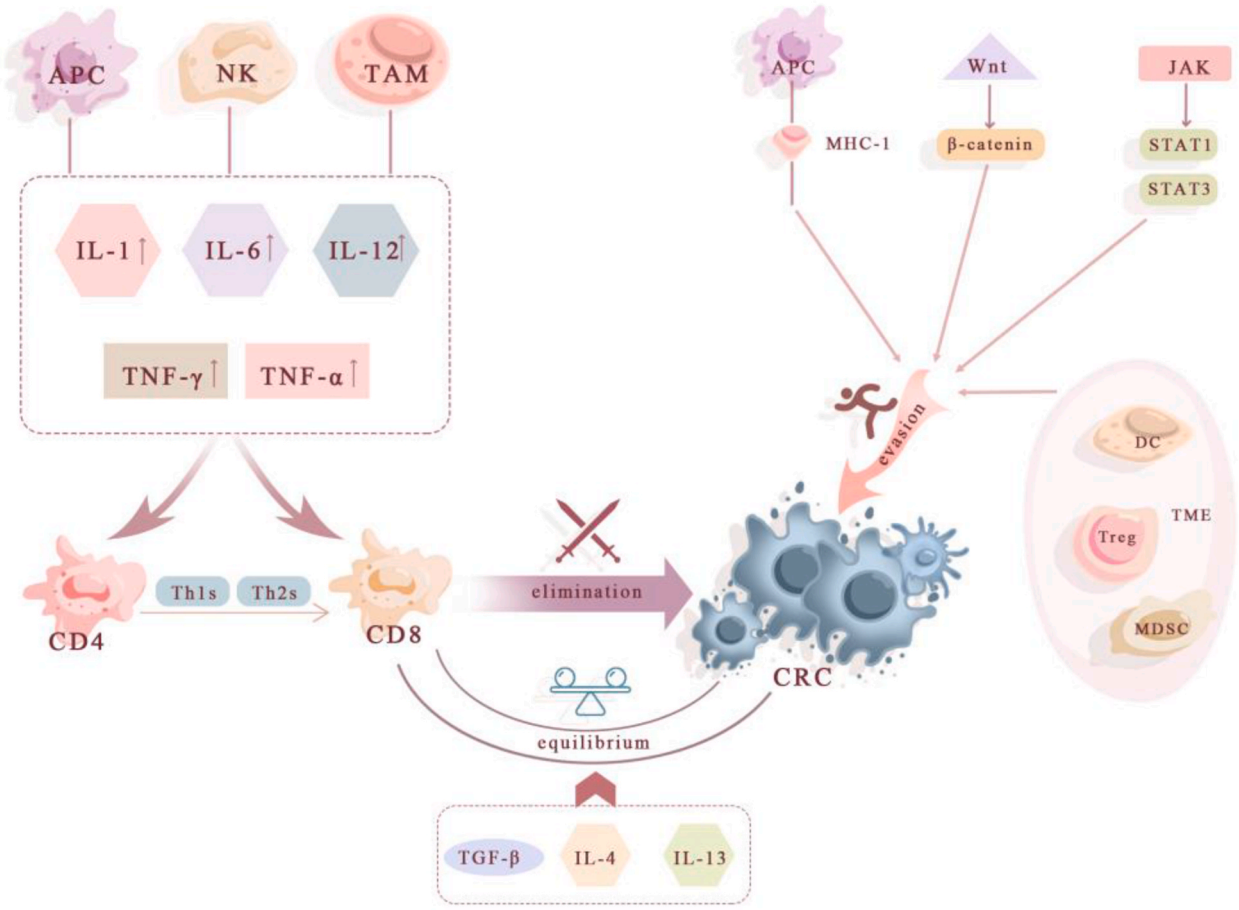

Fig. 1. CRC and the three stages of immunoediting. During the "elimination phase," components of the innate immune system such as APCs, NKs, and TAMs are first recruited, and then they stimulate immune cytokines secretion(such as IFN-γ, IL-1, IL-6, TNF-α, IL-12), and finally $CD4^+$ T-cells and $CD8^+$ T-cells are activated. In the second "equilibrium" phase, $CD4^+$ T-cells secrete T cells heterogeneous cytokines that activate $CD8^+$ T-cells through T helper 1 lymphocyte subtypes (Th1s) and T helper 2 lymphocyte subtypes (Th2s). $CD8^+$ T-cells can directly kill tumor cells. Tumors will selectively evade transforming growth factor-β (TGF-β), IL-4, IL-13, and other immunosuppressive factors and escape the killing of $CD8^+$ T-cells. In the third "escape stage," MHC-1, Wnt/β-catenin, JAK/STAT, and the TME can all lead to the immune escape of CRC.

the development of tumors in the "balance period," they cannot eliminate all cancer cells in the end. This is because tumors selectively escape the killing of immune cells by accumulating transforming growth factor-β (TGF-β), IL-4, IL-13 and other immunosuppressive factors, thus entering the third "escape phase" [25,26].

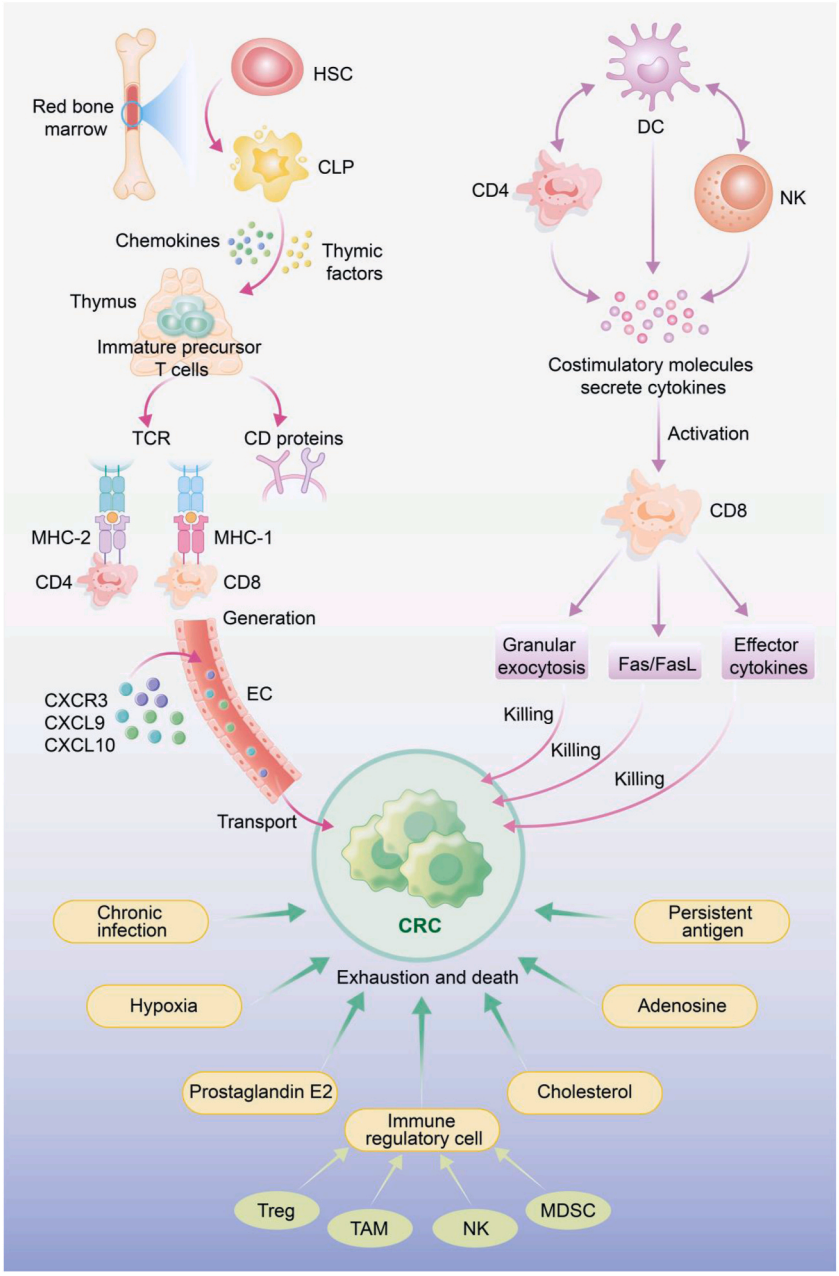

Fig. 2. Generation, trafficking, killing, and exhaustion of $CD8^+$ T-cells. $CD8^+$ T-cells originate from hematopoietic stem cells (HSCs) in the red bone marrow and mature into common lymphoid progenitors (CLPs). These immature precursor T cells are induced into the thymus and migrate to the subcapsular region. The same drug stimulated the manufacture of TCRs and CD proteins. T cells with TCRs appeal to MHC-1 become $CD8^+$ T-cells, while T cells with TCRs appeal to MHC-2 become $CD4^+$ T-cells. $CD8^+$ T-cells are transferred from lymphocyte tissues to the blood through the interaction of CXCR3, CXCL9 and CXCL10. DCs induce the differentiation of $CD4^+$ T-cells into antigen-specific effector T cells. $CD4^+$ T-cells promote the activation of DCs and induce the maturation. They express co-stimulatory molecules and secrete cytokines that stimulate $CD8^+$ T-cells priming. NKs have similar functions to $CD4^+$ T-cells and also stimulate the activation of $CD8^+$ T-cells through interaction with DCs. Activated $CD8^+$ T-cells mainly kill cancer cells through granular exocytosis, apoptosis mediated by Fas/FasL interaction, and secretion of effector cytokines. Possible mechanisms of $CD8^+$ T-cells exhaustion and death are chronic infection and persistent antigen stimulation, immune regulatory cells (Tregs, NKs, MDSCs, TAMs), hypoxia, and metabolites (prostaglandin E2, adenosine, cholesterol). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

The third "evasion stage" is mainly a result of the genetic instability of tumor cells, which makes the immune system "invisible" to them, forms a TME that promotes angiogenesis and makes cancer cells proliferate rapidly; then, tumor cells finally invades tissue to form metastasis [27,28]. Similar to other tumors, CRC also produces immune escape responses, including via multiple mechanisms (such as MHC-1, Wnt/β-catenin, JAK/STAT) and the TME. The MHC-I complex consists of heavy chains (encoded by HLA-A/B/C genes) and light chains (encoded by β2-microglobulin genes) [29]. When MHC-I expression is reduced or absent, it can lead to tumor immune escape [30,31]. The Wnt/β-catenin signaling pathway is one of the most representative signaling pathways in CRC, and this signaling pathway mainly leads to immune escape by interacting with the TME [32,33]. The Janus kinase signal sensor and transcription activator (JAK/STAT) signaling pathway is considered to be an essential signal transduction pathway during cell development, which can transmit anti-apoptosis, proliferation, and differentiation signals, and is critical to immune function, blood formation and tumor growth [34,35]. The current findings suggest that the activation of the JAK/STAT signaling pathway may modulate the expression of PD-L1 in tumors, alter the effectiveness of PD-L1 inhibitors in tumor immunotherapy, protect cancer cells from immune attack [36]. Furthermore, in the TME, some innate immune cells contribute to tumor progression. TAMs can evolve into M1 and M2 phenotypes. M1 macrophages can promote the Th1 response and absorb and kill tumor cells [37]. However, M2 macrophages can boost neovascularization, curb the infiltration and function of $CD8^+$ T-cells, and impede the adaptative immune response of $CD8^+$ T-cells, thus resulting in the occurrence and development of tumors [38]. Dendritic cells (DCs) are antigen-presenting cells that promote elevated levels of immunosuppressive IL-10 and decreased levels of immunostimulatory IL-12 and tumor necrosis factor-α (TNF-α) or CX chemokine ligand 1 (CXCL1), thereby enhancing tumor cell migration [39]. Regulatory T cells (Tregs) can inhibit the specification and function of APCs and reduce the interaction between APCs and T cells, thereby inhibiting the function of effector T cells, reducing the adaptive and innate immune system responses, and ultimately leading to immune tumor escape [40]. In summary, MHC-1, Wnt/β-catenin, JAK/STAT, and the TME are closely related to the immune escape of CRC, and $CD8^+$ T-cells in the TME are the key to immunotherapy for CRC. Therefore, this review will discuss the generation, activation, and depletion of $CD8^+$ T-cells and seek possible strategies to improve CRC immunotherapy through $CD8^+$ T-cells.

3. The TME and $CD8^+$ T-cells

The TME is a complicated cellular meshwork consisting of cancer cells, and various stromal cell populations, such as infiltrating immune cells (lymphocytes and TAMs) [41], neutrophils [42,43], fibroblasts [41,43] and adipocytes [44]as well as extracellular matrix components, soluble factors, and signaling molecules produced by these cells [41–43]. Among them, TAMs, mast cells, neutrophils, DCs, myeloid suppressor cells (MDSCs), and NKs are also called innate immune cells. $CD8^+$ T-cells, $CD4^+$ Th1 cells, $CD4^+$ Th17 cells, and regulatory T cells are also known as adaptive immune cells [25].

The TME is involved in nearly all aspects of tumor advancement and the metastatic cascade, including original implantation, development, and evasion. These cells are in a dynamic interaction that leads to changes in the expression of plasma membrane receptors and channels, releasing thousands of proteins and exerting their effects [45]. In the TME, following T-cell infiltration, naive $CD8^+$ T-cells severalize into effector $CD8^+$ T-cells, which are further differentiated and activated by cytotoxic proteins (such as perforin and granzymes) and memory $CD8^+$ T-cells to exert their targeting functions in tumor sites and destroy tumor cells.(Fig. 2).

3.1. *The generation and transport of $CD8^+$ T-cells*

$CD8^+$ T-cells are derived from hematopoietic stem cells (HSCs) within the red bone marrow and mature into common lymphoid progenitor cells (CLPs). These immature precursor T cells are induced into the thymus and migrate to the subcapsular region due to chemokines and thymic factors (such as thymopaclitaxol, thymosin and thymopoietin) produced in the thymus [46,47]. In the thymus, immature precursor T cells are conceived of as double-negative because they lack expression of the TCRs and the canonical coreceptors CD4 and CD8. However, under the impact of the thymus microenvironment, CLPs undergo a differentiation process; the same drug stimulates the manufacture of TCRs and CD proteins, and thymocytes supply MHC-1 and MHC-2 molecules for MHC-1 and TCRs-positive T cells to determine T-cell responsiveness and promote their maturation pathways [48,49]. Positive and negative selection processes exist in the thymus, which are based on exploiting the antigen specificity of T cells and identifying T cells with a low affinity for MHC-1 or MHC-2 molecules. T cells with a high affinity for self-peptide undergo apoptosis during counterselection, so cytotoxic $CD8^+$ T-cells with TCRs that recognize self-peptides are eliminated by clonal deletion. Thus, T cells with TCRs affinity for MHC-1 turn into $CD8^+$ T-cells, while T cells with TCRs affinity for MHC-2 turn into $CD4^+$ T-cells [50,51]. In conclusion, $CD8^+$ T-cells belong to a subset of lymphocytes that develop in the thymus and function to detect antigenic polypeptides presented by MHC-1 expressed in all tumor cell types [52]. Through the interaction of CXC chemokine receptor 3 (CXCR3) expressed by these cancer cells with CXC chemokine ligand 9 (CXCL9) and CXC chemokine ligand 10 (CXCL10) produced by DCs, $CD8^+$ T-cells from lymphocyte tissue transfer to blood [53]. The effectiveness of $CD8^+$ T-cells in detecting these antigens depends on their response to tumor cells [52]. Finally, T cells and endothelial cells (ECs) also have dynamic contacts and trafficking guided by interactions between chemokines, chemokine receptors, and adhesion molecules such as selectins and integrins. $CD8^+$ T-cells in the circulatory system must first adhere to endothelial cells, migrate along the endothelial cells to the tumor, firmly grasp the endothelial wall, and Finally enters the tumor through the endothelial wall junction [54,55].

3.2. *Activation and killing of $CD8^+$ T-cells*

The activation of $CD8^+$ T-cells begins with antigen loading on DCs and ends with $CD8^+$ T-cells directed tumor cell lysis. This process

is known as the tumor immune cycle [56]. The tumor immune cycle includes the following two phases: the initial phase and the action phase. The initiation of the $CD8^+$ T-cells response to antigens is called T cells initiation and is mainly related to DCs, NKs, and $CD4^+$ T-cells [57]. DCs are derived from the bone marrow and belong to the innate immune system. Neoantigens captured by DCs on MHC-1 molecules (tumor-associated antigens released by cancer cells) are presented to naïve $CD8^+$ T-cells, thereby inducing $CD8^+$ T-cells with cytotoxicity [58,59]. $CD4^+$ T-cells stimulate $CD8^+$ T-cells through cytokines [60]. In addition, DCs induce the differentiation of $CD4^+$ T-cells into antigen-specific effector T cells. Likewise, $CD4^+$ T-cells promote the activation of DCs and induce the maturation of DCs. They express costimulatory molecules and secrete cytokines that stimulate $CD8^+$ T-cells priming [60,61]. NKs have similar functions to $CD4^+$ T-cells and stimulate the activation of $CD8^+$ T-cells through interaction with DCs [62]. Activated $CD8^+$ T-cells mainly kill cancer cells through the following three mechanisms: the first is granule exocytosis, which cleaves substrates in cancer cells by releasing cytotoxic granules containing perforin and granules [63]. The second is apoptosis mediated by the Fas/FasL interaction. The Fas ligand expressed by effector $CD8^+$ T-cells binds to the Fas receptor expressed on cancer cell, activates FasL and cytochrome C release in target cells, and activates caspases. Ultimately, these activated caspases cleave cancer cells substrates, leading to apoptosis [64,65]. The third is to secrete effector cytokines, $CD8^+$ T-cells release IFN-γ and TNF-α, induce cancer cells to produce cytotoxicity, and stimulate M1-Tam to exert an antitumor effect [66,67].

3.3. Anergic, tolerant, exhaustion and death of $CD8^+$ T-cells

Whether it is colorectal cancer or other solid tumors, under the influence of various factors, the recognition and killing functions of TILs will be affected, leading to the inactivation and tolerance of TILs functions. $CD8^+$ T-cells are the main component of TILs, so this also applies to $CD8^+$ T-cells. In the TME, cancer cells can produce their own tumor antigens to weaken T cell responses, or they can secrete IL-10 and TGF-β leading to T cell tolerance, and loss of HLA class 1 expression can also impair T cells recognition [68]. MDSCs produce nitric oxide, reactive oxygen species, and arginase 1 to impair T cells function [69]. Tumor-infiltrating neutrophils can secrete matrix metalloproteinase 9, which not only promotes the inactivation of T cells function, but also activates latent TGF-β [70].

During the growth and development stage of T cells, when naive T cells encounter antigens presented by cancer cells or APCs that lack costimulatory ligands, it will affect the activation of TCRs, thus leading to the failure of $CD8^+$ T-cells to recognize and eliminate cancer cells [71]. In addition, changes in the expression of T cells' own receptors can also affect T cell function. For example, upregulation of inhibitory receptors (PD-1 and CTLA-4) can lead to suboptimal $CD8^+$ T-cells activation, thereby impairing anti-tumor activity [69].

In chronic infection and tumor settings, factors such as highly persistent antigens and inflammatory stimuli can lead to decreased $CD8^+$ T-cells function and, eventually, exhaustion. "T-cell exhaustion" is a term describing the T-cell response to chronic antigenic stimulation and represents a state of T cell functional energy [72]. It was proposed initially in chronic viral infection in mice and was defined as the absence or adverse effects on the persistence of antigen-specific T cells [73]. However, recent studies have found that the exhaustion of T cells is not only manifested as a progressive loss of function but also associated with impaired proliferation potential, decreased cytokine secretion, increased inhibitory receptors (such as PD-1TIM-3 and LAG- 3), decreased cytolytic activity, metabolic changes, epigenetic changes, and unique transcriptional regulation mechanisms [74–79]. Furthermore, in the context of cancer, depletion of $CD8^+$ T-cells is often induced in the TME. This is because many complex factors (such as cancer cells, metabolites, proinflammatory and anti-inflammatory mediators, and different immune cells) converge in the TME to form an immunosuppressive environment that leads to $CD8^+$ T-cells exhaustion and death. Here, we focus on the possible mechanisms leading to $CD8^+$ T-cells inactivation, tolerance, and exhaustion.

3.3.1. Chronic infection and persistent antigen stimulation

Long-term high-level antigen stimulation in chronic infection and the TME is the leading cause of $CD8^+$ T-cells exhaustion. In chronic infection, when the duration lasts 2–3 weeks, the molecular program of exhaustion is established [80]. Continuous antigenic stimulation has a strong correlation with the effector function of $CD8^+$ T-cells. Rapid induction of mitochondrial oxidative stress activates genes associated with T cells wasting while limiting the ability of T cells to participate in oxidative phosphorylation, leading to the bioenergetic limitation that prevents the expression of genes involved in T cells self-renewal. Therefore, the higher the antigen load, the longer the exposure to the antigenic environment and the more severe the depletion of $CD8^+$ T-cells [75,81]. Furthermore, the function of $CD8^+$ T-cells following long-term antigen depletion cannot be restored simply by depleting of antigen-stimulation [80, 82]. Angelosanto JM found that by transferring activated $CD8^+$ T-cells to a stable early stage (within 1–3 weeks), the function of $CD8^+$ T-cells was restored and transformed into memory T cells. In addition, studies have found that continuous antigen stimulation can destroy lymphoid tissue, impair the normal trafficking of $CD8^+$ T-cells, and induce the expression of inhibitory receptors (IRs), which remodels the metabolism of $CD8^+$ T-cells [83].

3.3.2. immune related cells

TAMs are the most ample immune cell subtype (up to 50 %) in solid neoplastic tissue [43,84,85], playing a dual role in the development of CRC [86]. In the context of TME stimuli and signals, TAMs can evolve into two distinct polarization states through specific differentiation [87]. In the initial stage of cancer development, classically activated M1 macrophages exert proinflammatory (such as IL-1β, IL-6, IL-12, IL-23 and TNF-α), immunostimulatory, and antitumor effects [88,89]. However, in the advanced stages of the tumor, they differentiate into M2-type TAMs after activation by IL-4, IL-10, or IL-13 [90,91]. M2 macrophages have immunosuppressive effects, can secrete IL-10, TGF-β and produce reactive oxygen species that inhibit the activity of $CD8^+$ T-cells [92]. TAMs promote the formation of new blood vessels in tumor tissue by releasing angiogenic factors and may extensively remodel the

extracellular matrix to secrete granule proteins or inhibit the secretion of chemokines by $CD8^+$ T-cells, thereby promoting tumor progression and even metastasis [16,93]. However, CRC is an extremely heterogeneous disease due to the disruption of cellular signaling regulatory mechanisms [94], and the related mechanism between TAMs and CRC is still unclear. Nonetheless, currently, TAMs have been shown to participate in many pathways significant for CRC, namely the NFKB1 signaling pathways, the signal transducer and activator of transcription 1 (STAT1) signaling pathways, signal transducer and activator of transcription 3 (STAT3) signaling pathways, the WNT5A signaling pathways, and the PI3K signaling pathways [95–99].

Tregs are a particular group of suppressor cells composed of $CD4^+$ T-cells with high expression of FoxP3 on the cell surface. They mainly secrete inhibitory cytokines (such as IL-10, IL-35, and TGF-β) and exert immunosuppressive effects [100,101]. Among them, IL-35 promotes the expression of $CD8^+$ T-cells inhibitory receptors (PD-1, TIM-3, and lag3). However, recent studies have found that when the secretion of IL-10 and IL-35 is absent, gene signaling is significantly downregulated in $CD8^+$ T-cells after PD-1 checkpoint blockade, the transcriptional profile of memory-related genes is upregulated, and CXC chemokine receptor 5 (CXCR5) signaling occurs. This also has more profound implications for immune-targeted therapy [102,103].

MDSCs are a heterogeneous population of myeloid lineage cells defined by their immunosuppressive features. According to their morphological characteristics, they can be divided into polymorphic MDSCs and mononuclear MDSCs, which have solid immunosuppressive functions. MDSCs mainly produce cytokines and chemokines, such as IL-6, IL-10, TGF-β, arginase-1, and nitric oxide [104,105]. Among them, IL-10 can not only activate the STAT3 pathway through NF-κB and IL-6-GP130-Janus kinase, causing immunosuppression, but IL-10 can also inhibit the inflammatory response, further restricting $CD8^+$ T-cells proliferation and activation [103,106]. Studies have found that IL-6 promotes DCs maturation and inhibits $CD8^+$ T-cells advancement. Furthermore, IL-6 can promote the differentiation of TAMs into the M2-like phenotype, limiting the function of $CD8^+$ T-cells [107,108]. TGF-β is a powerful inhibitor that promotes the depletion and early apoptosis of $CD8^+$ T-cells [109,110].

NKs have a bidirectional regulatory effect on $CD8^+$ T-cells. On the one hand, NKs can secrete IFN-γ to maintain the function of $CD8^+$ T-cells. Recent studies have shown that NKs can recruit DCs to act on tumors, thereby enhancing the induction response of $CD8^+$ T-cells [111]. On the other hand, NKs can attack $CD8^+$ T-cells through the NK receptor (NKp46) [112]. In addition, NKs can secrete IL-10,

Table 1
Summary of drugs, targets and mechanisms to improve immunotherapy of colorectal cancer through $CD8^+$ T-cells.

Strategy of immunotherapy	Action target/action component	Correlated pathway	Associated tumor cell lines	In vivo or in vitro	Reference
Protein expression changes	APOL3	APOL3-LDHA	HCT-116 HT29 CACO2	In vivo; in vitro	[125]
	MAP7D2	MAP7D2-MYH9-HMGB1	CT26 MC38 SW620 RKO	In vivo; in vitro	[126]
	FMOD	RP4-FMOD-Wnt/β-catenin	LoVo HCT116 CT26 293T	In vivo; in vitro	[127–129]
	TRIB3	P300-TRIB3-STAT1-CXCL10	MC38 CRC-30	In vivo; in vitro	[130]
	GBP2	GBP2-SHP1-STAT1	HT29 SW480 CT26	In vivo; in vitro	[131]
Related checkpoint	TiPE2	TiPE2-T-bet/Eomes–IFN–γ	MC38	In vivo; in vitro	[132]
	GITR	–	–	in vitro	[133]
Natural products	RCE	–	MC38	In vivo; in vitro	[134]
	SRE	–	MC38	In vivo; in vitro	[135]
	ATT-I	–	MC38 CT26 SW837 HCT116	In vivo; in vitro	[136]
cancer vaccine	ChAd68	–	–	In vivo	[137]
	ODF2	ODF2-IL-15	HT29 SW620 HCT116 SW480 RKO	In vivo; in vitro	[138]
intestinal flora	probiotic powder	–	–	In vivo	[139]
	Lachnosp-iraceae	RG,BP-lyso-glycerophospholipids	MC38 CT26	In vivo	[140]
RNA modification	YTHDF1	YTHDF-m6A-p65-CXCL1/CXCR2	–	In vivo	[141]
	METTL3	METTL3-m6a-BHLHE41-CXCL1	MC38 CT26	In vivo; in vitro	[142]
Mesenchymal	MSC	MSC-CX3CR-M1	MC38	In vivo; in vitro	[143]
Endostatin	Endostatin	–	CT26	In vivo; in vitro	[144]

which is also associated with $CD8^+$ T-cells exhaustion [113].

3.3.3. Other factors: include hypoxia, and metabolites (prostaglandin E2, adenosine, and cholesterol)

Hypoxia, a common condition in the TME, leads to the accumulation of HIF-1α and the activation of many HIF-1α-regulated genes (such as vascular endothelial growth factor (VEGF), and TGF-β1), thereby affecting cell metabolism, chromatin accessibility, and even viability. Studies have found that extracellular adenosine accumulation under hypoxia effectively inhibits $CD8^+$ T-cells immune function through interaction with A2AR receptor [114]. In addition, it has been shown that continuous stimulation of T cells under hypoxic conditions significantly reduces the expression level of the mitochondrial fusion protein MFN1, which leads to T cells mitochondrial dysfunction and accelerates the exhaustion of $CD8^+$ T-cells [115,116].

Prostaglandin E2 (PGE2) is an active lipid molecule with various hormonal effects in the body [117].The PGE2 signaling pathway is one of the key pathways controlling tumor advancement and immune dysfunction [43]. For CRC patients, overexpression of cyclo-oxygenase (COX-2) and PGE2 promotes tumor angiogenesis by increasing the survival of endothelial cells in tumor vessels [118]. However, the mechanism of the COX-2-PGE2 signaling pathway in the TME is not fully understood and needs further study, but it also provides a potential target for cancer immunotherapy.

Adenosine, formed by the sequential dephosphorylation of exonucleases CD39 and CD73 located on the cell surface, impairs the effector functions of $CD8^+$ T-cells by reducing immune cell infiltration, cytotoxicity, and cytokine production [119,120]. Beatris Mastelic-Gavillet and others found that A2AR/PKA/mTORC1 is the primary signaling pathway of adenosine, which can directly or indirectly impair the immune ability of peripheral T cells and TILs [121].

Cholesterol not only participates in the metabolism of various substances in the body, but also suppresses the immune system. Cholesterol content in $CD8^+$ T-cells was positively correlated with the upregulated expression of PD-1, TIM-3, and lag3 in T cells. The higher the cholesterol content is, the stronger the effect of suppressing the expression of $CD8^+$ T-cells, which accelerates their exhaustion [122]. Dong L found that the HLA gene family, which includes B2M, IRF4, STAT5A, and other genes, may be related to regulating cholesterol metabolism by $CD8^+$ T-cells [123]. Furthermore, the literature has reported that reduced NF-kB signaling mediated by retinoic acid-related orphan receptor α controls the homeostasis of cholesterol metabolism in $CD8^+$ T-cells so this epigenetic regulatory strategy may be beneficial for the treatment of solid tumors, including CRC [124].

4. $CD8^+$ T-cells and ameliorating CRC immunotherapy

Currently, one of the significant challenges in immunotherapy for CRC is the lack of $CD8^+$ T-cell infiltration, inefficiency, and exhaustion. This article summarizes the new methods to improve $CD8^+$ T-cells infiltration, low efficiency, and exhaustion that have been reported in recent years, mainly by regulating protein expression changes (APOL3, MAP7D2, FMOD, TRIB3, GBB2, GBP2), blocking or inhibiting related checkpoints (TiPE2, GITR), mining natural products (RCE, SRE, ATR-I), the development of anticancer vaccines (ChAd68, ODF2), the regulation of intestinal flora (probiotic powder, Ibacteriaceae), RNA modification (YTHDF1, METTTL 3), and the application of mesenchymal stem cells and endostatin (Table 1). It is hopeful that this review can provide a new idea for exploring immunotherapy.

4.1. Protein expression changes

Yang Lv found that apolipoprotein L3 (APOL3) may be an essential regulator of ferroptosis-associated $CD8^+$ T-cell infiltration in CRC. APOL3 and l-lactate dehydrogenase A (LDHA) binding increases ubiquitination and promotes degradation in CRC cells, including CACO2, HT29, and HCT116 cells. When LDHA is overexpressed, it can significantly inhibit the ferroptosis of CRC cells, but under the influence of APOL3, the expression of LDHA is reduced. Therefore, the APOL3-LDHA axis can promote tumor ferroptosis and the cytotoxicity of $CD8^+$ T-cells by increasing IFN-γ and decreasing the lactate concentration [125].

MAP7D2, a member of the microtubule-associated protein (MAP) family, acts as a cofactor for kinin-1, promoting microtubule recruitment [145]. Wu Qian found that MAP7D2 was highly expressed in MSS CRC patients, and that MAP7D2 inhibited HMGB1 secretion by blocking MYH9 ubiquitination; they also found that HMGB1 secretion was related to $CD8^+$ T-cell recruitment, leading to $CD8^+$ T-cell infiltration and promoting immunity to alter the microenvironment. Furthermore, MAP7D2 downregulation significantly increased the susceptivity of CRC cells to anti-PD-1 therapy in vivo, emphasizing that targeting of the MAP7D2-Myh9-Hmgb1 axis improves the effectiveness of anti-PD-1 therapy in CRC patients [126].

Fibromodulin (FMOD) is a secreted proteoglycan in the small leucine-rich repeat proteoglycan (SLRP) family. SLRP is an essential regulator of extracellular matrix assembly and cell signal transduction [146]. Evidence shows that FMOD is closely related to tumors, especially lung, prostate, and breast cancers [127,128]. Through screening, it was found that the 12-mer peptide RP4 targeting FMOD has a specific ability to block FMOD. When RP4 was combined with FMOD, by blocking the Akt and Wnt/β-catenin signaling pathways, it increased the abundance of $CD8^+$ T-cells and exerted antitumor effects [129].

Tribbles homolog 3 (TRIB3) is a cancer protein, and an increasing number of studies have found that TRIB3 can promote the occurrence of CRC and regulate the immune response [147–149]. Studies have found that TRIB3 is acetylated by the acetyltransferase P300, which inhibits its ubiquitination and proteasomal degradation and improves its stability. TRIB3 inhibits T cells infiltration through the STAT1-CXCL10 signaling pathway. When the acetylation of TRIB3 was inhibited by gene knockout or with C646, a highly selective inhibitor of P300, its degradation was promoted, the recruitment and infiltration of T cells were increased, and CRC was sensitive to immune checkpoint blockade therapy [130].

GBP2 belongs to the GTP enzyme family and is closely related to host immunity and most immune checkpoint genes [150,151].

Transfection of CRC cells with GBP2 has been reported to inhibit cell proliferation, increase paclitaxel sensitivity, and impair Wnt signaling [131]. In pMMR/MSS CRC, upregulation of GBP2 enhances the activation of the activator of transcription 1 by competing with SH2-containing protein tyrosine phosphatase 1 and binding to the phosphorylated STAT1. Studies have found that STAT1 negatively correlates with CRC tumorigenesis and tumor cell proliferation, resulting in significantly increased $CD8^+$ T-cells infiltration [152,153]. In addition, high expression of GBP2 can increase the sensitivity to anti-PD-1 therapy and promote immunotherapy effectiveness [154].

4.2. Related checkpoint

TiPE2 (tumor necrosis factor-alpha-inducible protein-8 like-2), a member of the Tipe (TNFAIP8) family, functions as a transfer protein of inositol phosphate as a secondary messenger, and a regulator of inflammation and carcinogenesis in vivo [155,156]. Loss of TIPE2 increases the activity of the transcription Factors T-bet and Eomes in NKs, increases the activity of IFN-γ, and indirectly improves the antitumor function of $CD8^+$ T-cells [132].

GITR, a tumor necrosis factor receptor superfamily (TNFRSF) checkpoint, has been shown in preclinical models to activate effector T cells, impair Treg function, and elicit robust antitumor responses using agonistic antibodies [157–159]. Yannick S. Rakké first comprehensively reported the expression of GITR in pMMR CRC tissues from human patients [133]. Checkpoint stimulation of the GITR pathway promotes $CD8^+$ T-cell expansion and enhances PD-1-mediated immune stimulation.

4.3. Natural products

Rubus coreanus Miquel extract (RCE) is a traditional medicinal fruit rich in polyphenolic compounds such as ellagic acid, which has anti-fatigue, anticancer, anti-osteoporosis, anti-inflammatory, and antioxidant properties [160]. Ji Hye Kim found that RCE can inhibit the growth of CRC [161]. Further studies showed that when REC was combined with oxaliplatin, the infiltration of $CD8^+$ T-cells into tumor tissues was significantly increased [134].

SRE (SR Extract) is an extract of the traditional Chinese herb White Safflower (SR), which has been reported to hinder the development of CRC. When SRE was combined with an anti-PD-1 antibody, tumor-infiltrating $CD8^+$ T-cells' activity significantly reduced CRC tumor growth [135].

Atractylodes lactone I (ATT-I), a phytochemical in *Atractylodes macrocephala*, is a natural sesquiterpene compound with immunomodulatory, antitumor, and anti-inflammatory effects [162,163]. When combined with PD-1 inhibitors, ATT-I enhanced the antitumor activity of tumor-infiltrating lymphocytes and cytotoxic T lymphocytes (especially $CD4^+$ T-cells and $CD8^+$ T-cells). Therefore, ATT-I can enhance the immune response and sensitize CRC tumors to immune checkpoint blockade therapy [136].

4.4. Cancer vaccines

A novel antigenic vaccine consisting of individualized hetero-chimpanzee adenovirus (ChAd68) and a fully synthetic Venezuelan equine encephalitis virus-based samRNA vector is being administered to patients with MSS CRC. Vaccination was found to induce widespread and durable $CD8^+$ T-cell responses in nonhuman primate patients, increase the number of $CD8^+$ T-cells, promote the survival of MSS-CRC, and reduce ctDNA [137].

Ranran Shi developed a peptide vaccine derived from ODF2 to activate tumor-specific cytotoxic T-cell (CTL) responses and improve T-cell infiltration. The expression of ODF2 was knocked down to increase the level of IL-15 in vitro, thereby enhancing the proliferation of $CD8^+$ T-cells. Further experiments showed that two immunogenic epitopes of ODF2 (P433 and P609) induced $CD8^+$ T-cells by enhancing the production of IFN-γ and granzyme B, which increased the cytolytic activity of non-msi-hCRC cells [138].

4.5. Gut microbiota

The gut microbiota also plays a vital role in CRC immunotherapy, especially in modulating the TME [164]. Yang Xiaojuan developed a new formula of probiotic powder (mainly including *Lactobacillus plantarum* powder, Bifidobacterium powder, starch sugar, wolfberry sugar, polysaccharides, isomaltose, and maltodextrin). Studies have shown that probiotic powder inhibits the activity of Tregs and increases the abundance of $CD8^+$ T-cells, $CD4^+$ T-cells, and $CD19^+$ T-cells in the TME. Although the potential targets and related mechanisms of gut microbiota and immune cells are currently understudied, this also improves the understanding and treatment strategies for CRC [139].

Zhang Xusheng found Ruminococcus jawum (Rg), Bacillus (Bp) and Proteus fungus (Df) by analyzing the tissue bacteria of patients with CRC. In a mouse model, fixed values of Rg and Bp in the TME increased the infiltration and activity of $CD8^+$ T-cells, and the activity following oral administration was greater than that following intramuscular injection. Further studies found that glycerol phosphate disrupted the activation of $CD8^+$ T-cells and inhibited their propagation and immune monitoring function, while Rg and Bp could degrade glycerol phosphate and restore the immune monitoring function of $CD8^+$ T-cells [140].

4.6. RNA modification

N6-methyladenosine (m6A) is one of the most abundant RNA modifications. M6A-encoded readers, such as YTH m6A RNA-binding protein 1/2/3 (YTHDF1/2/3), YTHDC1/2, and IGF-2B BP 1/2/3, bind to modified M6A and determine the M6A-modified mRNA

destiny [165]. Yi Bao confirmed that YTHDF1 gene deletion in MSS and MSI-H mouse CRC cells could induce the accumulation of MDSCs. When YTHDF1 is knocked out, it can induce $CD8^+$ T-cells infiltration through the YTHDF1-m6A-p65-CXCL1 axis, and targeting YTHDF1 can improve the anti-PD1 efficacy of MSI-H CRC and overcome the anti-PD-1 resistance of MSS CRC. Therefore, YTHDF1 is also a new target for CRC immunotherapy [141].

Likewise, m6A-encoded writer methyltransferase 3/4 (METTL3/4) plays an essential role in promoting the development of CRC [166]. Studies have found that CRC cells expressing METTL3 recruit MDSCs by secreting CXCL1, thereby inhibiting the proliferation of T cells and promoting tumor growth. When the expression of METTL3 was downregulated, the number of MDSCs decreased sharply, and the numbers of $CD4^+$ T-cells and $CD8^+$ T-cells increased. In addition, combined therapy targeting METTL3 and anti-PD1 showed promising antitumor effects [142].

4.7. Mesenchymal

Mesenchymal stem cells (MSCs) are an autologous intermediate cell population with a rich chemokine expression profile. They can recruit and modify various immune cells, affect tissue metabolism and inflammatory responses, and play an essential role in the immune metabolism of tumors [167,168]. Studies have found that MSCs can recruit more TAMs, mainly CX3CR1, to promote their M1 polarization, stimulate the proliferation and activation of $CD8^+$ T-cells, and reduce sensitivity to anti-PD1 therapy. When anti-PD1 was mixed with MSCs, the infiltration rate of $CD8^+$ T-cells was significantly increased. Therefore, MSCs combined with anti-PD1 antibody may be a potential therapeutic strategy for CRC [143].

4.8. Endostatin

Endostatin is a multitarget antiangiogenic agent that regulates the TME by modulating EC surface protein expression and cell signaling pathways to exert therapeutic effects at the molecular level [169]. Endostatin directly binds to VEGFR2, inhibits its phosphorylation, blocks the VEGF-VEGFR2 pathway, inhibits tumor angiogenesis, induces $CD8^+$ T-cells infiltration into CRC tumor tissue, and promotes the therapeutic effect of PD-L1 inhibitors [144].

5. Summary and prospect

Although various immunotherapies have made significant progress in cancer, they still have not achieved satisfactory results, especially in MSS CRC patients. How to increase the infiltration of $CD8^+$ T-cells, improve the efficacy of $CD8^+$ T-cells, and improve or even reverse the exhaustion of $CD8^+$ T-cells is still the key to and challenge of CRC immunotherapy. First, due to the complexity of the TME, many related mechanisms and signaling pathways are involved in the generation, activation, trafficking, killing, exhaustion, and death of $CD8^+$ T-cells. Therefore, our understanding and research on this process still need further improvement. With the progress of proteomics, genomics, immunoassays, single-cell transcriptomics, new antigen prediction, microbial flora, increasing immune checkpoint regulators, the discovery of natural products of traditional Chinese medicine, cell therapy, and cancer vaccines, more advanced insights and treatment strategies for CRC immunotherapy are being discovered. In addition, in CRC immunotherapy, there is no unified reference index for improving $CD8^+$ T-cell activity, such as increasing the number of infiltrating cells, enhancing the killing effect, and reducing exhaustion. Although ICI-based combined immunotherapy is being widely carried out, most studies are limited to a single targeted therapy, and more multicenter combined targeted therapies are needed. In addition, for CRC immunotherapy, we must consider the type and grade of the tumor and the different immune statuses of the same tumor to develop individualized treatment for combination therapy.

Ethical approval

manuscript is approved by all authors for publication.

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Data availability statement

The data cited in this review are from Pubmed, Web of Science, SCI-HUB, etc.

CRediT authorship contribution statement

Tao He: Writing – original draft. **Chencheng Hu:** Writing – original draft. **Shichao Li:** Data curation. **Yao Fan:** Methodology. **Fei Xie:** Validation. **Xin Sun:** Visualization. **Qingfeng Jiang:** Data curation. **Weidong Chen:** Investigation. **Yingtian Jia:** Project administration. **Wusheng Li:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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