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EDITORIAL

Challenges in immunotherapy for colorectal cancer: Perspectives from the immune microenvironment

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Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer-related mortality worldwide. Despite recent advances in systemic treatment strategies, the overall mortality burden remains high.[1] Immune-based therapeutic strategies, including immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis, ICI combination regimens, chimeric antigen receptor T-cell therapy, and cancer vaccines, have demonstrated antitumor activity in CRC. However, the clinical benefit of immunotherapy remains highly constrained. An increasing body of evidence suggests that heterogeneity in therapeutic efficacy is not solely determined by the treatment modality, but is also closely associated with the overall immune contexture of the tumor immune microenvironment (TIME). The immune microenvironment shapes and constrains the initiation and durability of antitumor immune responses at multiple levels by modulating antigen presentation and interferon γ signaling pathways, regulating the infiltration and functional maintenance of effector immune cells, and establishing complex immunosuppressive networks dominated by regulatory T cells. Such systemic constraints may collectively give rise to a series of challenges, including difficulties in predicting therapeutic efficacy, resistance of immunologically "cold" tumors to conversion, and inconsistent outcomes observed with combination treatment strategies.

Predictive biomarkers have long been regarded as the theoretical cornerstone for achieving precision therapy with ICIs. At present, tumor PD-L1 expression, deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H) status, and tumor mutational burden constitute the three most commonly cited predictive tools and have demonstrated discriminative capability in selected solid tumors. Accumulating evidence indicates that static indicators at the histopathological or genomic level are insufficient to comprehensively capture the dynamic nature of immune responses. Predicting the efficacy of immunotherapy requires an integrated assessment of the TIME and immune functional status, complemented by the incorporation of peripheral blood-based markers, liquid biopsy approaches, and gut microbiota profiles, to develop more rational and effective stratification strategies.[2] Immune microenvironment-driven precision stratification remains a key unresolved challenge in immunotherapy for CRC.

The difficulty in converting immunologically "cold" tumors represents one of

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the central challenges in CRC immunotherapy. Recent studies have sought to achieve a functional transition of immunologically "cold" tumors by reshaping the interactions among key immune cell populations within the TIME. Preclinical studies suggest that a trispecific antibody can simultaneously target T cells, tumor cells, and myeloid cells, thereby dismantling suppressive myeloid networks and enhancing T-cell effector functions. This approach offers an immuno-niche-reprogramming strategy for the conversion of immunologically "cold" tumors.[3] Nevertheless, the translational and clinical applicability of these highly engineered strategies has yet to be established.

In CRC, immune resistance is not a problem confined to a small subset of patients or restricted to specific disease stages, but rather represents a pervasive limitation of immunotherapeutic treatment. Both primary and acquired resistance in CRC are predominantly driven by the interplay between tumor-intrinsic mechanisms and the TIME. Even in dMMR/MSI-H CRC, which is considered the most responsive subtype to ICIs, substantial heterogeneity in treatment efficacy persists. Tumor-intrinsic factors include antigen loss or defects in antigen presentation, genetic alterations that promote T-cell exclusion, and intrinsic insensitivity to T-cell-mediated killing. In contrast, extrinsic factors are characterized by the enrichment of immunosuppressive cell populations, persistent expression of immune checkpoint molecules, and a suppressive cytokine milieu. Under therapeutic pressure, acquired resistance may further manifest as T-cell functional exhaustion, antigen downregulation, and immune escape-associated alterations.[4] Therefore, the development of integrative therapeutic strategies that simultaneously target tumor-intrinsic resistance pathways and immunosuppressive networks within the immune microenvironment represents a promising research direction in CRC immunotherapy.

To overcome the generally limited efficacy of immunotherapy in CRC, a wide range of combination immunotherapeutic strategies has been extensively explored. However, in the proficient mismatch repair/microsatellite stable subtype, randomized trials have failed to consistently translate these approaches into durable survival benefits, suggesting that simple combination regimens do not necessarily achieve a substantive transformation of the immune microenvironment. For example, the CheckMate 9X8 trial demonstrated that adding a PD-1 inhibitor to standard chemotherapy and anti-angiogenic therapy did not significantly improve primary survival endpoints.[5] A single-arm phase II study evaluating regorafenib combined with PD-1 blockade has reported modest antitumor signals; however, the magnitude of benefit was limited, and reproducibility remains insufficient, warranting further confirmation in randomized trials.[6]

Therefore, CRC immunotherapy urgently needs clearer, more actionable biomarker frameworks—not just more combination regimens—to identify patients most likely to benefit from immune-based interventions. The high cost and limited efficacy of ICIs render trial-and-error approaches clinically and economically unsustainable, further underscoring the importance of precision stratification. How insights into the immune microenvironment can be translated into validated and generalizable predictive tools to guide therapeutic decision-making remains a critical challenge that urgently needs to be addressed.

The success of immunotherapy in MSI-H CRC has demonstrated that this disease is not intrinsically immune-resistant; rather, its limited efficacy more often arises from failure to simultaneously fulfill key prerequisites, including an intact antigen presentation axis, effective infiltration of effector immune cells, and the sustained maintenance of immune effector functions. Future breakthroughs may lie not in the continual addition of new immune targets but in an immune microenvironment-centered approach that integrates basic research, clinical translation, and therapeutic strategy design to enable a rational understanding and precise intervention of this complex system. Only through such an approach can immunotherapy evolve from delivering benefits to a small subset of patients toward a more reproducible and accessible clinical practice.

Conflict of interest

Xianbin Kong is the Editorial Board Member of this journal and Guest Editor of this special issue, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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