ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2024 October 15; 16(10): 4037-4299

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 16 Number 10 October 15, 2024

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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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RESPONSIBLE EDITORS FOR THIS ISSUE

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NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5204/editorialboard.htm

PUBLICATION DATE
October 15, 2024

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World J Gastrointest Oncol 2024 October 15; 16(10): 4064-4079

DOI: 10.4251/wjgo.v16.i10.4064

ISSN 1948-5204 (online)

REVIEW

Research progress of tumor-associated macrophages in immune checkpoint inhibitor tolerance in colorectal cancer

Qi Fan, Zheng-Wei Fu, Ming Xu, Feng Lv, Jia-Song Shi, Qi-Qi Zeng, De-Hai Xiong

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade C

P-Reviewer: Cabezuelo AS

Received: June 5, 2024
Revised: August 3, 2024
Accepted: August 16, 2024
Published online: October 15, 2024
Processing time: 112 Days and 23.6 Hours

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Abstract

The relevant mechanism of tumor-associated macrophages (TAMs) in the treatment of colorectal cancer patients with immune checkpoint inhibitors (ICIs) is discussed, and the application prospects of TAMs in reversing the treatment tolerance of ICIs are discussed to provide a reference for related studies. As a class of drugs widely used in clinical tumor immunotherapy, ICIs can act on regulatory molecules on cells that play an inhibitory role-immune checkpoints-and kill tumors in the form of an immune response by activating a variety of immune cells in the immune system. The sensitivity of patients with different types of colorectal cancer to ICI treatment varies greatly. The phenotype and function of TAMs in the colorectal cancer microenvironment are closely related to the efficacy of ICIs. ICIs can regulate the phenotypic function of TAMs, and TAMs can also affect the tolerance of colorectal cancer to ICI therapy. TAMs play an important role in ICI resistance, and making full use of this target as a therapeutic strategy is expected to improve the immunotherapy efficacy and prognosis of patients with colorectal cancer.

Key Words: Colorectal cancer; Immune checkpoint inhibitor resistance; Tumor microenvironment; Tumor-associated macrophages; Review

Core Tip: This study reviews the role of tumor-associated macrophages (TAMs) in the treatment tolerance of immune checkpoint inhibitors in colorectal cancer. The effects of TAMs on immunotherapy through promoting immune escape, inhibiting T cell function, secreting pro-inflammatory factors and remodeling tumor microenvironment were discussed. In addition, the current therapeutic strategies against TAMs and their potential in improving the efficacy of immune checkpoint inhibitors are also introduced in this paper, aiming to provide new research directions and clinical application references for future colorectal cancer immunotherapy.

Citation: Fan Q, Fu ZW, Xu M, Lv F, Shi JS, Zeng QQ, Xiong DH. Research progress of tumor-associated macrophages in immune checkpoint inhibitor tolerance in colorectal cancer. *World J Gastrointest Oncol* 2024; 16(10): 4064-4079
URL: https://www.wjgnet.com/1948-5204/full/v16/i10/4064.htm
DOI: https://dx.doi.org/10.4251/wjgo.v16.i10.4064

INTRODUCTION

The incidence of colorectal cancer ranks second among malignant tumors in China, second only to that of lung cancer[1-3]. Current first-line treatments for patients with colorectal cancer include colectomy and radical rectotomy combined with regional lymph node removal, as appropriate[4-6]. In addition, preoperative detection can be performed, and neoadjuvant therapy based on fluorouracil is recommended for patients with complete mismatch repair (MMR) function/microsatellite stability, while combining multiple treatment strategies can be considered for patients with MMR deficit (dMMR)/highly microsatellite instability (MSI-H), which can greatly improve the overall survival rate and organ retention rate[7]. In patients with hepatic metastasis, drugs targeting vascular endothelial growth factor (VEGF) and mitogen-activated extracellular signal-regulated kinase are often added to improve tumor vascular infiltration and promote the recruitment of CD8+ T cells and antigen-presenting cells[8-10]. In colorectal cancer patients with H-cell lymphoma, combination treatment with multiple immune checkpoint inhibitors (ICIs) can enhance the antitumor effect by regulating the interaction between various immune cells and tumor cells in the microenvironment[11-14]. The development of colorectal cancer is influenced by both the type of tumor cells and the specific tumor microenvironment (TME), which together constitute a dense tissue environment with high osmotic pressure[15]. The TME is composed of an extracellular matrix and a variety of stromal cells, in which the extracellular matrix is composed mainly of collagen, fibronectin, elastin and other glycoproteins, while the stromal cells are mainly mesenchymal cells and various immune cells[16-18]. As tumor-associated macrophages (TAMs) have the highest proportion of immune cells in the TME, their phenotype and functional changes are closely related to the efficacy of ICIs. Native M0 macrophages can be induced by lipopolysaccharide, tumor necrosis factor-α, and interferon-γ (IFN-γ) to differentiate into M1 macrophages with proinflammatory and antitumor effects and are influenced by the inhibitory cytokines interleukin-4 (IL-4), IL-10, and transforming growth factor-β (TGF-β)[19-23]. These cells differentiated into M2-type macrophages with a tumor-promoting effect. Relevant studies have shown that M2 macrophages can promote the hypoxia-inducible factor-alpha/Tribble 3 axis by secreting TGF-β. Thus, the β-catenin/Wnt signaling pathway is activated, and the expression of programmed cell death protein 1 (PD-1) is enhanced, thereby promoting the invasion and metastasis of rectal cancer, which indirectly proves that TAMs play an important role in immune checkpoint therapy, but the underlying mechanism is still unclear[24-26].

This study briefly reviewed the research progress on TAMs in colorectal cancer patients with ICI resistance and clarified the effects of ICI treatment on TAM phenotype and function and the mechanism by which TAM feedback regulates ICI efficacy to provide a reference for improving immune checkpoint efficacy from the perspective of TAMs.

CLINICAL APPLICATION OF ICIS IN THE TREATMENT OF COLORECTAL CANCER

Common immune checkpoints include programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)[27-29]. PD-L1 is expressed on the surface of antigen-presenting cells and tumor cells and binds to PD-1 to inhibit CD4+ T-cell activity, ultimately promoting immune tolerance and immune escape[30-35]. CT-LA-4 is commonly expressed in T cells, B cells and thymocyte subsets and is closely related to the mechanism that inhibits its antitumor immune effect[36]. ICIs can target a variety of lymphocytes in the regulatory immune microenvironment, block immune checkpoint ligands on the surface of immune cells, and reverse the inhibitory immune microenvironment[37-40].

There are currently seven commonly used ICI drugs approved by the United States Food and Drug Administration, of which pabolizul, navulio, cimipril and dostamumab target PD-1, and attilizul, duvarumab and avitumab target PD-L1. Currently, the main ICI drugs used to treat colorectal cancer are pabolizumab and nebuliumab, and only a very small number of dMMR/MSI-H patients can benefit from them[41-44]. In addition, ipilimumab, a monoclonal antibody targeting CTLA-4, can also be combined with the above two ICIs to help prolong overall survival and progression-free survival in patients with colorectal cancer[45]. However, most patients with colorectal cancer are not sensitive to this therapy because of its low immunogenicity, low tumor mutation load, and low infiltration of tumor-infiltrating lymphocytes in the microenvironment[46-48]. In addition, even patients with dMMR/MSI-H colorectal cancer often face the dilemma of drug resistance.

Drug resistance to ICIs can be divided into primary and secondary resistance[49]. Primary resistance occurs when the patient does not respond to ICIs and the tumor progresses rapidly, and secondary resistance occurs when the patient initially responds to ICI treatment but eventually progresses to disease[50]. Primary drug resistance is mainly related to the activation and inhibition of intracellular pathways, including loss of phosphatase and tensin homolog expression and enhancement of the IL-6/signal transducer and activator of transcription 3 (STAT3) pathway, sustained activation of the mitogen-activated protein kinases pathway, loss and mutation of IFN-γ pathway-related proteins, and upregulation of PD-L1 expression on the cell surface[51-54]. Secondary drug resistance often involves antigen presentation defects, T-cell depletion, major histocompatibility complex-I class molecular mutations, and the release of various inhibitory immune factors (such as TGF-β)[55]. These mechanisms are influenced by the immunogenicity and immune microenvironment of colorectal cancer patients' own tumors[56]. According to the number of tumor-infiltrating lymphocytes, colorectal cancer can be roughly divided into hot tumors and cold tumors[57-59]. Only a small number of patients with strong immunogenicity and a sensitive response can respond to ICI treatment, while in the vast majority of patients with cold tumors, ICI treatment is ineffective and patients have a poor prognosis (Figure 1).

THE ROLE OF TAMS IN THE CLINICAL TREATMENT TOLERANCE OF COLORECTAL CANCER

At present, the polarization characteristics of TAMs play important roles in chemotherapy resistance, radiotherapy resistance and immune escape in colorectal cancer[60-62]. Relevant studies have shown that long noncoding RNA-MIR155HG induces the polarization of M2 macrophages in colorectal cancer cells by regulating annexin A2 and promotes oxaliplatin resistance[63-65]. In addition, another study revealed that activating tyrosine kinase receptors such as Tyro3 and Mertk on the surface of TAMs can regulate the Akt signaling pathway to promote PD-L1 surface reach and chemical resistance[66-68]. By expressing receptors such as VEGF receptor 2, M2 macrophages can promote the formation of new blood vessels, enhance permeability, and accelerate the excretion of various drugs[69].

In the microenvironment, TAMs can interact with fibroblasts to promote their epithelial-mesenchymal transition through the hypoxia-inducible factor-1 alpha factor, which further leads to chemotherapy resistance[70-74]. One study showed that M2 macrophages are positively correlated with colorectal cancer radiotherapy resistance[75], and another study showed that M2 macrophages secrete arginase-1 to consume arginine, thereby preventing its breakdown to produce nitric oxide to induce radiotherapy sensitization[76-78]. However, the detailed mechanism is not yet clear. In clinical treatment, most TAMs exhibit the M2 phenotype, and most M1-type TAMs have a better prognosis, while M2-type TAMs have a worse prognosis. Most of these toxins accelerate the occurrence of the above protumor response by affecting antigen presentation, releasing inhibitory cytokines and constructing an inhibitory immune microenvironment (Figure 2).

MECHANISMS RELATED TO TAMS IN ICI TREATMENT TOLERANCE

At present, the application of ICIs in the clinical treatment of colorectal cancer patients is relatively limited[79]. ICIs are only used in preoperative neoadjuvant immunotherapy and palliative therapy for dMMR/MSI-H patients, and most patients have difficulty benefiting from ICIs[80]. Clinically, most patients are immunobarren patients whose immune cells are restricted by the matrix surrounding the cancer nest and for whom it is difficult to produce an inflammatory response or for whom a large number of myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs) and M2 macrophages are present in the TME. Due to the lack of CD8+ T cells in immune rejection patients, both can be classified into the cold tumor category[81-83].

TAMs interact with a variety of cells in the TME, and TAMs can mediate M2-type macrophage differentiation through the depletion of CD8+ T cells through specific antigenic synaptic parameters; this effect is intensified under hypoxic conditions. The peroxisome proliferator-activated receptor γ-dependent increase in fatty acid oxidation[84-86]. In view of the above findings, how to target TAMs to improve the sensitivity of rectal cancer patients to ICI therapy, reverse cold tumors, and enhance the efficacy of ICI therapy in dMMR/MSI-H patients has become a new hotspot in colorectal cancer immunotherapy research (Figure 3).

ICIs induced phenotypic changes in TAMs

ICIs commonly used in patients with colorectal cancer mainly include pabolizumab, nabuliu, ipilimumab, attilizumab, and carbbertinimab, and the occurrence of drug resistance is mostly related to M2 differentiation of TAMs[87-90]. The greater the mutation load of tumors and the greater the infiltration degree of TAMs, the greater the possibility of ICI resistance[91]. TAMs were indirectly affected in related clinical trials by the combination of nabuliu and ipilimumab, which enhanced T-cell infiltration and facilitated immune cell interactions in the TME (Figure 4). ICIs can induce the secretion of cytokines and microRNAs (miRNAs) by tumor cells, and the soluble small molecules produced by ICIs can act on the Janus kinase/STAT pathway and phosphatidylinositol 3-kinase (PI3K)/Akt pathway, inhibit the Notch signaling pathway, affect the polarization of TAMs, and lead to the development of drug resistance[92-94].

Colorectal cancer can be divided into exosomes containing miR-934, miR-25-3p, miR-130b-3p, miR-425-5p, and other miRNAs[95]. By inhibiting the common target gene phosphatase and tensin homolog, activation of the PI3K/Akt pathway induces an M2-polarized macrophage phenotype, and studies have shown that this pathway can increase the occurrence of liver metastasis in patients[96-98]. After ICI treatment, tumor cells can suppress the secretion of miR-148a-3p and the activation of the Notch/Jagged1 signaling pathway, further reducing the transformation of M1-type

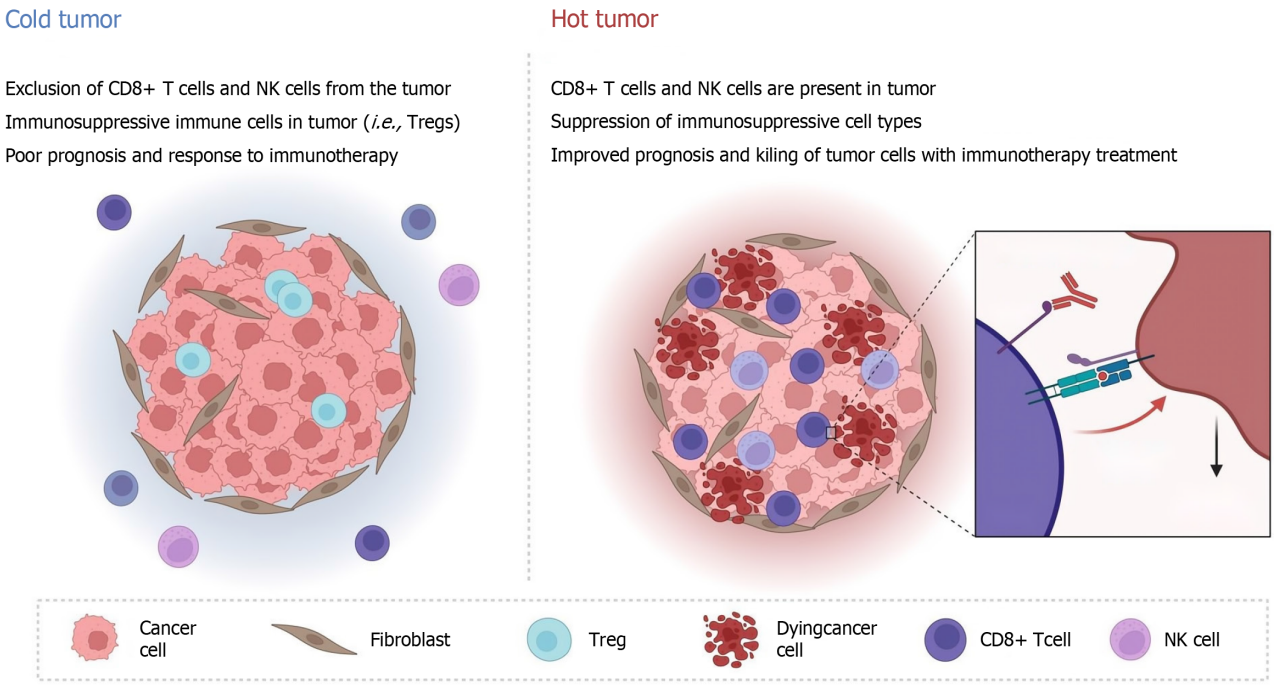

Figure 1 Immunogenicity and effects of immune microenvironment on cold and hot. NK: Natural killer; Treg: Regulatory T cell.

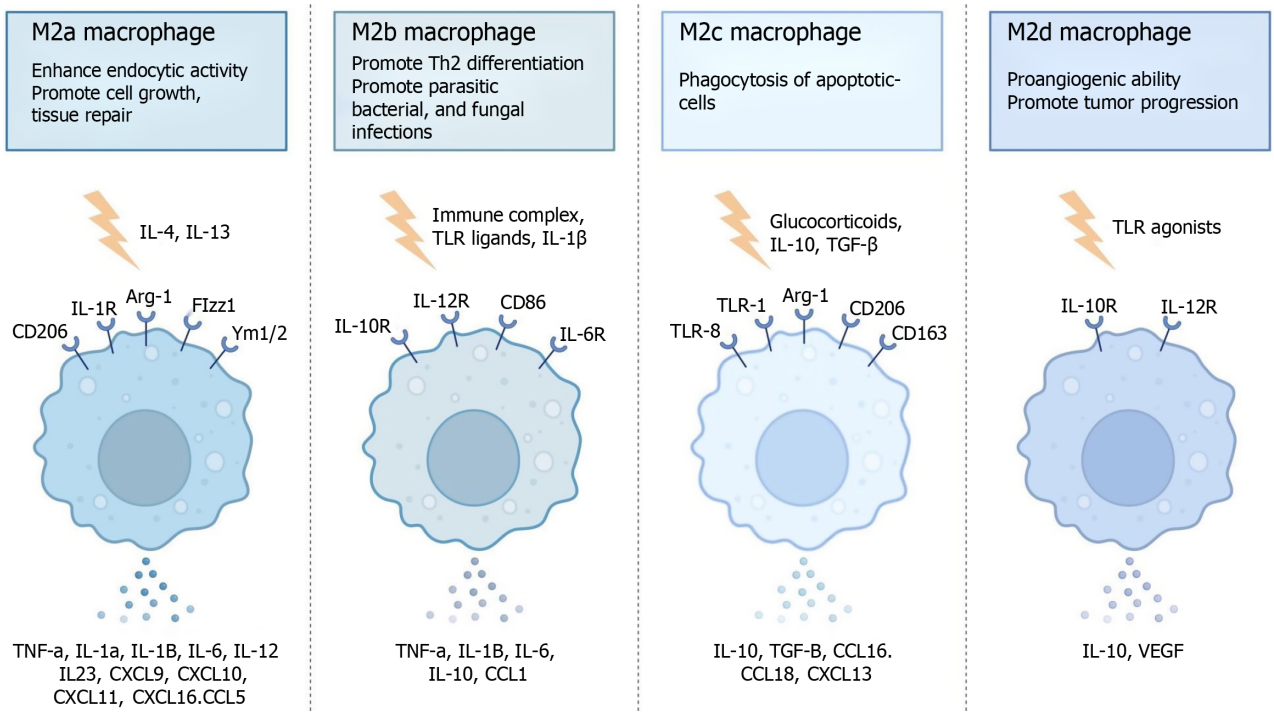

Figure 2 M2 macrophage subtypes. IL: Interleukin; TLR: Toll-like receptor; TGF: Transforming growth factor; CXCL: C-X-C motif chemokine ligand; CCL: C-C motif chemokine ligand; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor; Arg-1: Arginase-1.

macrophages and blocking the formation of an inflammatory microenvironment[99].

TAMs regulate drug tolerance to ICIs

A large number of M2 macrophages accumulate in the tumor stroma, which can affect the efficacy of ICIs and lead to ICI resistance in colorectal cancer patients[100]. TAMs can increase the formation of an immunosuppressive microenvironment in the TME by secreting IL-10 and TGF-β[101-103]. M2 macrophages supply tumor cells with a large amount of ATP through fatty acid oxidation and reshape the TME by secreting VEGF and matrix metalloproteinases, promoting angiogenesis and tumor metastasis and ultimately leading to ICI resistance. In addition, TAMs also interact with tumor cells, Tregs, cytotoxic T cells and MDSCs in the TME, resulting in secondary drug resistance. First, M2-type macrophages

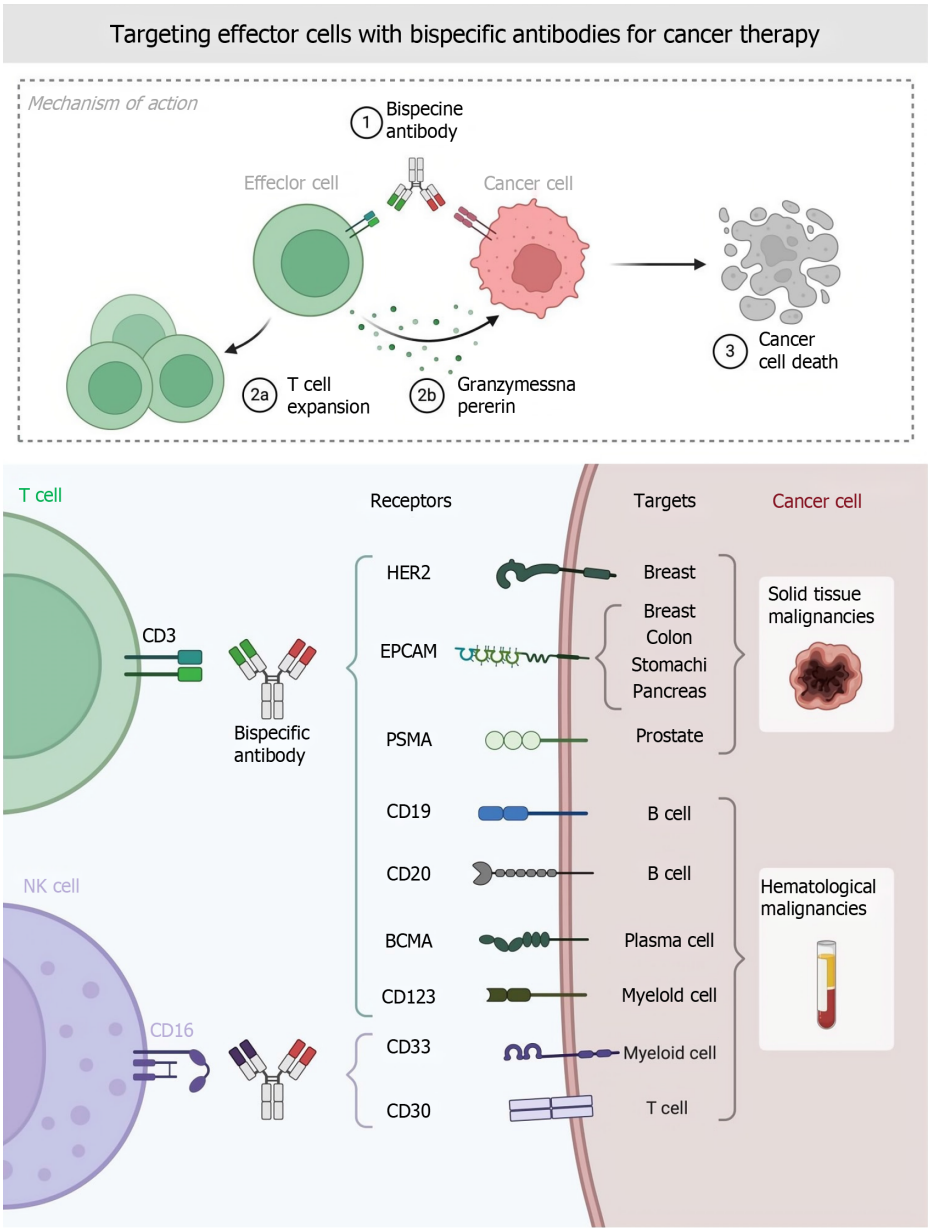

Figure 3 Targeting effector cells with bispecific antibodies for cancer therapy. NK: Natural killer; EPCAM: Epithelial cell adhesion molecule; PSMA: Prostate-specific membrane antigen; BCMA: Bulbospinal muscular atrophy.

can regulate the expression of CTLA-4 and other immune checkpoint molecules, secrete inhibitory cytokines such as TGF-β and IL-10, and secrete chemokines such as C-C motif chemokine ligand 17 (CCL17) and CCL22, which directly promote the formation of an inhibitory immune microenvironment[104-106]. Second, M2-derived prostaglandin E2, IL-10, and indoleamine 2,3-dioxygenase can induce T lymphocytes to convert to Tregs; secrete C-X-C motif chemokine ligand 12 (CXCL12), CCL5, CCL22, CCL10 and IL-8; and recruit MDSCs and Tregs into the TME[107-110]. At the same time, TAMs secrete TGF-β through the phosphate nuclear Smad2/3 protein and inhibit the mitochondrial respiratory chain, reducing the expression levels of IFN-γ and granase B in T cells, thereby inhibiting T cells from killing tumors and causing drug resistance (Figure 5).

Targeted regulation of TAMs can improve the efficacy of ICIs in colorectal cancer patients

Targeting TAMs has become a hot research direction for reversing ICI resistance, mainly by restricting macrophage recruitment, inhibiting M2-type polarization, targeting macrophage surface immune checkpoints and chimeric antigen receptor macrophage (CAR-M) therapy[111-113].

Limiting the number of TAMs in the TME

The aggregation of the colony-stimulating factor-1 (CSF-1)/CSF 1 receptor (CSF1R) axis and CCL2/CC chemokine receptor 2-axis are important macrophage chemokines. This has been shown to increase tumor sensitivity to PD-L1 ICIs, and the use of CSF1R small molecule inhibitors can induce repolarization of TAMs from the M2 to M1 phenotype and further reduce the risk of tumor invasion and invasion[114]. Studies have shown that targeting CCL5 and CC chemokine

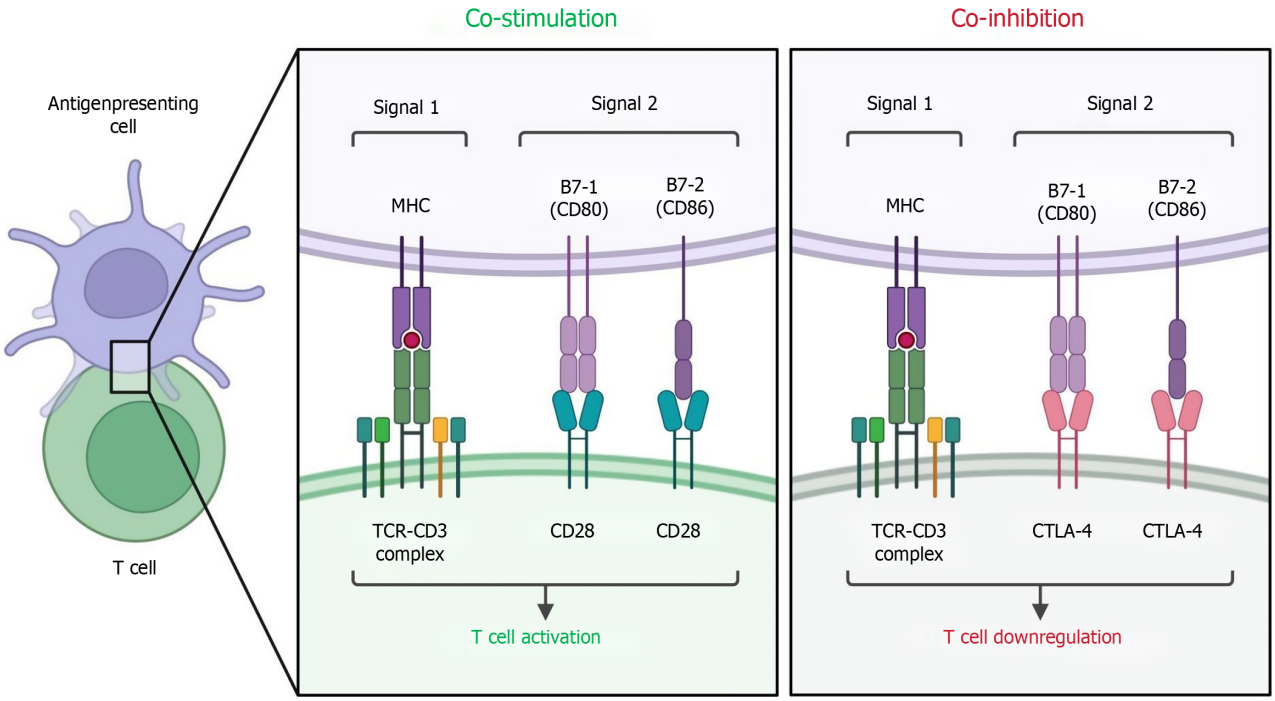

Figure 4 T cell co-stimulation and co-inhibition. TCR: T cell receptor; MHC: Major histocompatibility complex; CTLA: Cytotoxic T-lymphocyte-associated protein.

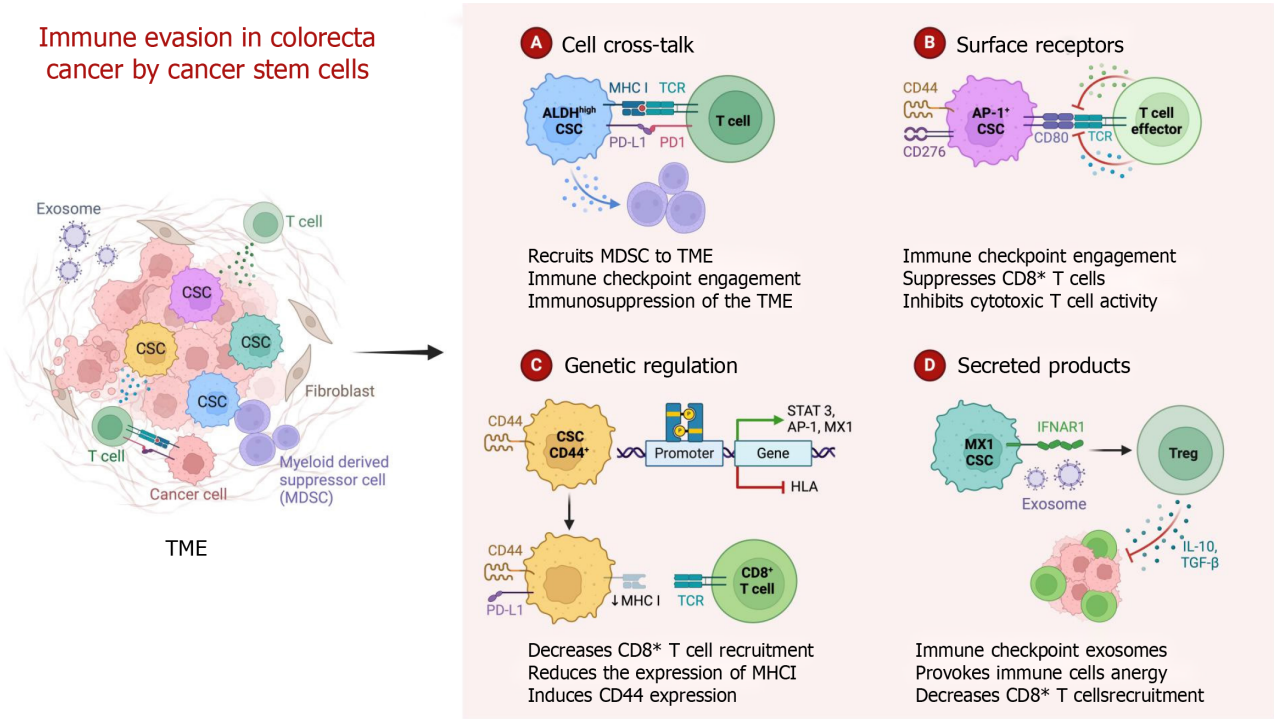

Figure 5 Mechanisms of immune evasion in colorectal cancer by cancer stem cells. CSC: Cancer stem cell; TME: Tumor microenvironment; TCR: T cell receptor; MHC: Major histocompatibility complex; MDSC: Myeloid-derived suppressor cell; PD-L1: Programmed cell death ligand 1; PD-1: Programmed cell death protein 1; STAT 3: Signal transducer and activator of transcription 3; AP-1: Activating protein-1; HLA: Human leukocyte antigen; IFNAR1: Interferon alpha/beta receptor 1; Treg: Regulatory T cell; IL: Interleukin; TGF: Transforming growth factor.

receptor 5 has similar effects[115-118].

M2-type polarization of TAMs was inhibited

Itaconate, fritinib, fuquinitinib, and regafenib have been shown to inhibit M2-type macrophage differentiation, and cetuximab can also restore the antitumor TME by regulating and reprogramming the polarization of TAMs from the M2-

like phenotype to the M1-like phenotype, including inhibiting IL-6 expression in TAMs[119-122]. The epidermal growth factor receptor axis is involved in the M2 polarization of TAMs through the PI3K/Akt/mechanistic target of rapamycin pathway, whereas inhibition of PI3K or epidermal growth factor receptor with monocrone inhibitors can reverse this process and polarize TAMs toward the antitumor M1 phenotype[123]. Murine double minute 2, a key negative regulator of p53, is highly expressed in tumors, and its antagonist APG115 can repolarize TAMs, causing them to exhibit an antitumor M1 phenotype and activate CD4+ T cells[124-126]. Moreover, inhibition of murine double minute 2 can upregulate the expression of PD-L1 on the surface of tumor cells and may lead to high immunogenicity (Figure 6).

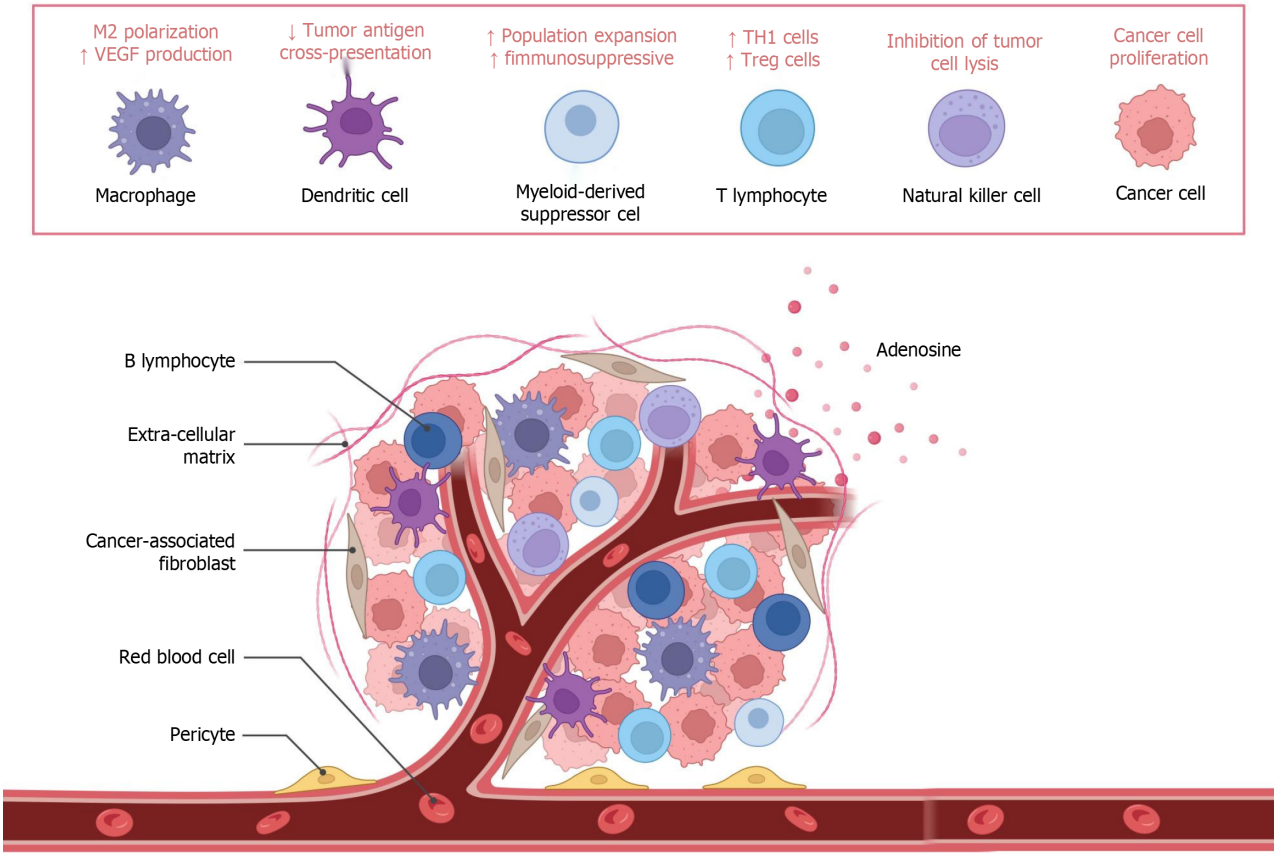

Figure 6 Effects of M2-type polarization from the tumor microenvironment. VEGF: Vascular endothelial growth factor; Th1: T helper 1; Treg: Regulatory T cell.

Targeting macrophage surface immune checkpoints

The presence of macrophages on the surface of the suppressive immune detection site, signal regulatory protein alpha axis/CD47, can induce tumor escape and reverse the transformation of TAMs to the M1 phenotype, and treatment targeting these macrophages has been shown to be effective in preclinical models of solid tumors[127-130].

CAR-M-cell therapy

CAR-Ms, which encode a specific gene for macrophages that enhances their tumor recognition ability, have entered clinical trials, and modified TAMs can be injected into patients to stimulate the activity of T cells in the TME and eventually reverse the immunosuppressive state[131-133]. It was found that macrophages were able to drive phagocytosis and targeted killing of tumor cells in a splenic tyrosine kinase-dependent manner without the addition of any soluble opsonics[134-136]. Adoptive cell therapy after large-scale expansion of CAR-Ms with a specific design has very good therapeutic potential, but in-depth clinical research on this topic is lacking[137-140].

In addition to the abovementioned therapeutic approaches, targeting macrophage-secreted cytokines is also a new therapeutic area, and VEGF and VEGF receptor inhibitors are widely used in the standard treatment of colorectal cancer, especially in cancer patients with RAS/RAF mutations[141-147]. An increase in CD4+Foxp3+ Tregs, M2-like macrophages and MDSCs and a decrease in CD8+ T cells are well-known immune features in tumors with high VEGFA expression[148-152]. As mentioned earlier, with respect to this cytokine-dependent immunosuppressive pathway, anti-VEGF therapy can enhance immunotherapy efficacy by reversing VEGF-mediated immunosuppression and increasing T-cell infiltration in tumors[153-155]. Anti-VEGF-r therapy may help control the immunosuppressive function of M2 TAMs in colorectal cancer[156-160].

CONCLUSION

In recent years, ICIs have become a hot topic in cancer treatment, but many cancer patients cannot benefit from ICI treatment[161-164]. The therapeutic effect of ICIs is closely related to the tumor immune microenvironment. As the main immune cells in the TME, TAMs play a central role in regulating the activation or inhibition of the immune microenvironment[165]. Therefore, summarizing the research progress on TAM and ICI treatment tolerance is helpful for providing a theoretical basis for expanding their application scope[166-170]. Promoting the transformation of TAMs into antitumor M1 macrophages, activating immunogenicity and reversing the inhibitory immune microenvironment are currently the focus of relevant research[171-173]. In addition, how to further reduce the recruitment of TAMs to the primary tumor site, discover more TAM surface molecules that play an important role in immune escape, and more effectively modify and mass-produce CAR-Ms are still problems to be overcome[174-180]. Perhaps other immune checkpoints, such as T cell immunoglobulin and mucin-domain containing 3 and lymphocyte activation gene-3, also play important roles in regulating the polarization and phagocytosis of macrophages, and combined treatment with multiple ICIs can help solve the current dilemma[181-186]. Exploring additional pathways that promote M1-type polarization, such as the toll-like receptor 4/nuclear transcription factor-kappa B pathway and IFN-γ pathway, and studying the regulation and association between these pathways to discover key proteins may also be beneficial for further improving the immunotherapy of macrophage-related colorectal cancer. It is necessary to further explore the mechanism by which TAMs promote ICI tolerance.

FOOTNOTES

Author contributions: Fan Q wrote the manuscript; Fu ZW, Xu M, Lv F, Shi JS, and Zeng QQ collected the data; Xiong DH guided the study. All authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country of origin: China

ORCID number: De-Hai Xiong 0009-0003-5455-7533.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Zhang L

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