**Name of Journal:** *World Journal of Clinical Oncology*

**Manuscript NO:** 80224

**Manuscript Type:** MINIREVIEWS

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

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

Shi-Xun Ma, Li Li, Hui Cai, Tian-Kang Guo, Lei-Sheng Zhang

**Shi-Xun Ma, Hui Cai, Tian-Kang Guo, Lei-Sheng Zhang,** Department of General Surgery, Gansu Provincial Hospital, Lanzhou 73000, Gansu Province, China

**Li Li,** Scientific Research Division, Gansu Provincial Hospital, Lanzhou 730000, Gansu Province, China

**Lei-Sheng Zhang,** Key Laboratory of Radiation Technology and Biophysics, Hefei Institute of Physical Science, Chinese Academy of Sciences, Hefei 230031, Anhui Province, China

**Author contributions:** Ma SX, and Li L wrote the paper; Zhang LS, Cai H, and Guo TK performed the data collection; All authors have read and approved the final manuscript.

## Supported by Key Laboratory of Gastrointestinal Tumor Diagnosis and Treatment of National Health and Health Commission, No. 2019PT320005; National Natural Science Foundation of China, No. 82260031; Key Laboratory of Molecular Diagnosis and Precision Therapy of Surgical Tumors in Gansu Province, No. 18JR2RA033; Gansu Provincial Key Talent Project of Gansu Provincial Party Committee Organization Department, No. 2020RCXM076; Basic Research Innovation Group of Gansu Province, No. 22JR5RA709; Natural Science Foundation of Gansu Province, No. 21JR11RA186 and No. 20JR10RA415; Gansu Provincial Hospital Intra-Hospital Research Fund Project, No. 21GSSYB-8 and No. 20GSSY5-2; The 2021 Central-Guided Local Science and Technology Development Fund, No. ZYYDDFFZZJ-1; Jiangxi Provincial Natural Science Foundation, No. 20224BAB206077 and No. 20212BAB216073.

**Corresponding author: Lei-Sheng Zhang, PhD, Professor,** Department of General Surgery, Gansu Provincial Hospital, No. 204 West Donggang RD, Lanzhou 730000, Gansu Province, China. leisheng\_zhang@163.com

**Received:** September 20, 2022

**Revised:** December 13, 2022

**Accepted:** February 7, 2023

**Published online:** February 24, 2023

**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

**©The** **Author(s) 2023.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation**: Ma SX, Li L, Cai H, Guo TK, Zhang LS. Therapeutic challenge for immunotherapy targeting cold colorectal cancer: A narrative review. *World J Clin Oncol* 2023; 14(2): 81-88

**URL**: https://www.wjgnet.com/2218-4333/full/v14/i2/81.htm

**DOI**: https://dx.doi.org/10.5306/wjco.v14.i2.81

**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.

**REFERENCES**

1 **Baidoun F**, Elshiwy K, Elkeraie Y, Merjaneh Z, Khoudari G, Sarmini MT, Gad M, Al-Husseini M, Saad A. Colorectal Cancer Epidemiology: Recent Trends and Impact on Outcomes. *Curr Drug Targets* 2021; **22**: 998-1009 [PMID: 33208072 DOI: 10.2174/1389450121999201117115717]

2 **Dekker E**, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet* 2019; **394**: 1467-1480 [PMID: 31631858 DOI: 10.1016/S0140-6736(19)32319-0]

3 **Fleming-de-Moraes CD**, Rocha MR, Tessmann JW, de Araujo WM, Morgado-Diaz JA. Crosstalk between PI3K/Akt and Wnt/β-catenin pathways promote colorectal cancer progression regardless of mutational status. *Cancer Biol Ther* 2022; **23**: 1-13 [PMID: 35944058 DOI: 10.1080/15384047.2022.2108690]

4 **Paty PB**, Garcia-Aguilar J. Colorectal cancer. *J Surg Oncol* 2022; **126**: 881-887 [PMID: 36087081 DOI: 10.1002/jso.27079]

5 **Xu M**, Chang J, Wang W, Wang X, Wang X, Weng W, Tan C, Zhang M, Ni S, Wang L, Huang Z, Deng Z, Li W, Huang D, Sheng W. Classification of colon adenocarcinoma based on immunological characterizations: Implications for prognosis and immunotherapy. *Front Immunol* 2022; **13**: 934083 [PMID: 35967414 DOI: 10.3389/fimmu.2022.934083]

6 **Majidpoor J**, Mortezaee K. The efficacy of PD-1/PD-L1 blockade in cold cancers and future perspectives. *Clin Immunol* 2021; **226**: 108707 [PMID: 33662590 DOI: 10.1016/j.clim.2021.108707]

7 **Galon J**, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. *Nat Rev Drug Discov* 2019; **18**: 197-218 [PMID: 30610226 DOI: 10.1038/s41573-018-0007-y]

8 **Le DT**, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA Jr. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015; **372**: 2509-2520 [PMID: 26028255 DOI: 10.1056/NEJMoa1500596]

9 **Chen DS**, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature* 2017; **541**: 321-330 [PMID: 28102259 DOI: 10.1038/nature21349]

10 **Lizardo DY**, Kuang C, Hao S, Yu J, Huang Y, Zhang L. Immunotherapy efficacy on mismatch repair-deficient colorectal cancer: From bench to bedside. *Biochim Biophys Acta Rev Cancer* 2020; **1874**: 188447 [PMID: 33035640 DOI: 10.1016/j.bbcan.2020.188447]

11 **Goodman AM**, Kato S, Bazhenova L, Patel SP, Frampton GM, Miller V, Stephens PJ, Daniels GA, Kurzrock R. Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. *Mol Cancer Ther* 2017; **16**: 2598-2608 [PMID: 28835386 DOI: 10.1158/1535-7163.MCT-17-0386]

12 **Goodman AM**, Sokol ES, Frampton GM, Lippman SM, Kurzrock R. Microsatellite-Stable Tumors with High Mutational Burden Benefit from Immunotherapy. *Cancer Immunol Res* 2019; **7**: 1570-1573 [PMID: 31405947 DOI: 10.1158/2326-6066.CIR-19-0149]

13 **Wang W**, Green M, Choi JE, Gijón M, Kennedy PD, Johnson JK, Liao P, Lang X, Kryczek I, Sell A, Xia H, Zhou J, Li G, Li J, Li W, Wei S, Vatan L, Zhang H, Szeliga W, Gu W, Liu R, Lawrence TS, Lamb C, Tanno Y, Cieslik M, Stone E, Georgiou G, Chan TA, Chinnaiyan A, Zou W. CD8(+) T cells regulate tumour ferroptosis during cancer immunotherapy. *Nature* 2019; **569**: 270-274 [PMID: 31043744 DOI: 10.1038/s41586-019-1170-y]

14 **Golstein P**, Griffiths GM. An early history of T cell-mediated cytotoxicity. *Nat Rev Immunol* 2018; **18**: 527-535 [PMID: 29662120 DOI: 10.1038/s41577-018-0009-3]

15 **Newman JH**, Chesson CB, Herzog NL, Bommareddy PK, Aspromonte SM, Pepe R, Estupinian R, Aboelatta MM, Buddhadev S, Tarabichi S, Lee M, Li S, Medina DJ, Giurini EF, Gupta KH, Guevara-Aleman G, Rossi M, Nowicki C, Abed A, Goldufsky JW, Broucek JR, Redondo RE, Rotter D, Jhawar SR, Wang SJ, Kohlhapp FJ, Kaufman HL, Thomas PG, Gupta V, Kuzel TM, Reiser J, Paras J, Kane MP, Singer EA, Malhotra J, Denzin LK, Sant'Angelo DB, Rabson AB, Lee LY, Lasfar A, Langenfeld J, Schenkel JM, Fidler MJ, Ruiz ES, Marzo AL, Rudra JS, Silk AW, Zloza A. Intratumoral injection of the seasonal flu shot converts immunologically cold tumors to hot and serves as an immunotherapy for cancer. *Proc Natl Acad Sci U S A*2020; **117**: 1119-1128 [PMID: 31888983 DOI: 10.1073/pnas.1904022116]

16 **Sobral D**, Martins M, Kaplan S, Golkaram M, Salmans M, Khan N, Vijayaraghavan R, Casimiro S, Fernandes A, Borralho P, Ferreira C, Pinto R, Abreu C, Costa AL, Zhang S, Pawlowski T, Godsey J, Mansinho A, Macedo D, Lobo-Martins S, Filipe P, Esteves R, Coutinho J, Costa PM, Ramires A, Aldeia F, Quintela A, So A, Liu L, Grosso AR, Costa L. Genetic and microenvironmental intra-tumor heterogeneity impacts colorectal cancer evolution and metastatic development. *Commun Biol* 2022; **5**: 937 [PMID: 36085309 DOI: 10.1038/s42003-022-03884-x]

17 **Wang X**, Li S, Yan S, Shan Y, Wang X, Jingbo Z, Wang Y, Shan F, Griffin N, Sun X. Methionine enkephalin inhibits colorectal cancer by remodeling the immune status of the tumor microenvironment. *Int Immunopharmacol* 2022; **111**: 109125 [PMID: 35988519 DOI: 10.1016/j.intimp.2022.109125]

18 **Chen J**, Zhu H, Yin Y, Jia S, Luo X. Colorectal cancer: Metabolic interactions reshape the tumor microenvironment. *Biochim Biophys Acta Rev Cancer* 2022; **1877**: 188797 [PMID: 36100193 DOI: 10.1016/j.bbcan.2022.188797]

19 **Lazarus J**, Maj T, Smith JJ, Perusina Lanfranca M, Rao A, D'Angelica MI, Delrosario L, Girgis A, Schukow C, Shia J, Kryczek I, Shi J, Wasserman I, Crawford H, Nathan H, Pasca Di Magliano M, Zou W, Frankel TL. Spatial and phenotypic immune profiling of metastatic colon cancer. *JCI Insight* 2018; **3** [PMID: 30429368 DOI: 10.1172/jci.insight.121932]

20 **Grothey A**, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381**: 303-312 [PMID: 23177514 DOI: 10.1016/S0140-6736(12)61900-X]

21 **Fondevila F**, Méndez-Blanco C, Fernández-Palanca P, González-Gallego J, Mauriz JL. Anti-tumoral activity of single and combined regorafenib treatments in preclinical models of liver and gastrointestinal cancers. *Exp Mol Med* 2019; **51**: 1-15 [PMID: 31551425 DOI: 10.1038/s12276-019-0308-1]

22 **Abou-Elkacem L**, Arns S, Brix G, Gremse F, Zopf D, Kiessling F, Lederle W. Regorafenib inhibits growth, angiogenesis, and metastasis in a highly aggressive, orthotopic colon cancer model. *Mol Cancer Ther* 2013; **12**: 1322-1331 [PMID: 23619301 DOI: 10.1158/1535-7163.MCT-12-1162]

23 **Fukuoka S**, Hara H, Takahashi N, Kojima T, Kawazoe A, Asayama M, Yoshii T, Kotani D, Tamura H, Mikamoto Y, Hirano N, Wakabayashi M, Nomura S, Sato A, Kuwata T, Togashi Y, Nishikawa H, Shitara K. Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603). *J Clin Oncol* 2020; **38**: 2053-2061 [PMID: 32343640 DOI: 10.1200/JCO.19.03296]

24 **Urban-Wojciuk Z**, Khan MM, Oyler BL, Fåhraeus R, Marek-Trzonkowska N, Nita-Lazar A, Hupp TR, Goodlett DR. The Role of TLRs in Anti-cancer Immunity and Tumor Rejection. *Front Immunol* 2019; **10**: 2388 [PMID: 31695691 DOI: 10.3389/fimmu.2019.02388]

25 **Nagarsheth N**, Wicha MS, Zou W. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. *Nat Rev Immunol* 2017; **17**: 559-572 [PMID: 28555670 DOI: 10.1038/nri.2017.49]

26 **Ros XR**, Vermeulen L. Turning Cold Tumors Hot by Blocking TGF-β. *Trends Cancer* 2018; **4**: 335-337 [PMID: 29709256 DOI: 10.1016/j.trecan.2018.03.005]

27 **He Y**, Fang Y, Zhang M, Zhao Y, Tu B, Shi M, Muhitdinov B, Asrorov A, Xu Q, Huang Y. Remodeling "cold" tumor immune microenvironment *via* epigenetic-based therapy using targeted liposomes with in situ formed albumin corona. *Acta Pharm Sin B* 2022; **12**: 2057-2073 [PMID: 35847495 DOI: 10.1016/j.apsb.2021.09.022]

28 **Janssen JBE**, Medema JP, Gootjes EC, Tauriello DVF, Verheul HMW. Mutant RAS and the tumor microenvironment as dual therapeutic targets for advanced colorectal cancer. *Cancer Treat Rev* 2022; **109**: 102433 [PMID: 35905558 DOI: 10.1016/j.ctrv.2022.102433]

29 **Sun Y**, Li Z, Wang W, Zhang X, Li W, Du G, Yin J, Xiao W, Yang H. Identification and verification of YBX3 and its regulatory gene HEIH as an oncogenic system: A multidimensional analysis in colon cancer. *Front Immunol* 2022; **13**: 957865 [PMID: 36059530 DOI: 10.3389/fimmu.2022.957865]

30 **Takahashi H**, Watanabe H, Hashimura M, Matsumoto T, Yokoi A, Nakagawa M, Ishibashi Y, Ito T, Ohhigata K, Saegusa M. A combination of stromal PD-L1 and tumoral nuclear β-catenin expression as an indicator of colorectal carcinoma progression and resistance to chemoradiotherapy in locally advanced rectal carcinoma. *J Pathol Clin Res* 2022; **8**: 458-469 [PMID: 35762092 DOI: 10.1002/cjp2.285]

31 **Dmitrieva-Posocco O**, Wong AC, Lundgren P, Golos AM, Descamps HC, Dohnalová L, Cramer Z, Tian Y, Yueh B, Eskiocak O, Egervari G, Lan Y, Liu J, Fan J, Kim J, Madhu B, Schneider KM, Khoziainova S, Andreeva N, Wang Q, Li N, Furth EE, Bailis W, Kelsen JR, Hamilton KE, Kaestner KH, Berger SL, Epstein JA, Jain R, Li M, Beyaz S, Lengner CJ, Katona BW, Grivennikov SI, Thaiss CA, Levy M. β-Hydroxybutyrate suppresses colorectal cancer. *Nature* 2022; **605**: 160-165 [PMID: 35477756 DOI: 10.1038/s41586-022-04649-6]

32 **Li J**, Ma X, Chakravarti D, Shalapour S, DePinho RA. Genetic and biological hallmarks of colorectal cancer. *Genes Dev* 2021; **35**: 787-820 [PMID: 34074695 DOI: 10.1101/gad.348226.120]

33 **Zhao EY**, Jones M, Jones SJM. Whole-Genome Sequencing in Cancer. *Cold Spring Harb Perspect Med* 2019; **9** [PMID: 29844223 DOI: 10.1101/cshperspect.a034579]

34 **Lv Y**, Wang Y, Zhang Z, Bao J, Su H. Potentials of long non-coding RNAs as biomarkers of colorectal cancer. *Clin Transl Oncol* 2022; **24**: 1715-1731 [PMID: 35581419 DOI: 10.1007/s12094-022-02834-7]

35 **Galon J**, Lanzi A. Immunoscore and its introduction in clinical practice. *Q J Nucl Med Mol Imaging* 2020; **64**: 152-161 [PMID: 32107902 DOI: 10.23736/S1824-4785.20.03249-5]

36 **Ren Y**, Miao JM, Wang YY, Fan Z, Kong XB, Yang L, Cheng G. Oncolytic viruses combined with immune checkpoint therapy for colorectal cancer is a promising treatment option. *Front Immunol* 2022; **13**: 961796 [PMID: 35911673 DOI: 10.3389/fimmu.2022.961796]

37 **Lian W**, Wang Z, Ma Y, Tong Y, Zhang X, Jin H, Zhao S, Yu R, Ju S, Zhang X, Guo X, Huang T, Ding X, Peng M. FABP6 Expression Correlates with Immune Infiltration and Immunogenicity in Colorectal Cancer Cells. *J Immunol Res* 2022; **2022**: 3129765 [PMID: 36033394 DOI: 10.1155/2022/3129765]

38 **Bolzacchini E**, Libera L, Church SE, Sahnane N, Bombelli R, Digiacomo N, Giordano M, Petracco G, Sessa F, Capella C, Furlan D. Tumor Antigenicity and a Pre-Existing Adaptive Immune Response in Advanced BRAF Mutant Colorectal Cancers. *Cancers (Basel)* 2022; **14** [PMID: 36010943 DOI: 10.3390/cancers14163951]

39 **Collienne M**, Loghmani H, Heineman TC, Arnold D. GOBLET: a phase I/II study of pelareorep and atezolizumab +/- chemo in advanced or metastatic gastrointestinal cancers. *Future Oncol* 2022; **18**: 2871-2878 [PMID: 35796248 DOI: 10.2217/fon-2022-0453]

40 **Wu JY**, Song QY, Huang CZ, Shao Y, Wang ZL, Zhang HQ, Fu Z. N7-methylguanosine-related lncRNAs: Predicting the prognosis and diagnosis of colorectal cancer in the cold and hot tumors. *Front Genet* 2022; **13**: 952836 [PMID: 35937987 DOI: 10.3389/fgene.2022.952836]

41 **Li S**, Na R, Li X, Zhang Y, Zheng T. Targeting interleukin-17 enhances tumor response to immune checkpoint inhibitors in colorectal cancer. *Biochim Biophys Acta Rev Cancer* 2022; **1877**: 188758 [PMID: 35809762 DOI: 10.1016/j.bbcan.2022.188758]

42 **Hubbard JM**, Tőke ER, Moretto R, Graham RP, Youssoufian H, Lőrincz O, Molnár L, Csiszovszki Z, Mitchell JL, Wessling J, Tóth J, Cremolini C. Safety and Activity of PolyPEPI1018 Combined with Maintenance Therapy in Metastatic Colorectal Cancer: an Open-Label, Multicenter, Phase Ib Study. *Clin Cancer Res* 2022; **28**: 2818-2829 [PMID: 35472243 DOI: 10.1158/1078-0432.CCR-22-0112]

43 **Li C**, Li T, Niu K, Xiao Z, Huang J, Pan X, Sun Y, Wang Y, Ma D, Xie P, Shuai X, Meng X. Mild phototherapy mediated by manganese dioxide-loaded mesoporous polydopamine enhances immunotherapy against colorectal cancer. *Biomater Sci* 2022; **10**: 3647-3656 [PMID: 35670464 DOI: 10.1039/d2bm00505k]

44 **Yu G**, Wang W, He X, Xu J, Xu R, Wan T, Wu Y. Synergistic Therapeutic Effects of Low Dose Decitabine and NY-ESO-1 Specific TCR-T Cells for the Colorectal Cancer With Microsatellite Stability. *Front Oncol* 2022; **12**: 895103 [PMID: 35774131 DOI: 10.3389/fonc.2022.895103]

45 **Gatenbee CD**, Baker AM, Schenck RO, Strobl M, West J, Neves MP, Hasan SY, Lakatos E, Martinez P, Cross WCH, Jansen M, Rodriguez-Justo M, Whelan CJ, Sottoriva A, Leedham S, Robertson-Tessi M, Graham TA, Anderson ARA. Immunosuppressive niche engineering at the onset of human colorectal cancer. *Nat Commun* 2022; **13**: 1798 [PMID: 35379804 DOI: 10.1038/s41467-022-29027-8]

46 **Qiao G**, Kone LB, Phillips EH, Lee SS, Brown GE, Khetani SR, Thakur A, Lum LG, Prabhakar BS, Maker AV. LIGHT enhanced bispecific antibody armed T-cells to treat immunotherapy resistant colon cancer. *Oncogene* 2022; **41**: 2054-2068 [PMID: 35177811 DOI: 10.1038/s41388-022-02209-w]

47 **Wen H**, Li F, Bukhari I, Mi Y, Guo C, Liu B, Zheng P, Liu S. Comprehensive Analysis of Colorectal Cancer Immunity and Identification of Immune-Related Prognostic Targets. *Dis Markers* 2022; **2022**: 7932655 [PMID: 35401882 DOI: 10.1155/2022/7932655]

48 **Zheng Y**, Fu Y, Wang PP, Ding ZY. Neoantigen: A Promising Target for the Immunotherapy of Colorectal Cancer. *Dis Markers* 2022; **2022**: 8270305 [PMID: 35211210 DOI: 10.1155/2022/8270305]

49 **Di Guida R**, Casillo A, Stellavato A, Kawai S, Ogawa T, Di Meo C, Kawamoto J, Kurihara T, Schiraldi C, Corsaro MM. Capsular polysaccharide from a fish-gut bacterium induces/promotes apoptosis of colon cancer cells *in vitro* through Caspases' pathway activation. *Carbohydr Polym* 2022; **278**: 118908 [PMID: 34973729 DOI: 10.1016/j.carbpol.2021.118908]

50 **Wang Z**, Moresco P, Yan R, Li J, Gao Y, Biasci D, Yao M, Pearson J, Hechtman JF, Janowitz T, Zaidi RM, Weiss MJ, Fearon DT. Carcinomas assemble a filamentous CXCL12-keratin-19 coating that suppresses T cell-mediated immune attack. *Proc Natl Acad Sci U S A* 2022; **119** [PMID: 35046049 DOI: 10.1073/pnas.2119463119]

51 **Kristensen LK**, Christensen C, Alfsen MZ, Cold S, Nielsen CH, Kjaer A. Monitoring CD8a(+) T Cell Responses to Radiotherapy and CTLA-4 Blockade Using [(64)Cu]NOTA-CD8a PET Imaging. *Mol Imaging Biol* 2020; **22**: 1021-1030 [PMID: 32086762 DOI: 10.1007/s11307-020-01481-0]

52 **Martinez NW**, Sánchez A, Diaz P, Broekhuizen R, Godoy J, Mondaca S, Catenaccio A, Macanas P, Nervi B, Calvo M, Court FA. Metformin protects from oxaliplatin induced peripheral neuropathy in rats. *Neurobiol Pain* 2020; **8**: 100048 [PMID: 32490289 DOI: 10.1016/j.ynpai.2020.100048]

53 **Taylor K**, Loo Yau H, Chakravarthy A, Wang B, Shen SY, Ettayebi I, Ishak CA, Bedard PL, Abdul Razak A, R Hansen A, Spreafico A, Cescon D, Butler MO, Oza AM, Lheureux S, Stjepanovic N, Van As B, Boross-Harmer S, Wang L, Pugh TJ, Ohashi PS, Siu LL, De Carvalho DD. An open-label, phase II multicohort study of an oral hypomethylating agent CC-486 and durvalumab in advanced solid tumors. *J Immunother Cancer* 2020; **8** [PMID: 32753546 DOI: 10.1136/jitc-2020-000883]

54 **Yu W**, Sun J, Liu F, Yu S, Hu J, Zhao Y, Wang X, Liu X. Treating Immunologically Cold Tumors by Precise Cancer Photoimmunotherapy with an Extendable Nanoplatform. *ACS Appl Mater Interfaces* 2020; **12**: 40002-40012 [PMID: 32805869 DOI: 10.1021/acsami.0c09469]

55 **Janji B**, Hasmim M, Parpal S, De Milito A, Berchem G, Noman MZ. Lighting up the fire in cold tumors to improve cancer immunotherapy by blocking the activity of the autophagy-related protein PIK3C3/VPS34. *Autophagy* 2020; **16**: 2110-2111 [PMID: 32892693 DOI: 10.1080/15548627.2020.1815439]

56 **Kleeman SO**, Leedham SJ. Not All Wnt Activation Is Equal: Ligand-Dependent versus Ligand-Independent Wnt Activation in Colorectal Cancer. *Cancers (Basel)* 2020; **12** [PMID: 33202731 DOI: 10.3390/cancers12113355]

57 **Biasci D**, Smoragiewicz M, Connell CM, Wang Z, Gao Y, Thaventhiran JED, Basu B, Magiera L, Johnson TI, Bax L, Gopinathan A, Isherwood C, Gallagher FA, Pawula M, Hudecova I, Gale D, Rosenfeld N, Barmpounakis P, Popa EC, Brais R, Godfrey E, Mir F, Richards FM, Fearon DT, Janowitz T, Jodrell DI. CXCR4 inhibition in human pancreatic and colorectal cancers induces an integrated immune response. *Proc Natl Acad Sci U S A* 2020; **117**: 28960-28970 [PMID: 33127761 DOI: 10.1073/pnas.2013644117]

58 **Matsumoto T**, Okayama H, Nakajima S, Saito K, Nakano H, Endo E, Kase K, Ito M, Yamauchi N, Yamada L, Kanke Y, Onozawa H, Fujita S, Sakamoto W, Saito M, Saze Z, Momma T, Mimura K, Kono K. Tn Antigen Expression Defines an Immune Cold Subset of Mismatch-Repair Deficient Colorectal Cancer. *Int J Mol Sci* 2020; **21** [PMID: 33260328 DOI: 10.3390/ijms21239081]

59 **Ren J**, Xu M, Chen J, Ding J, Wang P, Huo L, Li F, Liu Z. PET imaging facilitates antibody screening for synergistic radioimmunotherapy with a (177)Lu-labeled αPD-L1 antibody. *Theranostics* 2021; **11**: 304-315 [PMID: 33391476 DOI: 10.7150/thno.45540]

60 **Angelova A**, Ferreira T, Bretscher C, Rommelaere J, Marchini A. Parvovirus-Based Combinatorial Immunotherapy: A Reinforced Therapeutic Strategy against Poor-Prognosis Solid Cancers. *Cancers (Basel)* 2021; **13** [PMID: 33477757 DOI: 10.3390/cancers13020342]

61 **Fabian KP**, Malamas AS, Padget MR, Solocinski K, Wolfson B, Fujii R, Abdul Sater H, Schlom J, Hodge JW. Therapy of Established Tumors with Rationally Designed Multiple Agents Targeting Diverse Immune-Tumor Interactions: Engage, Expand, Enable. *Cancer Immunol Res* 2021; **9**: 239-252 [PMID: 33355290 DOI: 10.1158/2326-6066.CIR-20-0638]

62 **Fabian KP**, Padget MR, Fujii R, Schlom J, Hodge JW. Differential combination immunotherapy requirements for inflamed (warm) tumors versus T cell excluded (cool) tumors: engage, expand, enable, and evolve. *J Immunother Cancer* 2021; **9** [PMID: 33602696 DOI: 10.1136/jitc-2020-001691]

63 **Fathi M**, Pustokhina I, Kuznetsov SV, Khayrullin M, Hojjat-Farsangi M, Karpisheh V, Jalili A, Jadidi-Niaragh F. T-cell immunoglobulin and ITIM domain, as a potential immune checkpoint target for immunotherapy of colorectal cancer. *IUBMB Life* 2021; **73**: 726-738 [PMID: 33686787 DOI: 10.1002/iub.2461]

64 **Chen L**, Chen H, Ye J, Ge Y, Wang H, Dai E, Ren J, Liu W, Ma C, Ju S, Guo ZS, Liu Z, Bartlett DL. Intratumoral expression of interleukin 23 variants using oncolytic vaccinia virus elicit potent antitumor effects on multiple tumor models *via* tumor microenvironment modulation. *Theranostics* 2021; **11**: 6668-6681 [PMID: 34093846 DOI: 10.7150/thno.56494]

65 **Fang Y**, He Y, Wu C, Zhang M, Gu Z, Zhang J, Liu E, Xu Q, Asrorov AM, Huang Y. Magnetism-mediated targeting hyperthermia-immunotherapy in "cold" tumor with CSF1R inhibitor. *Theranostics* 2021; **11**: 6860-6872 [PMID: 34093858 DOI: 10.7150/thno.57511]

66 **Lee SJ**, Yang H, Kim WR, Lee YS, Lee WS, Kong SJ, Lee HJ, Kim JH, Cheon J, Kang B, Chon HJ, Kim C. STING activation normalizes the intraperitoneal vascular-immune microenvironment and suppresses peritoneal carcinomatosis of colon cancer. *J Immunother Cancer* 2021; **9** [PMID: 34145029 DOI: 10.1136/jitc-2020-002195]

67 **Chen D**, Bao X, Zhang R, Ding Y, Zhang M, Li B, Zhang H, Li X, Tong Z, Liu L, Zhou X, Wang S, Cheng X, Zheng Y, Ruan J, Fang W, Zhao P. Depiction of the genomic and genetic landscape identifies CCL5 as a protective factor in colorectal neuroendocrine carcinoma. *Br J Cancer* 2021; **125**: 994-1002 [PMID: 34331023 DOI: 10.1038/s41416-021-01501-y]

68 **Huis In 't Veld RV**, Da Silva CG, Jager MJ, Cruz LJ, Ossendorp F. Combining Photodynamic Therapy with Immunostimulatory Nanoparticles Elicits Effective Anti-Tumor Immune Responses in Preclinical Murine Models. *Pharmaceutics* 2021; **13** [PMID: 34575546 DOI: 10.3390/pharmaceutics13091470]

69 **Liu N**, Shan F, Ma M. Strategic enhancement of immune checkpoint inhibition in refractory Colorectal Cancer: Trends and future prospective. *Int Immunopharmacol* 2021; **99**: 108017 [PMID: 34352568 DOI: 10.1016/j.intimp.2021.108017]

70 **Wang Z**, Little N, Chen J, Lambesis KT, Le KT, Han W, Scott AJ, Lu J. Immunogenic camptothesome nanovesicles comprising sphingomyelin-derived camptothecin bilayers for safe and synergistic cancer immunochemotherapy. *Nat Nanotechnol* 2021; **16**: 1130-1140 [PMID: 34385682 DOI: 10.1038/s41565-021-00950-z]

71 **Matsumoto T**, Okayama H, Nakano H, Ito M, Nakajima S, Saito M, Saze Z, Momma T, Mimura K, Kono K. [Immunotherapy Targeting Tumor-Associated Carbohydrate Antigens in Deficient Mismatch Repair Colorectal Cancer]. *Gan To Kagaku Ryoho* 2021; **48**: 1275-1277 [PMID: 34657062]

72 **Baraibar I**, Mirallas O, Saoudi N, Ros J, Salvà F, Tabernero J, Élez E. Combined Treatment with Immunotherapy-Based Strategies for MSS Metastatic Colorectal Cancer. *Cancers (Basel)* 2021; **13** [PMID: 34944931 DOI: 10.3390/cancers13246311]

73 **Gao Y**, Päivinen P, Tripathi S, Domènech-Moreno E, Wong IPL, Vaahtomeri K, Nagaraj AS, Talwelkar SS, Foretz M, Verschuren EW, Viollet B, Yan Y, Mäkelä TP. Inactivation of AMPK Leads to Attenuation of Antigen Presentation and Immune Evasion in Lung Adenocarcinoma. *Clin Cancer Res* 2022; **28**: 227-237 [PMID: 34667030 DOI: 10.1158/1078-0432.CCR-21-2049]

74 **Shang S**, Yang YW, Chen F, Yu L, Shen SH, Li K, Cui B, Lv XX, Zhang C, Yang C, Liu J, Yu JJ, Zhang XW, Li PP, Zhu ST, Zhang HZ, Hua F. TRIB3 reduces CD8(+) T cell infiltration and induces immune evasion by repressing the STAT1-CXCL10 axis in colorectal cancer. *Sci Transl Med* 2022; **14**: eabf0992 [PMID: 34985967 DOI: 10.1126/scitranslmed.abf0992]

75 **Liu Z**, Guo Y, Yang X, Chen C, Fan D, Wu X, Si C, Xu Y, Shao B, Chen Z, Dang Q, Cui W, Han X, Ji Z, Sun Z. Immune Landscape Refines the Classification of Colorectal Cancer With Heterogeneous Prognosis, Tumor Microenvironment and Distinct Sensitivity to Frontline Therapies. *Front Cell Dev Biol* 2021; **9**: 784199 [PMID: 35083217 DOI: 10.3389/fcell.2021.784199]

**Footnotes**

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** September 20, 2022

**First decision:** November 28, 2022

**Article in press:** February 7, 2023

**Specialty type:** Oncology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Cabezuelo AS, Spain; Govindarajan KK, India; Jeong KY, South Korea **S-Editor:** Liu GL **L-Editor:** Filipodia **P-Editor:** Liu GL

**Figure Legends**

****

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



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2023 Baishideng Publishing Group Inc. All rights reserved.**