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**Therapeutic challenge for immunotherapy targeting cold colorectal cancer: A narrative review**

Ma SX *et al.* Immunotherapy for cold colorectal cancer

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**Abstract**

Cold colorectal tumors are not likely to trigger a robust immune response and tend to suppress the immune response. There may be three reasons. First, the complex tumor microenvironment of cold colorectal cancer (CRC) leads to tolerance and clearance of immunotherapy. Second, the modification and concealment of tumor-specific targets in cold CRC cause immune escape and immune response interruption. Finally, the difference in number and function of immune cell subsets in patients with cold CRC makes them respond poorly to immunotherapy. Therefore, we can only overcome the challenges in immunotherapy of cold CRC through in-depth research and understanding the changes and mechanisms in the above three aspects of cold CRC.

**Key Words:** Cold colorectal cancer; Immunotherapy; Tumor microenvironment; Immune targets; Immune cells

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**Core Tip:** Advanced colorectal tumors are poorly treated, and immunotherapy has improved these patients’ outcomes. However, cold colorectal tumors are less likely to trigger a robust immune response and tend to suppress it. To address this phenomenon, we discuss the role of the tumor microenvironment, immune targets, and immune cells in the treatment of cold colorectal tumors.

**INTRODUCTION**

Colorectal cancer (CRC) has the third highest incidence and fourth mortality (after lung cancer, hepatic carcinoma, and stomach cancer) worldwide, which also serves as a biological and genetic paradigm for dissecting the evolutionary paths of solid tumors[1]. The risk factors of CRC are advanced age, dietary habits, obesity, lack of physical activity, constipation, chronic enteritis, intestinal polyps, alcohol consumption, and smoking[2]. With the robust advancement of fundamental research and medical technology, the treatment options for CRC have gradually formed a personalized and comprehensive treatment schedule led by surgery (*e.g.*, manual surgery, robotic surgery)[3]. Current treatment options include local endoscopic resection, radical surgical resection, local radiotherapy, systemic chemotherapy, palliative surgery, radiofrequency ablation of metastases, targeted therapy, and immunotherapy[4]. Of note, the survival benefit of patients with various tumors has increased significantly due to the rapid development of immunotherapy and the combined utilization with surgery, chemotherapy, radiotherapy, and targeted therapy. Generally, cancer immunotherapy can be divided into monoclonal antibodies, cytokines, immune checkpoint inhibitors (ICIs), tumor vaccines, and immune cells (*e.g.*, natural killer cells, tumor-infiltrating cells, T lymphocytes)[5]. Despite the increase in overall survival of patients with advanced CRC, new challenges have continuously emerged in treating "cold" CRC due to the current strategies in triggering a robust immune response and suppressing cancer[6].

To manage this phenomenon, we discuss the role of the tumor microenvironment (TME), immune targets, and immune cells in treating colorectal tumors.

**LITERATURE SEARCH AND REVIEW**

For the purpose, we primarily searched the literature on CRC immunotherapy published in the last 5 years through PubMed and Google Scholar databases. After importing them into the literature management software EndNote and de-duplicating them, we double-checked their titles, abstracts, and texts one-by-one to screen out the literature related to cold CRC treatment. The article was written according to a pre-planned framework, and the references were added by selecting the National Library of Medicine mode.

**IMMUNOLOGICAL SIGNATURE-BASED CRC CLASSIFICATION**

Accurate monomolecular typing is essential to screen CRC patients who may benefit from immunotherapy and whose TME needs reprogramming for beneficial immune-mediated responses[5]. Based on the degree of immune infiltration, tumors can be classified as "hot tumors" with high infiltration, "variable tumors" with rejection and immunosuppression, and "cold tumors" without infiltration[7]. Overall, the subsets of the aforementioned cancers have variations in pathological features, genetic mutations, immune cell composition, immune phenotypes, cytokines, clinical outcomes, and responses to immunotherapy[5]. CRC patients with a resistant "cold" phenotype are extremely challenging to treat with immunotherapy due to the low tumor mutation rate and lack of immune cell infiltration[5]. Approximately 80%-85% of CRC patients are considered to have "cold" tumors with microsatellite stability (MSS) or low microsatellite instability (MSI-L) (referred to as MSS/MSI-L CRC), which lack response to ICIs[8-10]. Immunosubtype classification can identify altered immune microenvironments in CRC patients. In addition, immune subtyping can guide personalized CRC immunotherapy and tumor prognosis[11-15].

**RELATED STUDIES BASED ON THE TME**

CRC is a highly heterogeneous disease, and mutant gene polymorphisms create a diversity of tumor subtypes and their corresponding TME. Sobral *et al*[16] demonstrated, in a study of genetic and microenvironmental intra-tumor heterogeneity affecting the evolution and metastatic development of CRC, that the diversity of CRC is caused by asynchronous forms of molecular alterations in which mutations and chromosomal instability collectively contribute to the genetic and microenvironmental intra-tumor heterogeneity. Studies have shown that the greater the genetic mutation and TME differences, the lower the ability of tumors to metastasize. By contrast, advanced tumor gene mutations exploit tumor proliferation and metastasis. Wang *et al*[17] employed methionine enkephalin to inhibit colorectal carcinogenesis by reshaping the immune status of the TME. It has been shown that methionine enkephalin promotes antitumor immune responses, remodels the immune state of the tumor immune microenvironment in CRC, inhibits tumor development, and is a potential therapeutic agent for CRC, especially useful for improving the efficacy of immunotherapy. Chen *et al*[18] further proposed that metabolic changes in the TME were closely related to the development of CRC. In details, tumor cells secrete carriers beneficially utilized by surrounding cells in the TME to induce metabolic changes and cancer transformation. At the same time, tumor cells secrete pages that provide energy for their proliferation, metastasis, and drug resistance.

The tumor immune microenvironment is highly variable and extremely complex, and many immunosuppressive pathways have been identified in microsatellite-stabilized CRC[19]. Regorafenib, a tyrosine kinase inhibitor, is one of two drugs approved for treating MSS CRC[20]. The REGONIVO study showed a 36% response rate for regorafenib in metastatic MSS CRC[23]. Cabozantinib is another drug being investigated for the treatment of MSS CRC. Toll-like receptor (TLR) modulators are a new class of immunomodulatory drugs[24]. REVEAL is a phase 2 trial investigating TLR7/8 agonists in combination with nivolumab against tumors. Keynote-559 is a phase 1/2 trial investigating C-X-C motif chemokine ligand 12 (CXCL12) antagonists in combination with pembrolizumab for mCRC and metastatic pancreatic cancer. The chemokine CXCL12 promotes tumor proliferation, metastasis and angiogenesis by inducing signals, which can recruit B cells, plasma cells, and regulatory T cells to induce an immunosuppressive environment[25]. Investigators are devoted to developing multidisciplinary approaches to increase immune-mediated responses, improve the TME, and convert "cold" tumors into "hot" tumors to promote immunotherapy[15].

**RELATED STUDIES BASED ON IMMUNE TARGETS**

ICIs typically respond to CRCs with defective mismatch repair (dMMR) or high MSI (MSI-H). Approximately 85% of CRCs do not respond to immunotherapy or eventually become resistant due to MMR resistance or MSS[10]. MMR/MSS CRCs typically have low tumor mutational load, low chemotherapy response rates, low tumor-infiltrating lymphocytes, and poor prognosis compared to dMMR/MSI CRCs. Ros *et al*[26] verified that inhibition of transforming growth factor beta (TGF-β) could play a vital role in the development and metastasis of CRC by enhancing T-cell action. He *et al*[27] used *in situ*-forming albumin corpuscles to target liposomes and reshape the "cold" tumor immune microenvironment through epigenetic-based therapy. It was found that *in situ*-forming albumin corpuscles further enhanced tumor-targeted delivery, and that targeted liposome treatment effectively inhibited the effects between tumor metabolism and immune evasion by inhibiting glycolysis and immune normalization. Janssen *et al*[28] explained the available evidence for the potential impact of RAS mutations on the microenvironment of CRC in a study of mutated RAS and TME as dual therapeutic targets in advanced CRC[29]. Takahashi *et al*[30] showed that the combination of stromal programmed death ligand 1 (PD-L1)+ immune cells and nuclear β-catenin+ tumor budding might contribute to tumor progression in CRC and resistance to neoadjuvant chemotherapy in locally advanced rectal cancer. Dmitrieva-Posocco *et al*[31] found that the ketogenic diet exhibited strong tumor suppressive effects. The ketone body β-hydroxybutyric acid reduced colonic crypt cells proliferation and effectively inhibited intestinal tumor growth. It is suggested that oral or systemic interventions using a single metabolite could complement current CRC prevention and treatment strategies. High PD-L1 expression in tumors is a sign of poor prognosis, which also shows good responsiveness to ICIs and immunomodulatory drugs such as C-X-C motif chemokine receptor 4, poly (ADP-ribose) polymerase or TGF-β inhibitors in combination[6]. Li *et al*[32] investigated the relationship between genetic changes in CRC and intercellular transformation in cancer cell biology and TME. Key advances in the development of effective therapeutic approaches for this cancer were analyzed from immunological and single-cell perspectives[33]. Long-noncoding RNAs (lncRNAs) are important regulators of microRNA expression in CRC and might be promising biomarkers and potential therapeutic targets in CRC research. For example, Lv *et al*[34] provided insights into the pathogenesis, diagnosis, and development of therapeutic strategies for CRC by studying lncRNAs.

**RELATED STUDIES BASED ON IMMUNE CELLS**

The current therapeutic strategies have limited efficacy in CRC[35-38]. Approximately one-quarter of CRC patients are diagnosed with a combination of distant metastases[39-41], and of these, another one-quarter recurs or metastasizes within 5 years. The 5-year survival rate for CRC patients with combined metastases is approximately 15%[42-44]. Therefore, there is an urgent need for new approaches to treat CRC using immunotherapy[28,45]. The current cancer classification is based on the American Joint Committee on Cancer/Union for International Cancer Control - Tumor Node Metastasis (TNM) system, and the prediction of the effect of immunotherapy cannot be assessed[35]. Relevant evidence suggests that the prognosis of CRC patients correlates with the type, density, and function of immune cells within the tumor[46]. Galon *et al*[35] developed an immunohistochemical and digital pathology-based assay named Immunoscore, which quantified two tumor regions (core and invasive margin of the tumor) in two T-cell subsets [cluster of differentiation 3 (CD3) and (CD8)]. Immunoscore is an immune function-based scoring system that is more valuable than the traditional TNM score in determining the predictive value of patients with CRC[47-50]. Relative studies have also demonstrated the predictive value of Immunoscore for the prognosis of patients with colon cancer[51-53], which is conducive to classify tumors and guide clinical decisions[54-58]. Tumor lysis virus is a novel antitumor agent that both lyses tumor cells and modulates the TME, which can convert "cold" tumors into "hot" tumors and thus allows ICIs to work. For example, Ren *et al*[36] recently investigated the status of tumor lysing viruses and ICIs for treating CRC. The feasibility of combining tumor lysis virus with ICIs for treating CRC will be discussed in terms of the mechanism of action of tumor lysis virus for tumor treatment.

**FUTURE DIRECTIONS**

For cold CRC, immunotherapy strategies focus on converting "cold" tumors to "hot" tumors through various approaches[6,59-62]. Various immunotherapies or chemotherapy can be used to modulate the patient’s immune status[63-66]. Regulation of the number and function of *Escherichia coli* in the patient's intestine can improve the role of the patient's immune microenvironment[67-69]. Therapies that enhance the operation and number of immune cells may also improve treatment outcomes[70-72]. Further functional and mechanistic studies of mutated genes could identify new targets for cold CRC therapy[73-75].

**CONCLUSION**

In summary, the fundamental reasons for the challenge of immunotherapy for cold CRC are the low tumor mutational load and lack of immune cell infiltration. To conquer this phenomenon, we should conduct comprehensive research on the TME, immune targets and immune cells to warm up CRC (Figure 1). Meanwhile, we should also combine the aforementioned cancer immunotherapy with traditional tumor treatment remedies such as surgery, radiotherapy, and chemotherapy. Only personalized, comprehensive treatment plans for CRC, and a good prognosis for patients are the ultimate goals we pursue.

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**Figure Legends**

**图示

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**Figure 1 Pattern of immunotherapy strategies for cold colorectal cancer.**



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