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The Application and Limitations of Immunotherapy for Colorectal Cancer

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Abstract. Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide, driven by its molecular heterogeneity and resistance to conventional therapies. While surgery, chemotherapy, and radiotherapy form the backbone of CRC management, their efficacy diminishes in advanced disease, necessitating innovative approaches. Immunotherapy, particularly immune checkpoint inhibitors (ICIs), has emerged as a transformative strategy, achieving remarkable success in microsatellite instability-high (MSI-H) CRC due to its high tumor mutational burden. However, microsatellite stable (MSS) CRC, comprising the majority of cases, exhibits limited responsiveness, posing a significant challenge. This review elucidates the epidemiological and pathological features of CRC, evaluates the limitations of traditional treatments, and explores the evolution and mechanisms of immunotherapy. It highlights the progress of ICIs, tumor vaccines, and cell therapies in CRC, with a focus on clinical trial outcomes demonstrating durable responses in MSI-H cohorts but modest benefits in MSS tumors. Key challenges, including biomarker identification, the immunosuppressive tumor microenvironment, and drug resistance, are analyzed, alongside strategies to overcome them. Future directions emphasize personalized therapies, tumor microenvironment modulation, and technological innovations like neoantigen vaccines and microbiome-based interventions. By synthesizing current evidence and identifying research gaps, this paper underscores immunotherapy's potential to revolutionize CRC treatment while addressing its limitations, paving the way for precision oncology advancements.

Keywords: Colorectal cancer, Immunotherapy, Immune checkpoint inhibitors, Microsatellite instability

1. Background and treatment difficulties of colorectal cancer

1.1. Epidemiological and pathological characteristics of colorectal cancer

Colorectal cancer (CRC), which ranks among the most prevalent malignancies globally and is associated with significant morbidity and mortality, according to recent global cancer statistics, is the third most common cancer and the second leading cause of cancer - related deaths, with its incidence varying geographically due to lifestyle factors like high - fat diets, low fiber intake, and sedentary behavior especially in developed regions where rates are higher. Pathologically, arising

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from the epithelial lining of the colon or rectum predominantly as adenocarcinomas, molecularly, CRC exhibits heterogeneity characterized by distinct subtypes such as microsatellite instability - high (MSI - H), microsatellite stable (MSS), and KRAS - mutated tumors. MSI - H tumors, constituting around 15% of cases, being associated with defective DNA mismatch repair systems, lead to increased tumor mutational burden (TMB) and immunogenicity [1], while MSS tumors, which dominate sporadic CRC, display lower TMB and present challenges for immune - based therapies. The progression from adenoma to carcinoma, involving sequential genetic alterations including APC, KRAS, and TP53 mutations, underscores the complexity of CRC pathogenesis.

1.2. Current status and limitations of traditional treatment methods

Traditional CRC management relies on surgery, chemotherapy, and radiotherapy, tailored to disease stage. Surgical resection remains the cornerstone for localized disease, achieving high cure rates for early-stage CRC. However, over 50% of patients present with advanced or metastatic disease at diagnosis, necessitating systemic therapies. Chemotherapy regimens, such as FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin) and FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin), are standard for metastatic CRC (mCRC), often combined with targeted agents like anti-VEGF (bevacizumab) or anti-EGFR (cetuximab) therapies for KRAS wild-type tumors. Radiotherapy plays a limited role, primarily in rectal cancer, to reduce local recurrence [2]. Despite advances, these modalities face significant limitations. Chemotherapy offers modest survival benefits in mCRC, with median overall survival rarely exceeding 30 months. Toxicities, including neuropathy and myelosuppression, compromise patient quality of life. Targeted therapies are constrained by molecular eligibility (e.g., KRAS mutations preclude anti-EGFR efficacy) and acquired resistance. Moreover, recurrence rates remain high, particularly in stage III and IV disease, highlighting the need for novel therapeutic strategies.

1.3. Analysis of key difficulties in colorectal cancer treatment

The primary challenges in CRC treatment stem from its biological and clinical complexity. First, tumor heterogeneity complicates therapeutic targeting, as molecular subtypes respond variably to interventions. For instance, MSS tumors exhibit poor immunogenicity, limiting responsiveness to immune-based approaches. Second, the tumor microenvironment (TME) in CRC, characterized by immunosuppressive cells (e.g., myeloid-derived suppressor cells and regulatory T cells), hinders effective immune surveillance [3]. Third, drug resistance, whether intrinsic or acquired, undermines long-term efficacy. Resistance to chemotherapy and targeted therapies often arises from genetic adaptations, such as secondary KRAS mutations or activation of bypass signaling pathways. Finally, the high metastatic potential of CRC, particularly to the liver, poses a significant barrier, as metastatic lesions often exhibit distinct molecular profiles and reduced treatment sensitivity. Addressing these difficulties requires therapies that can overcome immunosuppression, target diverse molecular drivers, and prevent resistance[4].

2. Background and development of immunotherapy

2.1. Basic concepts and historical evolution of immunotherapy

Immunotherapy, which harnesses the immune system's specificity and adaptability in order to combat cancer, whose concept had its origin in the late 19th century due to William Coley's observations of tumor regression subsequent to bacterial infections, thereby laying the basis for

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immune stimulation strategies, and the modern era of which started with the identification of T - cell - mediated immunity as well as the discovery of immune checkpoints in the late 20th century. With key milestones such as the development of cytokine therapies like interleukin - 2 in the 1980s, adoptive cell therapies in the 1990s, and immune checkpoint inhibitors ICIs in the 2010s, the approval of ipilimumab (anti - CTLA - 4) in 2011 for melanoma, which marked a turning point, being followed by anti - PD - 1/PD - L1 therapies that revolutionized cancer treatment. Immunotherapy's evolution is a reflection of a deepening understanding of immune - tumor interactions, shifting from nonspecific immune stimulation to targeted modulation of immune responses[5].

2.2. Mechanisms and core principles of immunotherapy

Immunotherapy operates by enhancing the immune system’s ability to recognize and eliminate cancer cells. Its core mechanisms include: (1) Immune checkpoint blockade, which inhibits negative regulatory pathways (e.g., PD-1/PD-L1, CTLA-4) to unleash T-cell activity; (2) Adoptive cell therapy, such as chimeric antigen receptor (CAR) T-cell therapy, which engineers T cells to target tumor-specific antigens; (3) Tumor vaccines, which prime the immune system against tumor-associated antigens; and (4) Cytokine therapy, which amplifies immune responses through signaling molecules like interferon-alpha. The efficacy of immunotherapy hinges on the cancer-immunity cycle, encompassing antigen presentation, T-cell priming, infiltration into tumors, and effector function. However, success depends on overcoming immune evasion mechanisms, such as low antigenicity, immunosuppressive TME, and checkpoint upregulation, which are particularly pronounced in CRC.

2.3. Current progress of immunotherapy in the field of tumors

Immunotherapy, which has brought about a transformation in the treatment panorama of numerous cancers like melanoma, lung cancer, and renal cell carcinoma, encompasses various therapeutic modalities. Anti - PD - 1/PD - L1 therapies including pembrolizumab and nivolumab can achieve long - lasting responses in high - TMB tumors where the response rates go beyond 40% in certain cohorts, a phenomenon that has drawn extensive attention. CAR - T therapies, having demonstrated remarkable efficacy in hematologic malignancies especially B - cell lymphomas, have spurred the exploration of their application in solid tumors. Tumor vaccines, though having had less success, are advancing via personalized neoantigen - based approaches. Combination strategies that integrate ICIs with targeted therapies or radiotherapy are being developed to expand the therapeutic impact. In CRC, the success of immunotherapy is mostly limited to MSI - H tumors that respond robustly to ICIs because of their high neoantigen load. Nevertheless, MSS tumors, which represent the majority of CRC cases, still pose a significant challenge, thus stimulating research into novel immunomodulatory approaches as stated in reference [6].

3. Progress in the application of immunotherapy in colorectal cancer

3.1. Application of immune checkpoint inhibitors in colorectal cancer

ICIs, which have emerged as a sort of breakthrough for MSI-H CRC where elevated TMB along with neoantigen presentation results in robust responses, and regarding pembrolizumab and nivolumab that are both anti - PD - 1 agents, they received FDA approval for MSI - H/mismatch repair - deficient (dMMR) mCRC on the basis of trials that demonstrated objective response rates

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(ORRs) in the range of 30–50% and durable progression - free survival. As for combinations like nivolumab plus ipilimumab, they further enhance efficacy with ORRs approaching 60% in MSI - H cohorts. However, MSS CRC, which makes up 85% of cases, poorly responds to ICIs with ORRs below 10% in monotherapy settings [7]. Efforts aimed at sensitizing MSS tumors including combinations with chemotherapy, radiotherapy or targeted agents such as BRAF/MEK inhibitors, which show some modest improvements in preclinical models, and this differential response emphasizes the necessity for biomarkers to stratify patients and optimize the use of ICIs.

3.2. Exploration of tumor vaccines and cell therapy

Tumor vaccines and cell therapies represent promising yet underdeveloped avenues for CRC. Vaccines aim to stimulate T-cell responses against tumor-specific antigens, such as CEA or MUC1, but clinical trials have yielded limited success, with ORRs below 5% in advanced CRC. Recent advances focus on neoantigen vaccines tailored to individual tumor profiles, showing early promise in phase I studies. Cell therapies, including CAR-T and tumor-infiltrating lymphocyte (TIL) therapies, face challenges in CRC due to antigen heterogeneity and immunosuppressive TME. Preclinical studies targeting CEA or HER2 demonstrate tumor regression in mouse models, but clinical translation remains limited. Dendritic cell-based approaches, such as those using membrane microvesicles, are under investigation for their potential to enhance T-cell activation and tumor killing. These modalities require further optimization to achieve clinical relevance[8].

3.3. Clinical trial results and efficacy evaluation

Clinical trials of immunotherapy in CRC, where both successes and limitations are highlighted, with the KEYNOTE - 177 trial establishing pembrolizumab as a first - line therapy for MSI - H/dMMR mCRC demonstrating a median progression - free survival of 16.5 months in contrast to 8.2 months with chemotherapy and the CheckMate - 142 study confirming the efficacy of nivolumab - based regimens in MSI - H mCRC having durable responses in heavily pretreated patients, while in MSS CRC trials such as those testing atezolizumab (anti - PD - L1) combinations reporting disappointing results with ORRs below 15% and combination strategies including ICIs with BRAF/MEK inhibitors showing preliminary efficacy in BRAF - mutated mCRC with ORRs of 20–30%, all these findings emphasize the need for novel combinations as well as predictive biomarkers so as to extend immunotherapy’s benefits to MSS CRC in a rather complex and somewhat convoluted way that might be difficult to fully comprehend immediately.

4. Challenges and future prospects of immunotherapy in colorectal cancer

4.1. Difficulties in biomarker screening and personalized treatment

The criticality of biomarker - driven treatment for the success of immunotherapy cannot be overstated, yet the challenges that CRC uniquely poses remain a significant hurdle. Although MSI - H status and TMB, which are established as predictors of ICI response, their applicability is confined to just a minority of patients. Regarding MSS CRC, there are no consistently reliable biomarkers that can effectively predict the efficacy[9]. PD - L1 expression, which is widely employed in other cancers, shows a poor correlation with the response in CRC. Emerging candidates like tumor - infiltrating lymphocytes and gut microbiota signatures, on the other hand, are in urgent need of validation. Moreover, personalized treatment is further compounded by intratumoral heterogeneity, a factor that might give rise to discordant biomarker profiles between primary and

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metastatic lesions. Thus, developing comprehensive and cost - effective biomarker panels along with integrating multi - omics data is crucial for customizing immunotherapy to meet the individual needs of patients.

4.2. Effects of tumor microenvironment on immunotherapy

The CRC TME significantly impedes immunotherapy efficacy, particularly in MSS tumors. The TME is characterized by immunosuppressive cells, inhibitory cytokines (e.g., TGF-β), and physical barriers like dense stroma, which limit T-cell infiltration and function [10]. Tumor-associated macrophages and fibroblasts further promote immune evasion by upregulating checkpoints like PD-L1[10]. Strategies to reprogram the TME, such as TGF-β inhibitors or stroma-targeting agents, are under investigation but face challenges in specificity and toxicity. The gut microbiota, uniquely relevant in CRC, modulates TME immunogenicity, with specific microbial profiles linked to ICI responsiveness. Understanding and manipulating TME dynamics is critical for enhancing immunotherapy outcomes.

4.3. Mechanisms of drug resistance and response strategies

Resistance to immunotherapy in CRC, which is a rather intricate issue, arises through multiple mechanisms of sorts with primary resistance, specifically in MSS tumors, being driven by the low immunogenicity as well as the immunosuppressive TME; meanwhile, acquired resistance that is often observed in MSI - H tumors involves the loss of MHC class I expression or JAK1/2 mutations or the upregulation of alternative checkpoints like LAG - 3; combination therapies such as those of ICIs with targeted agents or radiotherapy aim, via enhancing antigen presentation and T - cell priming as mentions, to overcome this resistance; bispecific antibodies along with oncolytic viruses are emerging tools in efforts to restore immune sensitivity; additionally, the longitudinal monitoring of tumor evolution by making use of liquid biopsies has the potential to guide the adaptive treatment strategies so as to preempt resistance.

4.4. Future research directions and potential for technological breakthroughs

Future research in CRC immunotherapy should prioritize several areas: (1) Expanding ICI efficacy to MSS tumors through novel combinations, such as ICIs with TME-modulating agents; (2) Advancing personalized vaccines and cell therapies using neoantigen profiling and CRISPR-based engineering; (3) Leveraging artificial intelligence to integrate multi-omics data for biomarker discovery[11] [12]; and (4) Exploring the gut microbiome’s therapeutic potential, including fecal microbiota transplantation to enhance ICI response. Technological breakthroughs, such as single-cell sequencing and spatial transcriptomics, offer unprecedented insights into tumor-immune interactions, paving the way for precision immunotherapy. Collaborative, multidisciplinary efforts are essential to translate these innovations into clinical practice[13] [14].

5. Summary

Immunotherapy, which has revolutionized CRC treatment especially regarding MSI - H tumors where ICIs can bring about durable responses, is unfortunately the case that its application in MSS CRC is still restricted by factors like low immunogenicity, the immunosuppressive TME, as well as some resistance mechanisms. Traditional therapies, even though they prove effective for early - stage disease, yet are unable to handle the complexity of advanced CRC, which emphasizes the

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necessity of immune - based strategies. Although there is promise held by advances in vaccines, cell therapies along with combination approaches, challenges in biomarker development, TME modulation and resistance mitigation still stubbornly remain. Future research, thus, should be focused on personalized and TME - targeted therapies and also utilize emerging technologies so as to fully unlock the potential of immunotherapy in CRC, offering hope for enhancing outcomes across all molecular subtypes of this disease.

References

[1] George S , Johdi A N . Single Cell RNA Sequencing in Colorectal Cancer Immunology: Recent Updates, Application, and Emerging Challenges. [J]. Current molecular medicine, 2025,
[2] Jin K , Chu X , Qian J . Arginine and colorectal cancer: Exploring arginine-related therapeutic strategies and novel insights into cancer immunotherapies [J]. International Immunopharmacology, 2025, 148 114146-114146.
[3] So Y , Yim D , Kim K H , et al. Functional Nanosheet Immunoswitches Reprogramming Innate Macrophages for Immunotherapy of Colorectal Cancer and Sepsis. [J]. ACS nano, 2025,
[4] Giraldez D M . First-line dual immunotherapy to checkmate metastasic colorectal cancer with high microsatellite instability. [J]. Gastroenterology, 2025,
[5] Sagredo A A , Andrei P , Clayton K , et al. A constitutive interferon-high immunophenotype defines response to immunotherapy in colorectal cancer. [J]. Cancer cell, 2025, 43 (2): 292-307.e7.
[6] Wu S C . The role of CTLA-4 inhibition in immunotherapy for MSI-H/dMMR metastatic colorectal cancer. [J]. Clinical advances in hematology & oncology : H&O, 2025, 23 (1): 18-20.
[7] Kaviyarasan V , Das A , Deka D , et al. Advancements in immunotherapy for colorectal cancer treatment: a comprehensive review of strategies, challenges, and future prospective [J]. International Journal of Colorectal Disease, 2024, 40 (1): 1-1.
[8] Karami R , Fathi M , Jalali P , et al. The emerging role of TIM -3 in colorectal: a promising target for immunotherapy. [J]. Expert opinion on therapeutic targets, 2024, 28 (12): 1093-1115.
[9] Singer M , Valerin J , Zhang Z , et al. Promising Cellular Immunotherapy for Colorectal Cancer Using Classical Dendritic Cells and Natural Killer T Cells. [J]. Cells, 2025, 14 (3): 166-166.
[10] Gorría T , Boada S M , Rojas M , et al. Metabolic Singularities in Microsatellite-Stable Colorectal Cancer: Identifying Key Players in Immunosuppression to Improve the Immunotherapy Response. [J]. Cancers, 2025, 17 (3): 498-498.
[11] O'Leary K . Dual immunotherapy benefits certain patients with metastatic colorectal cancer [J]. Nature Medicine, 2025, (prepublish):
[12] Davola E M , Cormier O , Lepard M , et al. Humanized mouse models of KRAS-mutated colorectal and pancreatic cancers with HLA-class-I match for pre-clinical evaluation of cancer immunotherapies. [J]. Oncoimmunology, 2025, 14 (1): 2473163.
[13] Printz C . Immunotherapy combination shows longer progression-free survival than chemotherapy alone for patients with a rare type of metastatic colorectal cancer [J]. CA: A Cancer Journal for Clinicians, 2025, 75 (2): 87-89.
[14] Tak E , An I H , Lee S A , et al. Antitumor effects of immunotherapy combined with BRAF and MEK inhibitors in BRAF V600E metastatic colorectal cancer [J]. Cancer Immunology, Immunotherapy, 2025, 74 (5): 154-154.