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Advances in the role of T cells in colorectal cancer and related therapies

LI Yuetian*, HUANG Haining, CHEN Shuai, WANG Quanyi

**Clinical School of Medicine, Jining Medical University, Jining, Shandong 272000, China*

Corresponding author: WANG Quanyi, E-mail: wqy197312@sina.com

Abstract: T cells are closely associated with tumor development and the homeostasis of the tumor microenvironment (TME). The co-receptors of immune checkpoints on the surface of T cells collectively regulate immune responses and can inhibit or kill tumor cells by secreting various substances, correcting and restoring impaired anti-tumor immune responses. In recent years, there has been some progress in targeted T cell therapy, but some new immune test targets are still being studied. This article focuses on the role of T cells in the regulation of colorectal cancer (CRC) and TME, the mechanism of immune resistance to CRC and its targeted therapy, and discusses the relevant effects of T cells on the occurrence and development of CRC and the application prospect of targeted T cell therapy for CRC.

Keywords: Colorectal cancer; T cells; Tumor microenvironment; Immunotherapy; Immune checkpoint inhibitors; Adoptive cell therapy; Drug resistance

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In China, colorectal cancer (CRC) is a common and highly fatal malignancy of the digestive system [1]. CRC ranks third globally in terms of incidence and second in terms of mortality among malignant tumors, following only lung cancer [2]. Approximately 15% of CRC cases exhibit deficient DNA mismatch repair (dMMR), with two-thirds of these cases being secondary to hypermethylation of the *MLH1* gene promoter, which leads to microsatellite instability (MSI) [3]. The high mutation burden in these tumors generates numerous neoantigens, inducing a robust immune response within the tumor microenvironment (TME). Tumor-infiltrating immune cells (TIICs) in the TME, including Tregs, NK cells, macrophages, and myeloid-derived suppressor cells (MDSCs), significantly suppress effector T cells [4]. Clinical management of CRC primarily involves surgical resection, radiotherapy, and chemotherapy. However, CRC often presents with clinical symptoms and signs at an advanced stage, making traditional treatments less effective, prompting active research into immunotherapy. Studies have shown a close relationship between T cells and CRC progression. This review focuses on the regulatory roles of T cells in CRC and TME, CRC immune resistance mechanisms, and targeted therapies, exploring the impact of T cells on CRC development and the potential of T cell-targeted therapies in treating CRC.

1 Overview of T Cells

1.1 Origin of T cells

T cells play a role in immune surveillance of tumor cells [5]. Among them, $CD4^+$ helper T cells (Th) are a heterogeneous group of immune cells that can be categorized into Th0, Th1, Tfh, etc., based on the cytokines they secrete. Regulatory T cells (Tregs) are immunosuppressive cells in the TME, and inhibitory molecules in the TME can directly convert $CD4^+CD25^+$ T cells into $CD4^+CD25^+FoxP3^+$ Tregs [6]. CD8+ cytotoxic T lymphocytes (CTLs) can secrete interferon (IFN)-γ to inhibit tumor growth and also release perforin and granzymes to kill tumor cells.

1.2 Mechanisms of T cell suppression

Antigen-presenting cells (APCs) form major histocompatibility complex (MHC) with tumor antigens. When T cell antigen receptors (TCRs) bind to MHC-I, $CD8^+$ T cells are attracted to the TME [7], where T cells are activated through cell-cell interactions. Immune checkpoint proteins expressed on T cells interact with inhibitory ligands on APCs, such as programmed death receptor 1 (PD-1)/programmed death ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4)/CD80 (B7-1), leading to suppression of anti-tumor immune responses [8]. CTLA-4 is an inhibitory receptor that suppresses TCR-CD28-induced activation by competing with CD28 for CD80 [8]. Tumor-infiltrating lymphocytes (TILs) can secrete IFN-γ, inducing the upregulation of CD80 (B7-1) and PD-L1. Strategies to block the CD80 (B7-1) and PD-L1 pathways can restore impaired T cell responses.

1.3 T cell surface co-receptors

One mechanism of tumor immune escape involves the reprogramming of immune checkpoint receptors (ICRs). ICRs are divided into stimulatory co-receptors (e.g., CD28 and CD137) and inhibitory co-receptors [e.g., lymphocyte activation gene-3 (LAG-3) and PD-1]. MHC and $CD4^+/CD8^+$ co-receptors interact to promote calcium mobilization, protein kinase C activation, and Ras

pathway activation, enhancing T cell transcription. TCR stimulation is usually regulated by CTLA-4 and CD28 co-stimulatory receptors, with CTLA-4 having a higher affinity for CD80 [9]. CD28 activates in the presence of foreign antigens, stimulating downstream immune signaling, while CTLA-4 activates after the removal of foreign antigens to inhibit immune signaling and prevent overactive or autoimmune responses [9].

2 Regulation of CRC and TME by T Cells

2.1 Role of T cells in CRC proliferation

In the TME, IFN-γ mainly comes from TILs and NK cells. IFN-γ contributes to tumor immune escape by inducing the expression of immune suppressive molecules such as PD-L1, indoleamine 2,3-dioxygenase (IDO), and arginase [7]. PD-L1 is expressed on both tumor cells and immune cells, especially APCs in tumor-draining lymph nodes and the TME [10]. IFN-γ induces the activation of the JAK/STAT signaling pathway, which in turn activates interferon regulatory factor 1 (IRF1), promoting PD-L1 transcription [11].

2.2 Regulation of TME by T Cells

2.2.1 Composition of TME

The TME can be divided into two types: one with a high density of $CD8^+$ TILs, IFN, chemokines (such as CXCL9 and CCL10), and various inflammatory factors, known as an immune-inflammatory TME. The other is a non-immune-inflammatory TME, characterized by cytokines related to immune suppression or tolerance [such as IL-10, IL-35, IL-4, transforming growth factor-β (TGF-β)] and immune suppressive cells (such as Tregs). Tumors in an inflammatory TME exhibit stronger anti-tumor immune responses.

2.2.2 Effects of T Cells on the microenvironment

Adaptive immune cells are mainly composed of effector T cells and Tregs. Studies have shown that combined blockade of PD-1 and CTLA-4 pathways increases the infiltration of effector T cells into melanoma tumors and reduces the infiltration of Tregs and MDSCs, thereby decreasing immune suppression and promoting inflammatory cascades in the TME [13]. Tregs primarily employ three immune suppressive mechanisms. Firstly, Tregs secrete cytokines and cytotoxic molecules to inhibit effector T cells, including immune regulatory cytokines such as IL-10, IL-35, and TGF-β [14]. VEGF and TGF-β promote the conversion of $CD4^+$ T cells into Tregs and their accumulation in the TME. Cytotoxic molecules released by Tregs (such as granzymes and perforin) can directly kill effector T cells. Secondly, Tregs highly express ICRs and continuously regulate their functions (increasing the release of inhibitory cytokines or upregulation of IDO), promoting an immunosuppressive TME [4]. Additionally, Tregs interfere with the metabolism of effector cells, affecting their functions [4]. Tregs disrupt the metabolism of effector T cells by consuming IL-2 in the TME. They express CD39 and CD73 ecto-nucleotidases, converting ATP and ADP into adenosine. Adenosine can bind to adenosine receptor A2A on the surface of effector T cells, increasing intracellular cAMP and impairing their metabolism and function. cAMP also interacts with APCs and macrophages, inducing tolerogenic MDSCs and tumor-associated macrophages, further affecting T cells.

3 The Role of T Cells in CRC Immune Resistance

The hallmark of immunotherapy is the presentation of antigens by APCs, which are then recognized and targeted by host T cells. Thus, resistance to immunotherapy may develop due to tumor cells lacking antigens or ineffective antigen presentation. Ineffective antigen presentation mechanisms include decreased MHC-I expression, β2-microglobulin mutations, human leukocyte antigen (*HLA*)-I mutations, interactions between PD-1/PD-L1 and CTLA-4/B7, and loss of phosphatase and tensin homolog (PTEN) on chromosome 10, as well as activation of oncogenic signaling pathways.

3.1 Lack of T cell antigen recognition

The presentation and quantity of tumor neoantigens can impact T cell anti-tumor immunity. In dMMR-CRC, high mutation burden and neoantigen load correlate positively with immunotherapy efficacy. dMMR-CRC patients show better responses to anti-PD-1 therapy, mainly due to higher mutation loads, numerous neoantigens, and increased immune cell infiltration. Compared to microsatellite stable (MSS) tumors, dMMR-CRC TME shows intense upregulation of immune checkpoints like PD-L1, CTLA-4, LAG-3, and IDO.

3.2 Ineffective antigen presentation

3.2.1 Decreased MHC-I expression

Decreased MHC-I expression can reduce the efficacy of immune checkpoint blockade by blocking $CD8^+$ T cell activation or rendering effector T cells dysfunctional [15]. Tumor cells evade immune destruction by downregulating surface MHC-I expression, which is crucial for antigen presentation. Binding of TCR to MHC-I attracts $CD8^+$ T cells to the TME and activates anti-tumor immune responses. About 50% of diffuse large B-cell lymphoma cases are not recognized by CTLs due to lack of MHC-I expression [16].

3.2.2 β2-microglobulin mutations

β2-microglobulin is an extracellular component of MHC-I that induces/enhances MHC-I antigen presentation capability. Its loss leads to the absence of surface MHC-I, impacting anti-tumor immunity [17].

3.2.3 *HLA-I* mutations

HLA-I plays a crucial role in antigen presentation

[18]. In various tumor types, these molecules are often lost, leading to immune evasion of tumors [18]. HLA-I binds short peptides from intracellular proteins and presents them to T cells, which is vital for immune surveillance and anti-tumor responses [19]. In a study of 74 diffuse large B-cell lymphoma cases, 80% of MHC-I(-) tumors exhibited somatic inactivation of β2-microglobulin and *HLA-I* gene loci [16].

3.2.4 Interaction between PD-1/PD-L1 and CTLA-4/B7

Immune checkpoint proteins (PD-1/CTLA-4) expressed on T cells interact with their ligands (PD-L1/B7) on APC, inhibiting anti-tumor immune responses. IFN-γ-activated Stat1 promotes Tet1 binding to Irf1, regulating Irf1 demethylation and leading to downstream expression of PD-L1 on tumors [20]. T cells and NK cells produce IFN-γ [21].

3.2.5 Loss of PTEN

PTEN is a tumor-suppressor gene, inhibiting the phosphatidylinositol-3-kinase (PI3K) pathway. Its loss creates an immunosuppressive microenvironment [22]. Additionally, tumors with PTEN defects exhibit increased IDO and PD-L1 expression, aiding immune evasion [10]. PTEN mRNA stimulated anti-tumor immune activity and reversed the immunosuppressive TME, inducing tumor cell necrosis [23].

3.2.6 Oncogenic signaling pathways

Oncogenic signaling pathways, such as the mitogen-activated protein kinase (MAPK) [24] and WNT/β-catenin pathways, regulate cell recruitment necessary for anti-tumor immunity. They can affect IFN-γ and antigen presentation, suppress dendritic cell recruitment, prevent T cell infiltration, induce tumor cell apoptosis, or generate immunosuppressive factors in the TME, resulting in resistance [11]. The MAPK pathway upregulates IL-6 and IL-10 release, inhibiting T cell recruitment and function. IFN-γ induces the expression of immune suppressive molecules in the TME, including B7-1, PD-L1, IDO, and arginase.

4 CRC Clinical Targeted Therapy

4.1 Suppression or depletion of Treg

Tregs play a crucial role in tumor immune evasion. Targeting Tregs could be an effective adjunct to current immunotherapies, including Treg activity inhibition and depletion. Targeting CD39 *in vitro* can inhibit Treg activity, and *in vivo*, it can suppress tumor growth. Targeting CD73 Tregs might also have therapeutic benefits. Low-dose cyclophosphamide can deplete Tregs.

4.2 Adoptive cellular therapy (ACT)

ACT uses cells from the patient (autologous transfer) or other donors (allogeneic transfer) to enhance immune function. It involves isolating T cells from the patient's peripheral blood, expanding them *ex vivo*, and reintroducing them into the patient with chimeric antigen receptor T cell (CAR-T) expression and modification [25]. ACT includes three types: CAR-T insertion, use of TILs, and T cell receptor-engineered T cells (TCR-T). These modifications enhance T cell antigen recognition and avoid MHC restrictions. However, CAR-T therapy faces challenges, including cytotoxicity to non-tumor tissues expressing target antigens, leading to severe off-target toxicities [26].

4.3 Immune checkpoint inhibitors (ICIs)

ICIs restore anti-tumor immune responses by targeting checkpoint proteins (e.g., PD-1, PD-L1) and blocking immune suppressive signals. Combination therapies show enhanced efficacy. Although ICIs are currently effective only in metastatic diseases, evaluating ICIs for early dMMR-CRC as neoadjuvant and adjuvant therapy is a new research direction. Targeting CTLA-4 blocks this protein, allowing CD28 to bind B7, thereby stimulating T cell immune responses [27].

New immune checkpoint targets, such as T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT), LAG-3, and T cell immunoglobulin domain and mucin domain-3 (TIM-3), are undergoing preclinical research [3]. CD226 aids NK cells in tumor immune surveillance. TIGIT is upregulated in exhausted T cells and co-expressed with PD-1; blocking TIGIT can restore anti-tumor immune responses. The efficacy of anti-PD-1 and TIGIT is related to CD226 expression on $CD8^+$ T cells [28]. Relatlimab is an LAG-3 blocking antibody. In an international double-blind phase III study, nivolumab plus relatlimab significantly extended median progression-free survival from 4.6 months to 10.1 months compared to nivolumab alone (*HR*=0.75; 95%*CI*: 0.62-0.92; *P*=0.006) [29]. Other LAG-3 inhibitors are under investigation, including LBL-007, which has shown significant anti-tumor activity alone or in combination with anti-PD-1 antibodies in CRC xenografts [3]. Preclinical studies suggested that combined blockade of TIM-3 and PD-1 pathways was highly effective in treating solid tumors [30]. TIM-3 is highly expressed with increased TGF-β. Immunotherapeutic strategies targeting TIM-3, TGF-β in combination with PD-1/PD-L1 can overcome ICIs tolerance, especially CRC with CMS4 and MSI characterized by high levels of TIM-3 and TGF-β [31].

4.4 CRC-related therapeutic supplements

The product succinate from *Fusobacterium nucleatum* can reduce CRC sensitivity to anti-PD-1 monoclonal antibodies. Treating mice with metronidazole reduces *Fusobacterium nucleatum* and succinate production in the gut, restoring tumor sensitivity to immunotherapy [32]. In CRC patient cohorts, the expression of N6-methyladenosine RNA binding protein 1 is negatively correlated with $CD8^+$ T cell infiltration,

impairing anti-tumor immunity through the N6-methyladenosine-p65-CXCL1/CXCR2 axis, making it a target for immunotherapy [33]. In human CRC liver metastases, antagonizing IL-10 increased activation and cytotoxicity of CEA-specific CAR-T cells. Targeting IL-10/IL-10 receptor signaling has the potential to serve as a stand-alone therapy and enhance CAR-T function in human CRC liver metastases [33].

5 Conclusion

T cells have complex interactions with TME and play an important role in CRC progression, and targeting T cells to treat tumors is promising for clinical application. ICIs are currently effective in metastatic-only CRC, but evaluating ICIs as neoadjuvant and adjuvant therapy for early dMMR-CRC is a new research direction. New immune checkpoint targets, such as TIGIT, LAG-3, and TIM-3, are undergoing preclinical studies. Therefore, the mechanism of T cell interaction with CRC and TME should continue to be investigated, and the progress of targeted T cell therapy to better regulate tumor cells.

Conflict of interest None

Reference

[1] Guo MY, Peng WW, Fang Y, et al. Advances in immunotherapy of early-middle stage colorectal cancer with microsatellite instability-high and stability[J]. Chin J Clin Res, 2023, 36(12): 1886-1889.
[2] Bardelčíková A, Šoltys J, Mojžiš J. Oxidative stress, inflammation and colorectal cancer: an overview[J]. Antioxidants(Basel), 2023, 12(4): 901.
[3] Jin ZH, Sinicrope FA. Mismatch repair-deficient colorectal cancer: building on checkpoint blockade[J]. J Clin Oncol, 2022, 40(24): 2735-2750.
[4] Aristin Revilla S, Kranenburg O, Coffer PJ. Colorectal cancer-infiltrating regulatory T cells: functional heterogeneity, metabolic adaptation, and therapeutic targeting[J]. Front Immunol, 2022, 13: 903564.
[5] Koch U, Radtke F. Mechanisms of T cell development and transformation[J]. Annu Rev Cell Dev Biol, 2011, 27: 539-562.
[6] Ohue Y, Nishikawa H. Regulatory T (Treg) cells in cancer: can Treg cells be a new therapeutic target?[J]. Cancer Sci, 2019, 110(7): 2080-2089.
[7] Du W, Frankel TL, Green M, et al. IFNγ signaling integrity in colorectal cancer immunity and immunotherapy[J]. Cell Mol Immunol, 2022, 19(1): 23-32.
[8] Zhao W, Jin LJ, Chen P, et al. Colorectal cancer immunotherapy-Recent progress and future directions[J]. Cancer Lett, 2022, 545: 215816.
[9] Johdi NA, Sukor NF. Colorectal cancer immunotherapy: options and strategies[J]. Front Immunol, 2020, 11: 1624.
[10] Vidotto T, Melo CM, Castelli E, et al. Emerging role of PTEN loss in evasion of the immune response to tumours[J]. Br J Cancer, 2020, 122(12): 1732-1743.
[11] Kalbasi A, Ribas A. Tumour-intrinsic resistance to immune checkpoint blockade[J]. Nat Rev Immunol, 2020, 20(1): 25-39.
[12] Zhang QQ, Zhao Q, Li T, et al. Lactobacillus plantarum-derived indole-3-lactic acid ameliorates colorectal tumorigenesis via epigenetic regulation of CD8+ T cell immunity[J]. Cell Metab, 2023, 35(6): 943-960.e9.
[13] Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors[J]. Proc Natl Acad Sci U S A, 2010, 107(9): 4275-4280.
[14] Dikiy S, Rudensky AY. Principles of regulatory Tcell function[J]. Immunity, 2023, 56(2): 240-255.
[15] Dhatchinamoorthy K, Colbert JD, Rock KL. Cancer immune evasion through loss of MHC class I antigen presentation[J]. Front Immunol, 2021, 12: 636568.
[16] Fangazio M, Ladewig E, Gomez K, et al. Genetic mechanisms of HLA-I loss and immune escape in diffuse large B cell lymphoma[J]. Proc Natl Acad Sci U S A, 2021, 118(22): e2104504118.
[17] Bern MD, Parikh BA, Yang LP, et al. Inducible down-regulation of MHC class I results in natural killer cell tolerance[J]. J Exp Med, 2019, 216(1): 99-116.
[18] Anderson P, Aptsiauri N, Ruiz-Cabello F, et al. HLA class I loss in colorectal cancer: implications for immune escape and immunotherapy[J]. Cell Mol Immunol, 2021, 18(3): 556-565.
[19] Chowell D, Krishna S, Becker PD, et al. TCR contact residue hydrophobicity is a hallmark of immunogenic CD8+ T cell epitopes[J]. Proc Natl Acad Sci U S A, 2015, 112(14): E1754-E1762.
[20] Lv HW, Lv GS, Chen CA, et al. NAD+ metabolism maintains inducible PD-L1 expression to drive tumor immune evasion[J]. Cell Metab, 2021, 33(1): 110-127.e5.
[21] Gocher AM, Workman CJ, Vignali DAA. Interferon-γ: teammate or opponent in the tumour microenvironment?[J]. Nat Rev Immunol, 2022, 22(3): 158-172.
[22] Cetintas VB, Batada NN. Is there a causal link between PTEN deficient tumors and immunosuppressive tumor microenvironment?[J]. J Transl Med, 2020, 18(1): 45.
[23] Lin YX, Wang Y, Ding JX, et al. Reactivation of the tumor suppressor PTEN by mRNA nanoparticles enhances antitumor immunity in preclinical models[J]. Sci Transl Med, 2021, 13(599): eaba9772.
[24] Tian J, Chen JH, Chao SX, et al. Combined PD-1, BRAF and MEK inhibition in BRAFV600E colorectal cancer: a phase 2 trial[J]. Nat Med, 2023, 29(2): 458-466.
[25] Luo X, Tang YZ, Hu XD, et al. Current status and challenges of CAR-T therapy in colorectal cancer treatment[J]. Chin Bull Life Sci, 2023, 35(7): 916-924. **[In Chinese]**
[26] Flugel CL, Majzner RG, Krenciute G, et al. Overcoming on-target, off-tumour toxicity of CAR T cell therapy for solid tumours[J]. Nat Rev Clin Oncol, 2023, 20(1): 49-62.
[27] Sharma P, Goswami S, Raychaudhuri D, et al. Immune checkpoint therapy-current perspectives and future directions[J]. Cell, 2023, 186(8): 1652-1669.
[28] Viot J, Abdeljaoued S, Vienot A, et al. CD8+ CD226high T cells in liver metastases dictate the prognosis of colorectal cancer patients treated with chemotherapy and radical surgery[J]. Cell Mol Immunol, 2023, 20(4): 365-378.
[29] Thomas B, Burns M, Pervanas H, et al. Nivolumab/relatlimab-rmbw: a novel dual combination therapy to treat adult and pediatric patients with unresectable or metastatic melanoma[J]. Am J Ther, 2023, 30(6): e526-e534.
[30] Mokhtari Z, Rezaei M, Sanei MH, et al. Tim3 and PD-1 as a therapeutic and prognostic target in colorectal cancer: relationship with sidedness, clinicopathological parameters, and survival[J]. Front Oncol, 2023, 13: 1069696.
[31] Katagata M, Okayama H, Nakajima S, et al. TIM-3 expression and M2 polarization of macrophages in the TGFβ-activated tumor microenvironment in colorectal cancer[J]. Cancers, 2023, 15(20): 4943.
[32] Jiang SS, Xie YL, Xiao XY, et al. Fusobacterium nucleatum-derived succinic acid induces tumor resistance to immunotherapy in colorectal cancer[J]. Cell Host Microbe, 2023, 31(5): 781-797.e9.
[33] Bao Y, Zhai JN, Chen HR, et al. Targeting m6A reader YTHDF1 augments antitumour immunity and boosts anti-PD-1 efficacy in colorectal cancer[J]. Gut, 2023, 72(8): 1497-1509.
[34] Sullivan KM, Jiang X, Guha P,et al. Blockade of interleukin 10 potentiates antitumour immune function in human colorectal cancer liver metastases. Gut. 2023 Feb;72(2):325-337.

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·研究进展·

T 细胞在结直肠癌中的作用及相关治疗进展

李月天[1]，　黄海宁[2]，　陈帅[3]，　王全义[3]

1. 济宁医学院临床医学院，山东 济宁 272067；2. 济宁医学院附属医院临床药学科，山东 济宁 272029；
3. 济宁医学院附属医院病理科，山东 济宁 272029

摘要：T 细胞与肿瘤的发生发展及肿瘤微环境(TME)稳态密切相关。其表面免疫检查点共受体共同调节着免疫应答。它可通过分泌各种物质抑制或杀伤肿瘤细胞,纠正和恢复受损的抗肿瘤免疫反应。近年来,靶向 T 细胞治疗获得一些进展,但一些新的免疫检查靶点仍在研究中。本文重点探讨 T 细胞在调控结直肠癌(CRC)和 TME 中的作用、CRC 的免疫耐药机制及其靶向治疗等,论述 T 细胞对 CRC 发生发展的相关影响及靶向 T 细胞治疗 CRC 的应用前景。

关键词：结直肠癌；T 细胞；肿瘤微环境；免疫治疗；免疫检查点抑制剂；过继细胞疗法；耐药

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LI Yuetian*, HUANG Haining, CHEN Shuai, WANG Quanyi

** Clinical School of Medicine, Jining Medical University, Jining, Shandong 272067, China*

Corresponding author: WANG Quanyi, E-mail: wqy197312@sina.com

Abstract: T cells are closely associated with tumor development and the homeostasis of the tumor microenvironment (TME). The co-receptors of immune checkpoints on the surface of T cells collectively regulate immune responses and can inhibit or kill tumor cells by secreting various substances, correcting and restoring impaired anti-tumor immune responses. In recent years, there has been some progress in targeted T cell therapy, but some new immune test targets are still being studied. This article focuses on the role of T cells in the regulation of colorectal cancer (CRC) and TME, the mechanism of immune resistance to CRC and its targeted therapy, and discusses the relevant effects of T cells on the occurrence and development of CRC and the application prospect of targeted T cell therapy for CRC.

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在我国,结直肠癌(colorectal cancer, CRC)是一种常见且死亡率较高的消化系统恶性肿瘤[1]。CRC 于全球恶性肿瘤发病率居第三,恶性肿瘤死亡率中居第二[2],仅次于肺癌。大约 15%的 CRC 有 DNA 错配修复功能缺陷(deficient DNA mismatch repair, dMMR),其中三分之二的病例是继发于 *MLH1* 基因启动子高甲基化,这会导致微卫星不稳定(microsatellite instability, MSI)[3]。肿瘤的高度突变,将产生大量的新抗原,在肿瘤微环境(tumor microenvironment, TME)中引起强烈的免疫反应。在 TME 中,肿瘤浸润性免疫细胞(tumor-infiltrating immune cells, TIIC)包括 Treg、自然杀伤(natural killer, NK)细胞、巨噬细胞和髓系来源抑制细胞(myeloid-derived suppressor cells, MDSCs)等[4],其对效应 T 细胞有显著的抑制作用。CRC 的临床治疗主要包括手术切除、放疗和化疗。传统的治疗方法在晚期 CRC 往往不能取得满意的效果,其相关的免疫治疗研究正在积极进展中。研究显示,T 细胞与 CRC 的进展有密切的关系。本文主要围绕 T 细胞对 CRC 和 TME 的调控作用、CRC 免疫耐药机制及其靶向治疗等展开综述,探讨 T 细胞对 CRC 发生发展的相关影响及靶向 T 细胞治疗 CRC 的应用前景。

1　T 细胞概述

1.1　T 细胞的来源　T 细胞对肿瘤细胞起免疫监视作用[5]。

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通信作者：王全义，E-mail：wqy197312@sina.com

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QR code for English version

其中，$CD4^+$辅助 T 细胞（helper T cell，Th）是一组异质性免疫细胞，根据其分泌细胞因子的不同，可分为 Th0、Th1、Tfh 等。调节性 T 细胞（regulatory T cell，Treg）是 TME 中的免疫抑制性细胞，TME 中的抑制性分子能直接将 $CD4^+CD25^+$T 细胞转化为 $CD4^+CD25^+FoxP3^+$的 Treg[6]。$CD8^+$细胞毒性 T 细胞（cytotoxic T lymphocyte，CTL）可分泌干扰素（inferferon，IFN）-γ 抑制肿瘤生长，也可分泌穿孔素和颗粒酶杀伤肿瘤细胞。

1.2　*T 细胞抑制机制*　抗原提呈细胞（antigen-presenting cell，APC）与肿瘤抗原形成主要组织相容性复合体（major histocompatibility complex，MHC），当 T 细胞抗原受体（T-cell antigen receptor，TCR）与 MHC-Ⅰ结合，$CD8^+$T 细胞将被吸引到 TME[7]，T 细胞通过细胞间相互作用被激活。T 细胞表面表达的免疫检查点蛋白与 APC 表面的抑制性配体相互作用，如程序性死亡受体 1（PD-1）/程序性死亡配体 1（PD-L1）、CTLA-4/CD80（B7-1），将会抑制抗肿瘤免疫反应[8]。CTLA-4 是抑制性受体，通过与 CD28 竞争 CD80 而抑制 TCR-CD28 诱导的活化[8]。肿瘤浸润淋巴细胞（tumor-infiltrating lymphocyte，TIL）可分泌 IFN-γ，诱导 CD80（B7-1）、PD-L1 的上调。

1.3　*T 细胞表面共受体*　肿瘤免疫逃逸的机制之一是免疫检查点受体（immune checkpoint receptor，ICR）的重编程。ICR 分为刺激性共受体（如 CD28 和 CD137）、抑制性共受体［如淋巴细胞活化基因（lymphocyte activation gene，LAG）-3、PD-1 等］，二者共同调节着 T 细胞的免疫应答。MHC 和 $CD4^+$/$CD8^+$共受体相互作用，会促进钙动员、蛋白激酶 C 的活化和 Ras 通路的激活，进而促进 T 细胞转录。通常，TCR 刺激受到 CTLA-4 共抑制及 CD28 共刺激受体的调节，但 CTLA-4 对 CD80 亲和力更高[9]。CD28 在有异物时激活，刺激下游的免疫信号传导；CTLA-4则在异物消除后激活，以抑制免疫信号传导[9]。

2　T 细胞对 CRC 和 TME 的调控

2.1　*T 细胞对 CRC 增殖的作用*　在 TME 中，IFN-γ 主要来自 TIL 和 NK 细胞。IFN-γ 有助于肿瘤免疫逃避，其诱导免疫抑制分子［如 PD-L1、吲哚胺 2，3-双加氧酶（IDO）和精氨酸酶］的表达[7]。PD-L1 在肿瘤细胞和免疫细胞上表达，特别是肿瘤引流淋巴结和肿瘤微环境中的 APC[10]。IFN-γ 会诱导 JAK/STAT 信号通路激活，继而激活干扰素调节因子 1（interferon regulatory factor 1，IRF1），促进 PD-L1 的转录[11]。

2.2　*T 细胞对 TME 的调控作用*

2.2.1　*TME 的组成*　TME 大体可以分为两类：一类是含有较高密度的 $CD8^+$TILs、IFN、趋化因子（如 CXCL-9、CLCL-10）及各种炎性因子，被称为免疫炎性的 TME[12]。另一类是非免疫炎性的 TME，含有与免疫抑制或耐受有关的细胞因子［如白细胞介素（IL）-10、IL-35、IL-4、转化生长因子（transforming growth factor，TGF）-β］及免疫抑制细胞（如 Treg）。

2.2.2　*T 细胞对微环境的作用*　适应性免疫细胞主要由效应 T 细胞和 Treg 组成。研究报道，PD-1 和 CTLA-4 通路的联合阻断增加了黑色素瘤肿瘤中的效应 T 细胞浸润，减少了 Tregs 和 MDSC 的浸润，从而减少免疫抑制并促进 TME 中的炎症级联反应[13]。Treg 主要有三种免疫抑制机制。首先，Treg 可分泌细胞因子和细胞毒性分子来抑制效应 T 细胞。包括免疫调节细胞因子 IL-10、IL-35 和 TGF-β[14]。促进肿瘤发展的 VEGF 和 TGF-β，促进 $CD4^+$T 细胞转化为 Treg 细胞，并在 TME 中积聚。Treg 释放的细胞毒性分子（如颗粒酶和穿孔素），可直接杀死效应 T 细胞。其次，Treg 细胞高度表达 ICR，增加抑制性细胞因子的释放或 IDO 的上调，促进免疫抑制性 TME[4]。此外，Treg 细胞干扰效应细胞的代谢，从而影响其功能[4]。Treg 通过消耗 TME 中的 IL-2 破坏效应 T 细胞的代谢。它表达 CD39 和 CD73 外核苷酸酶，将 ATP 和 ADP 转化为腺苷，腺苷可以与效应 T 细胞表面的腺苷受体 A2A 结合，增加细胞内 cAMP 并破坏其代谢和功能。

3　T 细胞在 CRC 免疫耐药中的作用

免疫疗法的标志是 APC 呈递抗原，宿主 T 细胞将其识别并杀伤肿瘤细胞。因此，对免疫疗法的耐药性可以由肿瘤细胞缺乏抗原或抗原呈递无效发展而来。抗原呈递无效机制包括 MHC-Ⅰ表达下降，β2-微球蛋白突变、人类白细胞抗原（human leukocyte antigen，*HLA*-Ⅰ）突变、PD-1/PD-L1 及 CTLA-4/B7 的相互作用、10 号染色体缺失的磷酸酶及张力蛋白同源物（phosphatase and tensin homolog，PTEN）的缺失和致瘤信号通路激活，具体如下。

3.1　*T 细胞缺乏抗原识别*　肿瘤新抗原的呈递和数量可能会影响 T 细胞抗肿瘤免疫，在 dMMR-CRC 中，高突变和新抗原数量与免疫治疗效果呈正相关。在 dMMR-CRC 患者中，抗 PD-1 效果更好，主要是因为它的高突变负荷、新抗原数量多和免疫细胞浸润增加。与微卫星稳定（microsatelite stable，MSS）肿瘤相比，dMMR-CRC 的 TME 表现出免疫检查点的强烈上调，如 PD-L1、CTLA-4、LAG-3 和 IDO。

3.2　*抗原呈递无效*

3.2.1　*MHC-Ⅰ表达下降*　MHC-Ⅰ可以通过阻断 $CD8^+$T 细胞的活化或使效应 T 细胞失能来降低免疫检查点阻断的疗效[15]。肿瘤细胞通过下调对抗原呈递至关重要的细胞表面 MHC-Ⅰ表达来逃避免疫杀伤。TCR 与 MHC-Ⅰ的结合，$CD8^+$T 细胞将被吸引到 TME，抗肿瘤免疫反应被激活。50% 的弥漫大 B 细胞淋巴瘤由于缺乏 MHC-Ⅰ的表达，无法被 CTL 识别[16]。

3.2.2　*β2-微球蛋白突变*　β2-微球蛋白是 MHC-Ⅰ类的细胞外成分，可诱导/增强 MHC-Ⅰ类抗原呈递的能力。β2-微球蛋白的缺失会导致表面 MHC-Ⅰ缺失[17]，影响抗肿瘤免疫。

3.2.3　*HLA-Ⅰ突变*　HLA-Ⅰ抗原在提呈方面有着关键作用[18]。在不同类型的肿瘤中，这些分子经常丢失，导致肿瘤对 CTL 的免疫逃避[18]。*HLA*-Ⅰ与细胞内蛋白的特异性短肽结合，向 T 细胞呈递细胞抗原，这对免疫监测和抗肿瘤免疫反应至关重要[19]。对 74 例患弥漫大 B 细胞淋巴瘤者进行了全外显子组和靶向 HLA 深度测序，发现 80% 的 MHC-Ⅰ阴性肿瘤中存在 β2-微球蛋白和 *HLA*-Ⅰ基因位点的体细胞失活[16]。

3.2.4　PD-1/PD-L1 及 CTLA-4/B7 的相互作用　T 细胞表面表达的免疫检查点蛋白(PD-1/CTLA-4)与其在 APC 表面的配体(PD-L1/B7)相互作用,将会抑制抗肿瘤免疫反应。IFN-γ 激活的 STAT1 可促进 TET1 与 IRF1 结合,从而调节 IRF1 的去甲基化,导致下游 PD-L1 在肿瘤上的表达[20]。T 细胞和 NK 等细胞产生 IFN-γ[21]。

3.2.5　*PTEN* 的缺失　*PTEN* 是抑癌基因,对磷酸肌醇 3-激酶(phosphatidylinositol 3-kinase, PI3K)通路有抑制作用。其缺失将产生抑制性免疫微环境[22]。PTEN 缺陷的肿瘤 IDO 和 PD-L1 表达增多,有助于肿瘤细胞免疫逃避[10]。研究表明,*PTEN* 的 mRNA 可以刺激抗肿瘤免疫活性并逆转免疫抑制性 TME,从而诱导肿瘤细胞坏死[23]。

3.2.6　致瘤信号通路　致瘤信号通路,如丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)[24] 途径和 WNT/β-catenin通路,调控抗肿瘤免疫所需的细胞募集。它们可影响 IFN-γ 和抗原呈递,抑制树突状细胞募集,防止 T 细胞浸润,诱导肿瘤细胞凋亡或者在 TME 中诱导免疫抑制因子,从而产生耐药性[11]。MAPK 途径上调 IL-6 和 IL-10 的释放,抑制 T 细胞的募集和功能。IFN-γ 诱导 TME 中免疫抑制分子的表达,包括 B7-1、PD-L1、IDO 和精氨酸酶。

4　CRC 临床靶向治疗

4.1　*抑制或耗竭 Treg*　Treg 在肿瘤免疫逃逸中发挥重要作用。靶向 Treg 可能是目前免疫疗法的有效补充,包括抑制 Treg 活性和 Treg 的耗竭。靶向 CD39 在体外可抑制 Treg 细胞活性,在体内可抑制肿瘤生长。研究表明靶向 CD73 Treg 细胞也可能具有治疗益处。还可用低剂量环磷酰胺来耗竭 Treg。

4.2　*过继细胞疗法*(adoptive cellular therapy, ACT)　ACT 使用来自患者(自体转移)或其他供体(同种异体转移)的细胞以改善免疫功能。它从患者外周血中分离 T 细胞,进行体外扩增、嵌合抗原受体(chimeric antigen receptor T cells,CAR-T)表达及修饰后回输至患者体内[25]。ACT 包括 CAR-T 的插入、TIL 的使用和 T 细胞受体工程 T 细胞(T cell receptor-engineered T cells, TCR-T)的修饰。这些修饰可增强 T 细胞的抗原识别能力和避免 MHC 的限制性识别。然而,CAR-T 疗法对表达靶抗原的非肿瘤组织也有细胞毒性,从而导致临床上严重的靶向非肿瘤毒性风险[26]。

4.3　*免疫检查点抑制剂*(immune checkpoint inhibitors,ICIs)　ICIs 是通过靶向受体或配体的检查点蛋白的阻断免疫抑制肿瘤信号,如 PD-1 和 PD-L1,从而恢复抗肿瘤免疫反应,且联合治疗效果更佳。尽管 ICIs 的益处目前仅限于转移性疾病,但评估 ICIs 作为早期 dMMR-CRC 的新辅助和辅助治疗是未来一个新的研究方向。靶向 CTLA-4,以结合、阻断该蛋白。从而允许 CD28 与 B7 结合[27],刺激 T 细胞免疫反应。

新的免疫检查点靶点,如 T 细胞免疫球蛋白和免疫受体酪氨酸抑制性基序结构域(TIGIT)、LAG-3 及 T 细胞免疫球蛋白黏蛋白分子 3(TIM3),正在进行临床前研究[3]。CD226 有助于 NK 细胞对肿瘤的免疫监测。TIGIT 在衰竭的 T 细胞中上调并与 PD-1 共表达,阻断 TIGIT 可恢复抗肿瘤免疫反应,抗 PD-1 和 TIGIT 的效果与 $CD8^+$ T 细胞上的 CD226 表达有关[28]。Relatlimab 是一种 LAG-3 阻断抗体。在一项国际双盲随机Ⅲ期研究中,与纳武利尤单抗单药治疗 714 名晚期黑色素瘤患者相比,纳武利尤单抗联合 relatlimab 可将中位无进展生存期从 4.6 个月显著延长至 10.1 个月($HR=0.75$, 95%CI: 0.62~0.92, $P=0.006$)[29]。其他 LAG-3 抑制剂正在研究中,包括 LBL-007,其在 CRC 异种移植中单独或与 anti-PD-1 抗体联合显示出显著的抗肿瘤活性[3]。临床前研究表明,联合阻断 TIM-3 和 PD-1 通路在治疗实体瘤方面非常有效[30]。TIM-3 随着 TGF-β 的增加而高度表达。靶向 TIM-3、TGF-β 与 PD-1/PD-L1 相结合的免疫治疗策略可以克服 ICIs 耐受,特别是以高水平 TIM-3 和 TGF-β 为特征的 CMS4 和 MSI 的 CRC[31]。

4.4　*CRC 相关治疗补充*　具核梭酸杆菌的产物琥珀酸可降低 CRC 对抗 PD-1 单克隆抗体的敏感性。用甲硝唑治疗小鼠,减少其肠道具核梭酸杆菌的数量和琥珀酸的产生,从而恢复肿瘤对免疫疗法的敏感性[32]。在多组 CRC 患者中,N6-甲基腺苷 RNA 结合蛋白 1 的表达与 $CD8^+$T 细胞浸润呈负相关,其通过 N6-甲基腺苷-p65-CXCL1/CXCR2 轴损害抗肿瘤免疫,是免疫治疗靶点[33]。人类 CRC 肝转移的切片中,拮抗 IL-10 增加了 CEA 特异性 CAR-T 细胞的激活和 CAR-T 细胞的细胞毒性。靶向 IL-10/IL-10 受体信号传导在人 CRC 肝转移中有作为独立治疗和增强 CAR-T 功能的潜力[34]。

5　结　语

T 细胞与 TME 有着复杂的相互作用关系,对 CRC 的进展也有重要作用,靶向 T 细胞来治疗肿瘤很有临床应用前景。ICIs 目前仅在转移性 CRC 中效果不错,但评估 ICIs 作为早期 dMMR-CRC 的新辅助和辅助治疗是未来一个新的研究方向。新的免疫检查点靶点,如 TIGIT、LAG-3 和 TIM-3,正在进行临床前研究。因此,应继续研究 T 细胞与 CRC 和 TME 的相互作用机制,靶向 T 细胞治疗的进展,更好地调控肿瘤细胞。

利益冲突　无

参考文献

[1] 郭梦雅,彭炜惟,方瑛,等.早中期微卫星高度不稳定及稳定型结直肠癌的免疫治疗进展[J].中国临床研究,2023,36(12):1886-1889.
Guo MY, Peng WW, Fang Y, et al. Advances in immunotherapy of early-middle stage colorectal cancer with microsatellite instability-high and stability [J]. Chin J Clin Res, 2023, 36(12): 1886-1889.

[2] Bardelcíková A, Šoltys J, Mojžiš J. Oxidative stress, inflammation and colorectal cancer: an overview [J]. Antioxidants (Basel), 2023, 12(4): 901.

[3] Jin ZH, Sinicrope FA. Mismatch repair-deficient colorectal cancer: building on checkpoint blockade[J]. J Clin Oncol, 2022, 40(24): 2735-2750.

[4] Aristin Revilla S, Kranenburg O, Coffer PJ. Colorectal cancer-infiltrating regulatory T cells: functional heterogeneity, metabolic adaptation, and therapeutic targeting[J]. Front Immunol, 2022, 13: 903564.

[5] Koch U, Radtke F. Mechanisms of T cell development and transformation[J]. Annu Rev Cell Dev Biol, 2011, 27: 539-562.

[6] Ohue Y, Nishikawa H. Regulatory T (Treg) cells in cancer: can Treg cells be a new therapeutic target? [J]. Cancer Sci, 2019, 110(7): 2080-2089.

[7] Du W, Frankel TL, Green M, et al. IFNγ signaling integrity in colorectal cancer immunity and immunotherapy[J]. Cell Mol Immunol, 2022, 19(1): 23-32.

[8] Zhao W, Jin LJ, Chen P, et al. Colorectal cancer immunotherapy-Recent progress and future directions[J]. Cancer Lett, 2022, 545: 215816.

[9] Johdi NA, Sukor NF. Colorectal cancer immunotherapy: options and strategies[J]. Front Immunol, 2020, 11: 1624.

[10] Vidotto T, Melo CM, Castelli E, et al. Emerging role of PTEN loss in evasion of the immune response to tumours[J]. Br J Cancer, 2020, 122(12): 1732-1743.

[11] Kalbasi A, Ribas A. Tumour-intrinsic resistance to immune checkpoint blockade[J]. Nat Rev Immunol, 2020, 20(1): 25-39.

[12] Zhang QQ, Zhao Q, Li T, et al. *Lactobacillus plantarum*-derived indole-3-lactic acid ameliorates colorectal tumorigenesis via epigenetic regulation of $CD8^+$ T cell immunity[J]. Cell Metab, 2023, 35(6): 943-960.e9.

[13] Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors[J]. Proc Natl Acad Sci U S A, 2010, 107(9): 4275-4280.

[14] Dikiy S, Rudensky AY. Principles of regulatory Tcell function[J]. Immunity, 2023, 56(2): 240-255.

[15] Dhatchinamoorthy K, Colbert JD, Rock KL. Cancer immune evasion through loss of MHC class I antigen presentation[J]. Front Immunol, 2021, 12: 636568.

[16] Fangazio M, Ladewig E, Gomez K, et al. Genetic mechanisms of HLA-Ⅰ loss and immune escape in diffuse large B cell lymphoma[J]. Proc Natl Acad Sci U S A, 2021, 118(22): e2104504118.

[17] Bern MD, Parikh BA, Yang LP, et al. Inducible down-regulation of MHC class I results in natural killer cell tolerance[J]. J Exp Med, 2019, 216(1): 99-116.

[18] Anderson P, Aptsiauri N, Ruiz-Cabello F, et al. HLA class I loss in colorectal cancer: implications for immune escape and immunotherapy[J]. Cell Mol Immunol, 2021, 18(3): 556-565.

[19] Chowell D, Krishna S, Becker PD, et al. TCR contact residue hydrophobicity is a hallmark of immunogenic $CD8^+$ T cell epitopes[J]. Proc Natl Acad Sci U S A, 2015, 112(14): E1754-E1762.

[20] Lv HW, Lv GS, Chen CA, et al. NAD^+ metabolism maintains inducible PD-L1 expression to drive tumor immune evasion[J]. Cell Metab, 2021, 33(1): 110-127.e5.

[21] Gocher AM, Workman CJ, Vignali DAA. Interferon-γ: teammate or opponent in the tumour microenvironment? [J]. Nat Rev Immunol, 2022, 22(3): 158-172.

[22] Cetintas VB, Batada NN. Is there a causal link between PTEN deficient tumors and immunosuppressive tumor microenvironment? [J]. J Transl Med, 2020, 18(1): 45.

[23] Lin YX, Wang Y, Ding JX, et al. Reactivation of the tumor suppressor PTEN by mRNA nanoparticles enhances antitumor immunity in preclinical models[J]. Sci Transl Med, 2021, 13(599): eaba9772.

[24] Tian J, Chen JH, Chao SX, et al. Combined PD-1, BRAF and MEK inhibition in $BRAF^{V600E}$ colorectal cancer: a phase 2 trial[J]. Nat Med, 2023, 29(2): 458-466.

[25] 罗霞,唐语哲,胡晓东,等.CAR-T 细胞治疗结直肠癌的现状及挑战[J].生命科学,2023,35(7):916-924.
Luo X, Tang YZ, Hu XD, et al. Current status and challenges of CAR-T therapy in colorectal cancer treatment[J]. Chin Bull Life Sci, 2023, 35(7): 916-924.

[26] Flugel CL, Majzner RG, Krenciute G, et al. Overcoming on-target, off-tumour toxicity of CAR T cell therapy for solid tumours[J]. Nat Rev Clin Oncol, 2023, 20(1): 49-62.

[27] Sharma P, Goswami S, Raychaudhuri D, et al. Immune checkpoint therapy-current perspectives and future directions[J]. Cell, 2023, 186(8): 1652-1669.

[28] Viot J, Abdeljaoued S, Vienot A, et al. $CD8^+$ $CD226^{high}$ T cells in liver metastases dictate the prognosis of colorectal cancer patients treated with chemotherapy and radical surgery[J]. Cell Mol Immunol, 2023, 20(4): 365-378.

[29] Thomas B, Burns M, Pervanas H, et al. Nivolumab/relatlimab-rmbw: a novel dual combination therapy to treat adult and pediatric patients with unresectable or metastatic melanoma[J]. Am J Ther, 2023, 30(6): e526-e534.

[30] Mokhtari Z, Rezaei M, Sanei MH, et al. Tim3 and PD-1 as a therapeutic and prognostic targets in colorectal cancer: relationship with sidedness, clinicopathological parameters, and survival[J]. Front Oncol, 2023, 13: 1069696.

[31] Katagata M, Okayama H, Nakajima S, et al. TIM-3 expression and M2 polarization of macrophages in the TGFβ-activated tumor microenvironment in colorectal cancer[J]. Cancers, 2023, 15(20): 4943.

[32] Jiang SS, Xie YL, Xiao XY, et al. *Fusobacterium nucleatum*-derived succinic acid induces tumor resistance to immunotherapy in colorectal cancer[J]. Cell Host Microbe, 2023, 31(5): 781-797.e9.

[33] Bao Y, Zhai JN, Chen HR, et al. Targeting m^6A reader YTHDF1 augments antitumour immunity and boosts anti-PD-1 efficacy in colorectal cancer[J]. Gut, 2023, 72(8): 1497-1509.

[34] Sullivan KM, Jiang X, Guha P,et al. Blockade of interleukin 10 potentiates antitumour immune function in human colorectal cancer liver metastases. Gut. 2023 Feb; 72(2): 325-337.

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