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WORD COUNT 1947
TIME SUBMITTED 26-DEC-2022 02:20PM
PAPER ID 94372983

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

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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 leads to tolerance and clearance of immunotherapy. Secondly, the modification and concealment of tumor-specific targets in cold colorectal cancer caused immune escape and immune response interruption. Finally, the difference in the number and function of immune cell subsets in patients with cold colorectal cancer makes them respond poorly to immunotherapy. Therefore, we can only overcome the challenges in immunotherapy of cold colorectal cancer through in-depth research and understanding of the changes and mechanisms in the above three aspects of cold colorectal cancer.

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

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 has the third and second highest incidence and mortality rates worldwide, respectively [1]. The risk factors are advanced age, dietary habits, obesity, lack of physical activity, constipation, chronic enteritis, intestinal polyps, alcohol consumption, and smoking [2]. With the advancement of medical technology, the treatment of colorectal cancer has gradually formed a personalized and comprehensive treatment plan led by surgery [3]. Current treatment methods include local endoscopic resection, radical surgical resection, local radiotherapy, systemic chemotherapy, palliative surgery, radiofrequency ablation of metastases, targeted therapy, and immunotherapy [4]. Due to the rapid development of immunotherapy, the survival benefit of patients with various tumors has increased significantly, and it is juxtaposed with surgery, chemotherapy, radiotherapy, and targeted therapy. It mainly includes treatment with monoclonal antibodies, cytokines, immune checkpoint inhibitors, tumor vaccines, and immune cells [5]. This array of measures has led to an increase in the overall survival of patients with advanced colorectal cancer. Still new challenges have emerged in treating "cold" colorectal cancer. Because it is less likely to trigger a robust immune response and tends to suppress it [6]. To address this phenomenon, we discuss the role of the tumor microenvironment, immune targets and immune cells in treating colorectal tumors.

LITERATURE SEARCH AND REVIEW

This review is mainly of narrative type. We primarily searched the literature on colorectal cancer immunotherapy published in the last five years through PubMed and Google Scholar databases. After importing them into the literature management software NedNote and de-duplicating them, we read their titles, abstracts, and texts one by one to screen out the literature related to cold colorectal cancer treatment. The article was written according to the pre-planned framework, and the references were added by selecting the NLM mode.

IMMUNOLOGICAL SIGNATURE-BASED COLORECTAL CANCER CLASSIFICATION

Accurate monomolecular typing is essential to screen colorectal cancer patients who may benefit from immunotherapy and whose tumor microenvironment (TME) needs reprogrammed 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]. They are associated with different pathological features, genetic mutations, immune cell composition, immune phenotype, cytokines, clinical outcome and response to immunotherapy [5]. Colorectal cancer 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 colorectal cancer patients are considered to have "cold" tumors with microsatellite stability (MSS) or low microsatellite instability (MSI-L) (referred to as MSS/MSI-L colorectal cancer), which lack response to immune checkpoint inhibitors (ICIs) [8-10]. Immunosubtype classification can identify altered immune microenvironments in colorectal cancer patients. In addition, immune subtyping can guide for personalized colorectal cancer immunotherapy and tumor prognosis [11-15].

RELATED STUDIES BASED ON TUMOR MICROENVIRONMENT

Colorectal cancer is a highly heterogeneous disease, and mutant gene polymorphisms create a diversity of tumor subtypes and their corresponding tumor microenvironments. Daniel et al. demonstrated in a study of genetic and microenvironmental intra-tumor heterogeneity affecting the evolution and metastatic development of colorectal cancer that the diversity of colorectal cancer is caused by asynchronous forms of molecular alterations, in which mutations and chromosomal instability together contribute to the s genetic and microenvironmental intra-tumor heterogeneity. It was found that the greater the genetic mutation and tumor microenvironment differences, the lower the ability of tumors to metastasize. In contrast, advanced tumor gene mutations exploit tumor proliferation and metastasis [16]. Wang et al. used methionine enkephalin to inhibit colorectal carcinogenesis by reshaping the immune status of the tumor microenvironment. It was shown that methionine enkephalin promotes antitumor immune responses, it remodels the immune state of the tumor immune microenvironment in colorectal cancer, inhibits tumor development, and is a potential therapeutic agent for colorectal cancer, especially useful for improving the efficacy of immunotherapy [17]. Chen et al. proposed that metabolic changes in the tumor microenvironment are closely related to the development of colorectal cancer. Tumor cells secrete carriers beneficially utilized by surrounding cells in the tumor microenvironment 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 [18].

The tumor immune microenvironment is highly variable and extremely complex, and many immunosuppressive pathways have been identified in microsatellite-stabilized colorectal cancer [19]. Regorafenib, a tyrosine kinase inhibitor (TKI), is one of two drugs approved for treatig MSS colorectal cancer [20]. The REGONIVO study showed a 36% response rate for regorafenib in metastatic MSS colorectal cancer [23]. Cabozantinib is also one of the drugs being investigated for the treatment of MSS colorectal cancer. Toll-like receptor (TLR) modulators are a new class of immunomodulatory drugs [24]. REVEAL is a phase II trial investigating TLR7/8

agonists in combination with nivolumab against tumors.Keynote-559 is a phase 1/2 trial investigating CXCL12 antagonists in combination with pembrolizumab for mCRC and metastatic pancreatic cancer. The chemokine CXCL12 promotes tumor proliferation, metastasis and angiogenesis by inducing signals. It also recruits B cells, plasma cells and regulatory T cells to induce an immunosuppressive environment [25]. Scientists are using various approaches to increase immune-mediated responses, improve the tumor microenvironment, and convert "cold" tumors into "hot" tumors to promote immunotherapy [15].

RELATED STUDIES BASED ON IMMUNE TARGET

Immune checkpoint inhibitors typically respond to colorectal cancers with defective mismatch repair (dMMR) or high microsatellite instability (MSI-H). Approximately 85% of colorectal cancers do not respond to immunotherapy or eventually become resistant due to MMR resistance or microsatellite stability [26]. MMR/MSS colorectal cancers typically have low tumor mutational load, low chemotherapy response rates, low tumor-infiltrating lymphocytes, and poor prognosis compared to dMMR/MSI colorectal cancers. Tauriello et al. showed that inhibition of TGF- β can play a vital role in the development and metastasis of colorectal cancer by enhancing T-cell action [27]. He et al. 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[28]. Janssen et al. explained the available evidence for the potential impact of RAS mutations on the microenvironment of colorectal cancer in a study of mutated RAS and tumor microenvironment as dual therapeutic targets in advanced colorectal cancer [29] [30]. Takahashi et al. showed that the combination of stromal PD-L1+ immune cells and nuclear β -catenin+ tumor budding might contribute to tumor progression in colorectal cancer and resistance to

neoadjuvant chemotherapy in locally advanced rectal cancer [31]. Dmitrieva et al. 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 colorectal cancer prevention and treatment strategies [32]. High PD-L1 expression in tumors is a sign of poor prognosis. Yet, it shows good responsiveness to immune checkpoint inhibitors and immunomodulatory drugs such as CXCR4, PARP or TGF- β inhibitors in combination [6]. Li et al. investigated the relationship between genetic changes in colorectal cancer and intercellular transformation in cancer cell biology and tumor microenvironment. Key advances in the development of effective therapeutic approaches for this cancer were analyzed from immunological and single-cell perspectives [33] [34]. It was shown that lncRNAs are important regulators of microRNA expression in colorectal cancer and may later be promising biomarkers and potential therapeutic targets in colorectal cancer research. Lv et al. provided insights into the pathogenesis, diagnosis and development of therapeutic strategies for colorectal cancer by studying lncRNAs [35].

RELATED STUDIES BASED ON IMMUNE CELLS

The current treatment system has limited efficacy in colorectal cancer [36-39]. Approximately one-quarter of colorectal cancer patients are diagnosed with a combination of distant metastases [40-44], and of these, another quarter recurs or metastasize within five years. The 5-year survival rate for colorectal cancer patients with combined metastases is approximately 15% [45-47]. Therefore, there is an urgent need for new approaches to treating colorectal cancer using immunotherapy [48, 49]. The current cancer classification is based on the AJCC/UICC-TNM system, and the prediction of the effect of immunotherapy cannot be assessed [36]. Relevant evidence suggests that the prognosis of colorectal cancer patients correlates with the type, density, and function of immune cells within the tumor [50]. Galon et al.

developed an immunohistochemical and digital pathology-based assay called Immunoscore, which quantifies two tumor regions (core and invasive margin of the tumor) in two T-cell subsets (CD3 and CD8) [36]. 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 colorectal cancer [51-56]. Other studies have also demonstrated the predictive value of Immunoscore for the prognosis of patients with colon cancer [57-59]. It can classify tumors and guide clinical decisions [60-64]. Tumor lysis virus is a novel antitumor agent that both lyse tumor cells and modulates the tumor microenvironment, which can convert "cold" tumors into "hot" tumors and allow immune checkpoint inhibitors to work. Ren et al. investigated the status of tumor lysing viruses and ICIs for treating colorectal cancer. The feasibility of combining tumor lysis virus with ICIs for treating colorectal cancer will be discussed in terms of the mechanism of action of tumor lysis virus for tumor treatment [37].

FUTURE DIRECTIONS

For cold colorectal cancer, immunotherapy strategies focus on converting "cold" tumors to "hot" tumors through various approaches [6, 65-73]. Various immunotherapies or chemotherapy can be used to modulate the patient’s immune status [73-78]. Regulation of the number and function of E. coli in the patient's intestine can improve the role of the patient's immune microenvironment [79-81]. Therapies that enhance the operation and number of immune cells may also improve treatment outcomes [83-84]. Further functional and mechanistic studies of mutated genes could identify new targets for cold colorectal cancer therapy[85-87].

CONCLUSION

In summary, the fundamental reason for the challenge of immunotherapy for cold colorectal cancer is the low tumor mutational load and lack of immune cell infiltration. To address this phenomenon, we should conduct comprehensive research

on the tumor microenvironment, immune targets and immune cells to warm up the tumor (Figure 1). At the same time, we should also combine traditional tumor treatment methods such as surgery, radiotherapy and chemotherapy. Only personalized, comprehensive treatment plans for colorectal cancer and a good prognosis for patients is the ultimate goal we pursue.

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