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Mini Review

Mechanisms Underlying Immunotherapy Resistance in Microsatellite-stable Colorectal Cancer

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Abstract

Microsatellite-stable colorectal cancer, which accounts for roughly 80–85% of cases, remains largely refractory to immune checkpoint inhibitors compared with microsatellite instability-high tumors. This review synthesizes current evidence on tumor-intrinsic and microenvironmental mechanisms underlying immune checkpoint inhibitor resistance in microsatellite-stable colorectal cancer—including low neoantigen burden and impaired antigen presentation, activation of Wnt/β-catenin and MAPK signaling that exclude T cells, an immunosuppressive cellular milieu (regulatory T cells, myeloid-derived suppressor cells, M2-like tumor-associated macrophages, cancer-associated fibroblasts), metabolic reprogramming, and gut microbiome dysbiosis—and evaluates translational strategies aimed at overcoming these barriers. Preclinical and early-phase clinical data indicate that rational, mechanism-guided combinations (vascular normalization, myeloid reprogramming, metabolic inhibitors, antigen-priming approaches, and microbiome modulation) can enhance immune infiltration and produce benefits in biomarker-defined subgroups. Moving the field forward will require biomarker-driven, adaptive clinical trials with embedded translational endpoints to optimize patient selection and manage toxicity.

Introduction

Immunotherapy achieves its antitumor effects by activating the host immune system and has shown remarkable success in treating various malignancies.[1] Immune checkpoints are pivotal regulatory molecules that maintain immune homeostasis under physiological conditions by limiting T cell overactivation and proliferation. However, in pathological contexts such as cancer, these checkpoints can be exploited by tumor cells to evade immune detection. When T cell activation is severely suppressed, or when T cells undergo apoptosis, antitumor immune responses are blunted, contributing to the formation of an immunosuppressive tumor microenvironment (TME).

Among current immunotherapeutic strategies, immune checkpoint inhibitors (ICIs) are the most widely implemented in clinical oncology. ICIs function by blocking inhibitory pathways that restrict T cell activation, such as the programmed cell death1 (PD-1)/programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) axes, thereby enabling the immune system to bypass these regulatory "brakes". This results in the reactivation of cytotoxic T lymphocytes (CTLs) capable of recognizing and destroying tumor cells.[2] Despite their success in microsatellite instability-high (MSI-H) colorectal cancer (CRC), the effectiveness of ICIs in microsatellite-stable (MSS) CRC remains limited, prompting intense research into the underlying resistance mechanisms and strategies to overcome them.

CRC accounts for approximately 10% of all malignancies and has now become the second leading cause of cancer-related death worldwide.[3,4] The immunogenic subtype of CRC is closely linked to both the efficacy and durability of immunotherapeutic responses.[5] From the perspective of genomic instability, CRC can be classified into two principal pathways: chromosomal instability, characterized by whole-chromosome or segmental chromosomal alterations, and MSI, defined by insertion or deletion of base pairs within microsatellite regions. MSI arises primarily from defects in the mismatch repair (MMR) system; tumors exhibiting deficient MMR (dMMR) display high tumor mutational burden (TMB) and an abundance of neoantigens,[6] features that facilitate T cell recognition and activation. In contrast, tumors with proficient MMR (pMMR)/MSS status fail to respond to ICIs, likely due to the expression of immunosuppressive factors and a paucity of neoantigens, culminating in a "cold tumor" phenotype. Therefore, eluci-

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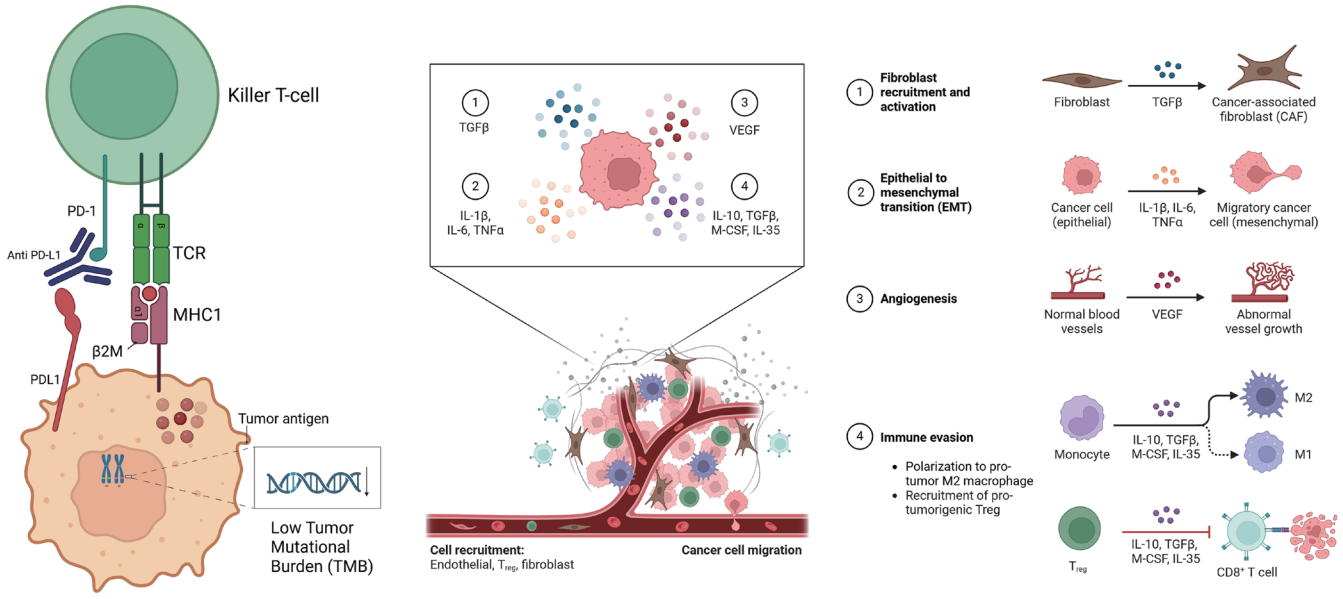

Fig. 1. Mechanisms of immunotherapy resistance in MSS CRC. Created in BioRender.com. (a) Low neoantigen burden results in insufficient T-cell priming and activation. (b) An immunosuppressive tumor microenvironment underlies primary resistance in MSS CRC: ① Monocytes and Macrophages: Monocytes differentiate into distinct macrophage subsets; M2-polarized macrophages foster immune escape and tumor angiogenesis. Regulatory T cells (Tregs): Secrete immunosuppressive cytokines (IL-10, TGF-β), inhibit antitumor T-cell responses, and reprogram the microenvironment via fatty-acid accumulation and metabolic modulation. ② Myeloid-derived suppressor cells (MDSCs): Inhibit natural killer (NK) cell cytotoxicity and IFN-γ production, impairing NK-mediated activation of effector T cells; sustain immunosuppression through lipid-metabolism reprogramming. Neovasculature: Endothelial cells and tumor-associated vessels secrete VEGF, further dampening immune-cell infiltration and function. ③ Cancer-associated fibroblasts (CAFs): Resident fibroblasts, upon TGF-β stimulation, acquire a CAF phenotype that supports tumor growth and immune evasion. ④ Epithelial–mesenchymal transition (EMT): Tumor cells undergo phenotypic conversion, enhancing invasiveness and resistance to immune attack. CRC, colorectal cancer; IFN-γ, interferon-gamma; IL, interleukin; M-CSF, macrophage colony-stimulating factor; MHC1, major histocompatibility complex class I; MSS, microsatellite stable; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; TCR, T-cell receptor; TGF-β, transforming growth factor-beta; TMB, tumor mutational burden; VEGF, vascular endothelial growth factor.

dating the mechanisms underlying the refractoriness of MSS CRC to immunotherapy and exploring potential therapeutic strategies is of paramount importance. This review summarizes the putative mechanisms driving immunotherapy insensitivity in MSS CRC and discusses approaches to enhance antitumor immunity, aiming to convert "cold tumors" into "hot tumors" (Fig. 1).

Low neoantigen expression

Neoantigens are immunogenic peptides derived from tumor-specific mutations that can activate cytotoxic T cells to eliminate cancer cells.[5] They arise via diverse mechanisms—including point mutations, small insertions/deletions, and gene fusions—and are processed within tumor cells into short peptide epitopes that bind to MHC class I or class II molecules for T cell recognition. The overall expression level of these mutation-derived antigens is a critical determinant of the ensuing immune response. Indeed, the median neoantigen burden in MSI-H CRC is roughly 20-fold higher than that observed in MSS CRC.[7,8] In contrast, the vast majority of MSS CRC patients (with the exception of a small hypermutated subset) generate no more than 14 tumor-specific neoantigens, compared to a median of 121 neoantigens in MSI-H tumors.[8] TMB serves as a useful surrogate for neoantigen load—the more mutations per megabase, the greater the probability of novel antigen formation. MSS/pMMR tumors carry an average TMB of only approximately four mutations per megabase, whereas MSI-H/dMMR tumors harbor up to approximately 30 mutations per megabase.[9] This paucity of abnormal proteins and resultant low neoantigen density leads to insufficient T cell priming and activation, representing a primary mechanism by which MSS CRC evades effective immune checkpoint blockade (Fig. 1a).

In the TME, $CD8^+$ T cells are the most potent cytotoxic lymphocytes, exerting antitumor effects by eliminating antigen-expressing target cells. Clinical data have shown that tumors with high $CD8^+$ T cell infiltration also exhibit elevated expression of specific chemokines—such as C-X3-C motif chemokine ligand 1 (CX3CL1), C-X-C motif chemokine ligand 9 (CXCL9), and CXCL10—which correlate with favorable prognosis.[10] Although the precise mechanisms by which neoantigen expression modulates T cell functionality remain incompletely understood, several pathways have been proposed: an insufficient quantity of neoantigens can lead to impaired immediate T cell priming, low-level neoantigen expression may drive progressive T cell exhaustion, and a limited repertoire of neoantigens may hinder effective cross-priming, all of which contribute to suboptimal antitumor immunity in MSS CRC.

Immunosuppressive microenvironment

The immune microenvironment of CRC plays a pivotal role in tumor initiation and progression. The immune system's capacity to recognize and eliminate nascent cancer cells, termed "immune surveillance", was first proposed by Paul Ehrlich; when this function is compromised, unchecked tumor cell proliferation and cancer de-

velopment ensue (Fig. 1b).[11] The cancer immunoediting paradigm delineates three sequential phases: elimination, equilibrium, and escape. During elimination, effector cells of both the innate immune system (e.g., natural killer cells) and the adaptive arm ($CD4^+$ and $CD8^+$ T cells) collaborate to eradicate emerging tumor cells. In the equilibrium phase, a dynamic balance is maintained between immune effectors and residual tumor cells, suppressing tumor growth but allowing the survival of variants with immune-evasive traits. Finally, in the escape phase, tumor cells fully circumvent immune control, enabling unchecked proliferation.[12] Maintenance of immune homeostasis underlies proper immune function, yet in the context of tumorigenesis, this equilibrium is disrupted, leading to dysfunctional immune cell activity within the TME. The CRC TME exerts decisive influence over tumor growth and progression. As one of the most prevalent solid malignancies, CRC displays pronounced heterogeneity and the ability to resist immune attack. Its TME comprises an array of innate immune cells (including natural killer (NK) cells, tumor-associated macrophages (TAMs), dendritic cells (DCs), and mast cells), as well as adaptive immune populations (T and B lymphocytes).[1] Furthermore, the CRC milieu contains various malignant and stromal components, such as transformed epithelial cells, cancer-associated fibroblasts (CAFs), mesenchymal cells, endothelial cells, and cancer stem cells, together forming a complex, immunosuppressive tumor ecosystem.[13]

Immune cell populations within the TME

The immune compartment of the TME is composed chiefly of DCs, macrophages, NK cells, T lymphocytes, B lymphocytes, and other innate immune effectors.[14] These cells orchestrate tumor immune surveillance, with the innate immune system forming the first line of defense against neoplastic transformation. In particular, DCs, macrophages, and NK cells play central roles in initiating and shaping adaptive antitumor responses. NK cells recognize tumor-associated antigens via activating and inhibitory receptors on their surface and exert direct cytotoxicity to curb tumor growth. Numerous clinical studies have demonstrated that high intratumoral densities of NK cells and $CD8^+$ T cells are significantly associated with improved prognosis in CRC patients. Moreover, both the relative abundance and functional status of these immune populations critically influence tumor biology and patient outcomes.[15]

In the adaptive immune response, $CD4^+$ helper T cells and CTLs act in concert to suppress tumor growth, whereas regulatory T cells (Tregs) facilitate immune evasion and tumor progression. CTLs, predominantly $CD8^+$ T cells, serve as the principal antitumor effectors: upon recognition of tumor-derived peptide antigens presented by professional antigen-presenting cells such as DCs, they release perforin and granzymes to induce apoptosis in malignant targets.[16] $CD4^+$ helper T cells not only provide critical signals for CTL priming and differentiation but also secrete cytokines that sustain CTL proliferation, effector function, and the establishment of long-lived memory responses.

Tregs, a specialized subset of $CD4^+$ T cells, normally maintain immune homeostasis by suppressing excessive immune activation; however, in CRC they promote immune evasion through several mechanisms: (1) secretion of anti-inflammatory cytokines such as interleukin (IL)-10 and transforming growth factor-beta (TGF-β), and (2) direct cell–cell interactions mediated by inhibitory surface proteins including CTLA-4 and PD-1.[17] Accumulation of Tregs within the TME correlates strongly with poor prognosis and therapeutic resistance in CRC.[18] Notably, Treg enrichment can counteract the effector T-cell activation induced by ICIs, thereby diminishing their clinical efficacy, a finding that underscores Tregs as a promising intervention target to enhance ICI responses in CRC. Beyond their direct immunosuppressive effects, Tregs further sculpt a highly suppressive TME by promoting the differentiation and expansion of other regulatory populations such as myeloid-derived suppressor cells (MDSCs) and by secreting chemokines like C-C motif chemokine ligand 22 (CCL22) to recruit additional Tregs, tumor-associated macrophages, and tolerogenic DCs to the tumor site.[19] Given their central role in tumor immune escape and therapy resistance, multiple strategies to target Tregs, ranging from depletion and functional reprogramming to blockade of key cytokine signals such as TGF-β, are currently under development, with the goal of bolstering antitumor immunity and improving outcomes for CRC patients undergoing immunotherapy.

Tumor-promoting features of the immunosuppressive microenvironment

The TME of CRC harbors multiple immunosuppressive cell populations—including Tregs, TAMs, MDSCs, and CAFs—that collectively drive tumor progression and immune escape. $FoxP3^+$ Tregs, a key TME component, not only express immune checkpoint molecules such as CTLA-4, PD-1, and lymphocyte-activation gene 3 but also secrete immunosuppressive cytokines including IL-10, TGF-β, and IL-35, thereby creating a protumorigenic niche.[20] Emerging evidence highlights the IL-33/ST2 signaling axis as a critical regulator of Treg activation and TME remodeling, potentially explaining the aberrant accumulation of Tregs in CRC.[29] Notably, the density of $FoxP3^+$ Tregs in early-stage CRC may serve as a prognostic biomarker, reflecting their central role in shaping an immunosuppressive milieu that fosters tumor growth and therapeutic resistance.

Macrophages within the TME exhibit remarkable plasticity, polarizing into two functional phenotypes: classically activated M1 macrophages, which secrete pro-inflammatory cytokines and exert antitumor effects, and alternatively activated M2 macrophages, which promote tumor growth and metastasis.[21] TAMs predominantly resemble the M2 phenotype; in the CRC microenvironment, they not only enhance tumor invasion and dissemination but also establish an immunosuppressive milieu by inhibiting M1 macrophage–mediated cytotoxicity and impairing T-cell function.[22]

MDSCs are a heterogeneous population of immature myeloid cells that serve as central regulators of tumor immune escape by suppressing antitumor responses. They are broadly categorized into two subsets based on origin: monocytic MDSCs and polymorphonuclear MDSCs.[23] Clinical studies have demonstrated that peripheral blood levels of monocytic MDSCs are significantly elevated in CRC patients compared to healthy controls, correlating closely with disease progression and poor prognosis.[24] Recruitment of MDSCs into the TME is chiefly driven by chemokines such as CCL2 produced by tumor cells, stromal elements, and other immune populations; these factors not only attract MDSCs but also potentiate their suppressive functions, thereby fostering tumor growth and immune evasion.[25] Within the TME, MDSCs inhibit T-cell activity through multiple mechanisms: (1) generation of reactive oxygen species, nitric oxide, and arginase-1 to directly impair T-cell activation and proliferation; (2) promotion of Treg expansion; and (3) interference with antigen presentation. Given the positive association between MDSC abundance, advanced disease stage, and resistance to immunotherapy, MDSCs have emerged as potential prognostic biomarkers in CRC.[26] Therapeutic strategies targeting MDSCs, such as blockade of the CCL2 axis, depletion of MDSC populations, or reprogramming them toward a pro-inflammatory phenotype, offer promising avenues to enhance

antitumor immunity and improve clinical outcomes in CRC.

CAFs, a major non-immune cell component within the TME, play a pivotal role in tumor progression. Under stimuli such as TGF-β signaling and p53 mutations, quiescent fibroblasts are reprogrammed into activated CAFs.[27] These CAFs not only engage in crosstalk with immunosuppressive populations—such as Tregs, TAMs, and MDSCs—but also directly inhibit the cytotoxic functions of CTLs and NK cells. Notably, the degree of CAF activation in the CRC microenvironment correlates strongly with local TGF-β levels, underscoring their central role in establishing an immunosuppressive niche and offering new insights into the mechanisms by which the TME thwarts effective antitumor immunity.[28]

Tumor-associated neutrophils (TANs) differentiate and expand in response to IL-8 and TGF-β within the TME, accelerating disease progression by promoting angiogenesis and tumor growth.[29] TANs exert protumorigenic effects through multiple mechanisms: (1) secretion of matrix metalloproteinase-9 to degrade extracellular matrix and facilitate invasion and metastasis; (2) upregulation of vascular endothelial growth factor (VEGF), a key driver of neovascularization that supplies oxygen and nutrients to malignant cells; and (3) induction of hepatocyte growth factor expression, which activates oncogenic signaling pathways involved in tumor proliferation, survival, and epithelial–mesenchymal transition, thereby enhancing invasiveness and distant dissemination.[30] Neutrophil extracellular traps (NETs)—web-like structures composed of chromatin fibers and neutrophil proteins—represent another critical mechanism by which TANs promote CRC progression.[31] NETs provide a supportive scaffold for cancer cells, shield them from immune attack, and augment tumor cell adhesion, migration, and metastasis. Recent preclinical studies demonstrate that degrading NETs with DNase I significantly inhibits tumor growth and spread (DNase I → NET clearance; NET formation targeting), highlighting a promising therapeutic avenue for CRC intervention.[32] Given the multifunctional and context-dependent roles of TANs, strategies aimed at reprogramming or depleting these cells, inhibiting NET formation, or blocking key protumor factors such as VEGF and hepatocyte growth factor hold potential to improve clinical outcomes in CRC.

Angiogenesis

Following tumor onset, the angiogenic process must supply sufficient oxygen and nutrients to sustain rapid cancer cell proliferation—a function largely driven by VEGF. By binding to VEGF receptors (hereinafter referred to as VEGFRs) on endothelial cells, VEGF not only stimulates neovascularization and endothelial cell migration but also acts as a potent immunosuppressive mediator.[33] First, VEGF/VEGFR signaling directly impairs antitumor immunity by blocking the differentiation of monocytes into DCs. Second, VEGF compromises effector T-cell function: it inhibits progenitor differentiation into $CD4^+$ and $CD8^+$ lymphocytes, and it reduces endothelial adhesion molecule expression, thereby hindering T-cell adhesion to vessel walls and limiting their recruitment into tumors—adhesion being essential for immune cell infiltration.[34] In MSS CRC, VEGF-A further promotes T-cell exhaustion by upregulating TOX protein. Moreover, VEGF increases the abundance of Tregs and MDSCs within the TME; Tregs suppress effector T cells, while MDSCs enhance Treg expansion, secrete IL-10, and produce reactive oxygen species to facilitate immune escape.[33] Finally, VEGF drives TAM infiltration. TAMs, which polarize into pro-inflammatory M1 or anti-inflammatory M2 phenotypes, are predominantly M2 in CRC; these M2-like TAMs overproduce VEGF to further fuel angiogenesis and accumulate extensively in colorectal tumors, thereby accelerating tumor growth and metastasis.[34]

Wnt/β-catenin signaling and T-cell infiltration

Activation of the Wnt/β-catenin pathway is frequently associated with poor intratumoral T-cell infiltration.[35] In melanoma, pathway activation impairs recruitment of $CD103^+$ DCs, leading to defective T-cell priming, T-cell exclusion, and resistance to immunotherapy.[36] Similarly, in CRC, Wnt/β-catenin signaling upregulates activating transcription factor 4, which suppresses CCL3 production by Batf3-dependent $CD103^+$ DCs, thereby reducing $CD8^+$ T-cell activation and tumor infiltration.[37] IL-1β may further enhance β-catenin activity in CRC cells via phosphorylation of GSK3β, and the epithelial–mesenchymal transition-associated transcription factor Snail can stimulate macrophages to secrete IL-1β, creating a feed-forward loop.[38] MSS CRC exhibits higher β-catenin expression than MSI-H tumors, contributing to its "cold" phenotype. Additionally, Wnt/β-catenin signaling promotes the survival of Tregs, which further reinforces immune suppression and facilitates tumor progression.

Tumor metabolism

In CRC, tumor cells engage in aerobic glycolysis to produce copious amounts of lactate, leading to acidification of the TME. This acidic milieu impairs the function of immune effector cells such as NK cells and $CD8^+$ CTLs, thereby weakening their capacity to clear malignant cells.[39] Excess lactate also skews TAMs toward an M2-like phenotype, which promotes tumor progression via activation of the CD47–signal regulatory protein αaxis.[40] Amino acid metabolism, particularly tryptophan catabolism, similarly plays a pivotal role in modulating antitumor immunity in CRC. Enhanced indoleamine-2,3-dioxygenase (IDO) activity leads to increased tryptophan breakdown, fostering expansion of immunosuppressive Tregs and bolstering tumor cell survival.[41] A comprehensive understanding of these metabolic alterations and their effects on TME components will be crucial for the development of novel therapeutic strategies aimed at improving outcomes in CRC.

Lactate metabolism

Tumor cells frequently engage in aerobic glycolysis—even under normoxic conditions—to meet their energetic and biosynthetic demands, a phenomenon known as the *Warburg effect*.[42] In this process, glucose is converted to lactate, which not only serves as an alternative energy substrate but also acidifies the TME, thereby impairing the function of infiltrating immune cells and promoting tumor invasiveness and immune evasion.[43] Beyond its role as a metabolite, lactate critically modulates the behavior of monocytes and macrophages within the TME. For example, lactate substantially inhibits human macrophage secretion of TNF and IL-1β in response to Mycobacterium tuberculosis, creating a negative feedback loop that dampens glycolytic flux and downstream pro-inflammatory cytokine production.[44] Furthermore, lactate and the associated proton load act as immunosuppressive regulators, skewing macrophage polarization toward an M2-like phenotype characterized by anti-inflammatory mediator release and tissue-repair functions.[45] Macrophage polarization is tightly linked to metabolic programming: M1 macrophages rely predominantly on aerobic glycolysis to fuel pro-inflammatory responses, whereas M2 macrophages depend mainly on oxidative phosphorylation and fatty acid oxidation to support tissue-remodeling and immunosup-

pressive activities. In the context of MSS CRC, persistent lactate production sustains this immunosuppressive axis, undermining effective antitumor immunity and contributing to resistance against immune checkpoint blockade. Thus, targeting lactate generation (e.g., via inhibition of lactate dehydrogenase (LDH)) or buffering intratumoral acidosis may restore macrophage antitumor functions and enhance the efficacy of immunotherapies in MSS CRC.[46] In summary, tumor-derived lactate and the resulting acidosis establish an immunosuppressive milieu by inhibiting NK and $CD8^+$ T-cell function and by skewing macrophages toward an M2 phenotype. Therapeutic strategies that limit lactate production (e.g., LDH inhibitors), block lactate transport (monocarboxylate transporter 1/4 (MCT1/4) inhibitors), or buffer intratumoral pH may reverse macrophage polarization and restore effector functions, thereby improving ICI responsiveness in MSS CRC.

Amino acid metabolism

Metabolic reprogramming of amino acid pathways in cancer cells fosters an immunosuppressive TME and facilitates immune escape, thereby driving tumor progression.[47] For example, genetic ablation of glutaminase (GLS) or methionine adenosyltransferase IIα (MAT2A) in murine tumor models enhances T-cell–mediated tumor control, underscoring the role of glutamine and methionine metabolism in regulating antitumor immunity.[48,49] Tumor cells commonly overexpress the methionine transporter SLC43A2, effectively outcompeting T cells for extracellular methionine and impairing their proliferative capacity.[50] Likewise, hyperactivation of IDO leads to accumulation of kynurenine, which promotes local immunosuppression by directly inhibiting effector T-cell function and inducing regulatory T-cell differentiation.[51]

Tryptophan is an essential amino acid whose availability in the TME critically influences T-cell reactivity and antitumor efficacy. Many tumors upregulate IDO, catalyzing the degradation of tryptophan into kynurenine and depleting local tryptophan pools. This enzymatic activity not only starves effector T cells of a key nutrient but also generates immunomodulatory metabolites that further suppress immune surveillance. Clinical studies in CRC have revealed that reduced serum tryptophan levels correlate with markers of immune activation, diminished quality of life, and accelerated disease progression, highlighting the multifaceted impact of tryptophan metabolism on patient outcomes.[52] Collectively, these findings suggest that targeting amino acid-metabolizing enzymes—such as GLS, MAT2A, or IDO—or modulating transporters like SLC43A2 may restore nutrient availability for effector T cells and dismantle tumor-induced immunosuppression. Such strategies hold promise for overcoming resistance to ICIs in MSS CRC. In summary, dysregulated tryptophan, methionine, and glutamine pathways create a nutrient-depleted and metabolite-rich TME that suppresses effector T cells and expands regulatory populations. Candidate translational targets include IDO1/TDO2 (tryptophan catabolism), MAT2A (methionine metabolism), GLS (glutaminolysis), and transporters such as SLC43A2. Combining metabolic inhibitors with ICIs warrants further clinical testing with appropriate pharmacodynamic readouts.

Branched-chain amino acid (BCAA) metabolism has likewise emerged as a crucial regulator of tumor immunity across multiple malignancies, including hepatocellular carcinoma, breast cancer, pancreatic ductal adenocarcinoma, and non–small cell lung cancer.[53,54] Tumor cells often upregulate BCAA transporters to secure an abundant supply of leucine, isoleucine, and valine. Importantly, BCAAs modulate immune cell differentiation and effector function: in mice with defective BCAA catabolism, intracellular BCAA accumulation within $CD8^+$ T cells drives their hyperactivation and enhances antitumor responses.[55] Beyond T cells, BCAAs support neutrophil and NK-cell activity and influence monocyte differentiation, indicating a broad immunoregulatory potential. Central to these effects is the mammalian target of rapamycin kinase, which senses BCAA availability—particularly leucine—via the SLC7A5 transporter to orchestrate T-cell differentiation and cytokine production.[56] Collectively, these insights suggest that targeting key enzymes (e.g., GLS, MAT2A, IDO1) or transporters (e.g., SLC43A2, SLC7A5) involved in amino acid and BCAA metabolism may restore nutrient availability for effector lymphocytes and dismantle tumor-induced immunosuppression, offering promising strategies to overcome resistance to immune checkpoint blockade in microsatellite-stable CRC. In summary, BCAA metabolism modulates mammalian target of rapamycin signaling and multiple immune cell subsets ($CD8^+$ T cells, NK cells, neutrophils). Targeting key nodes of BCAA sensing (e.g., SLC7A5/SLC3A2 transporters or BCAT enzymes) could rebalance intratumoral nutrient competition and potentiate immunotherapy; however, careful preclinical-to-clinical translation is needed given the systemic roles of BCAAs.

Role of immunotherapy in recurrent disease

Immunotherapy plays a clearly defined role in recurrent CRC that depends critically on tumor molecular subtype.[57] For recurrent MSI-H/dMMR disease, ICIs now represent a standard of care in many settings: these tumors, by virtue of high TMB and abundant neoantigens, demonstrate reproducible, durable responses to PD-1 blockade and to PD-1/CTLA-4 combinations reported in pivotal trials. By contrast, recurrent MSS/pMMR tumors, which account for the majority of recurrent CRC, remain largely refractory to ICI monotherapy because of low neoantigen burden, impaired antigen presentation, and an immune-excluded TME. Nonetheless, the recurrent setting presents several translationally tractable opportunities. Mechanism-based combinations have produced occasional objective responses in early-phase series of recurrent MSS disease, suggesting that local microenvironmental remodeling can sensitize some recurrent lesions to immunotherapy.[58] In addition, integration of local-regional therapies (surgical resection, stereotactic radiotherapy, thermal ablation) with systemic ICIs can increase tumor antigen release and cross-priming, providing a rational basis for combined-modality strategies in the oligorecurrent setting.[59] Early clinical experiences, while encouraging in selected patients, remain limited in scale and require prospective validation.

From a translational perspective, the recurrent disease context is particularly amenable to biomarker-guided immunotherapeutic deployment. Minimal residual disease monitoring by circulating tumor DNA (ctDNA) can identify high-risk patients after definitive therapy who may benefit from adjuvant immunotherapy or early combinatorial intervention, while longitudinal tissue or liquid biopsies of recurrent lesions permit dynamic assessment of tumor immune composition and emergent resistance mechanisms.[60,61] Adoptive cellular therapies (e.g., tumor-infiltrating lymphocytes, engineered T-cell receptor/chimeric antigen receptor constructs) and personalized neoantigen vaccine approaches are also being explored in heavily pretreated and recurrent CRC and could offer alternative paths when checkpoint blockade alone is ineffective.[62] Taken together, although immunotherapy has an established and durable benefit in recurrent MSI-H disease, extending similar success to recurrent MSS CRC will likely require rigorous biomarker-driven trial designs, rationally sequenced or staged combination regimens, and embedding of translational endpoints (serial biop-

sies, ctDNA, immune and microbiome profiling) to identify the patients most likely to benefit and to clarify mechanisms of response and resistance.

Gut microbiota and immunotherapy response in MSS CRC

The gut microbiota exerts profound and multifaceted effects on host antitumor immunity, and perturbations of this ecosystem can tip the balance toward an immunosuppressive TME that undermines ICI efficacy. Multiple lines of evidence, from mechanistic preclinical work to clinical correlation and interventional studies, support a causal role for the microbiome in determining ICI outcomes.[63]

Certain bacterial taxa have been repeatedly associated with better ICI outcomes, while other species linked to CRC progression—most notably *Fusobacterium nucleatum*—are associated with local immune suppression and worse prognosis.[64] Enrichment of beneficial taxa correlates with improved antigen presentation, more robust $CD8^+$ T-cell infiltration, and greater systemic immune activation; conversely, *Fusobacterium nucleatum* and related pathobionts can promote myeloid-driven immunosuppression, inhibit cytotoxic responses, and even confer chemoresistance in CRC.[65] These taxon-level associations provide biologic plausibility for microbiome-based biomarkers and targets in MSS CRC.

Microbiota-derived small molecules mediate many of the microbiome's immune effects. Short-chain fatty acids (SCFAs), such as butyrate and propionate, influence T-cell and myeloid cell function—SCFAs can promote regulatory T-cell differentiation and modulate DC maturation, but they may also support antitumor $CD8^+$ memory programs in certain contexts; the net effect depends on concentration, systemic exposure, and tumor context.[66,67] Elevated systemic SCFA levels have, in some studies, been associated with reduced efficacy of CTLA-4 blockade through enhancement of Treg programs.[67] Separately, microbiota-derived tryptophan metabolites (indoles and kynurenine pathway derivatives) activate the aryl hydrocarbon receptor in tumor-associated macrophages and other myeloid cells, skewing them toward immunosuppressive phenotypes and impairing antitumor immunity.[68] Together, these metabolite pathways create a metabolically instructed TME that can blunt ICI responses.

Observational meta-analyses and cohort studies have consistently found that broad-spectrum antibiotic exposure around the time of ICI initiation is associated with worse progression-free and overall survival—consistent with antibiotic-induced dysbiosis diminishing ICI effectiveness.[69] Conversely, interventional studies have shown that fecal microbiota transplantation (FMT) from ICI responders can restore or enhance anti-PD-1 activity in ICI-refractory patients, providing direct translational proof of principle that modulating the microbiome can change therapeutic outcomes.[70] These clinical data motivate microbiome-centered trials in MSS CRC, although CRC-specific trials are still relatively limited and require careful safety, donor screening, and regulatory oversight. Therapeutic strategies under study include FMT from ICI responders, defined probiotic consortia, dietary or prebiotic modulation, targeted antibiotics to remove pathogenic species, and engineered commensals that deliver immunomodulatory payloads. Key challenges include interindividual variability in baseline microbiomes, reproducibility of beneficial taxa across cohorts, the complexity of microbe–metabolite–host interactions, safety (especially for FMT in immunocompromised patients), and regulatory hurdles.[71,72] For MSS CRC specifically, future clinical trials should integrate longitudinal microbiome and metabolome profiling, on-treatment tumor biopsies, and mechanistic correlative studies to identify which microbiome-modifying interventions are most likely to sensitize tumors to ICIs.

Clinical prospects and challenges

In recent years, multi-modal combination strategies have emerged as the most promising translational avenue for overcoming the profound immune resistance of MSS CRC (Table 1).[52,73–89] Broadly speaking, these approaches fall into several complementary classes. First, combining ICIs with anti-angiogenic agents or small-molecule kinase inhibitors aims to normalize tumor vasculature and thereby improve lymphocyte trafficking; exploratory clinical studies of such regimens in advanced MSS CRC have demonstrated manageable safety and objective responses in selected patients, supporting further evaluation in biomarker-defined cohorts.[90] Second, targeting immunosuppressive myeloid and stromal pathways can reprogram tumor-associated macrophages and weaken physical and biochemical stromal barriers, with several agents already in early-phase or platform combination trials.[91] Third, metabolic and antigen-enhancement strategies, such as blockade of IDO1/tryptophan catabolism, inhibition of GLS or LDH/MCT-mediated pathways, and antigen-priming approaches (radiotherapy, oncolytic viruses, or personalized neoantigen vaccines), have shown in preclinical models the capacity to restore antigen presentation or relieve metabolite-driven suppression and may produce clinically meaningful benefit when rationally paired with ICIs in molecularly selected subgroups.[92] Finally, manipulation of the gut microbiome represents a systemically pliable adjunct that has yielded encouraging early signals for potentiating ICI responses—an approach with particular biological plausibility in CRC given the anatomical proximity of tumor and microbiota. Collectively, these multi-targeted, stratified combinations offer feasible routes to convert "cold" MSS tumors into immunologically inflamed lesions, but their broad clinical validation will require carefully designed, biomarker-driven trials, adaptive platform designs, and integrated translational endpoints to establish reproducibility and define the patients most likely to benefit.

Although the strategies outlined above are promising, their clinical translation faces several pivotal challenges that must be addressed in future trial designs. First, some combinations underpinned by clear biological rationale have faltered in large randomized trials or delivered disappointing efficacy. For example, the IDO1 inhibitor epacadostat, when paired with pembrolizumab in the phase III ECHO-301/KEYNOTE-252 trial, failed to improve progression-free survival compared with pembrolizumab alone, casting doubt on the blanket scaling of early signals directly to large trials.[93] Such failures underscore the necessity of rigorous optimization of target engagement, dosing, and treatment sequencing, as well as the importance of selecting the right patient populations before embarking on large trials. Second, combination therapies often carry added toxicity burdens and complex safety management.[94] Immune-related adverse events may overlap or synergize with the adverse effects of targeted or metabolic agents, necessitating careful assessment of dose tolerability, administration timing, and robust guidelines for discontinuation or dose modification. Third, many promising observations to date stem from small, non-randomized trials or cohorts with substantial heterogeneity, limiting confidence in generalizability. Thus, future efforts should emphasize randomized or adaptive trials stratified by predictive biomarkers and incorporate longitudinal translational endpoints (serial biopsies, ctDNA, immunogenomics, metabolomics,

Table 1. Potential therapeutic strategies to overcome immunotherapy resistance in MSS CRC

Primary resistance mechanism	Target/pathway	Interventional strategy	Representative agents/approaches	References
Low TMB	Tumor antigenicity	Increase antigenicity / prime immunity	Radiotherapy, oncolytic viruses, personalized neoantigen vaccines	73
Antigen-presentation defects	MHC I, TAP, β2-microglobulin; DC activation	Restore presentation/ enhance DC cross-priming	STING agonists, TLR agonists, DC vaccines, CD40 agonists	74
Immune checkpoints	PD-1/PD-L1, CTLA-4, LAG-3, TIGIT	Checkpoint blockade; rational combinations	Pembrolizumab, nivolumab, ipilimumab, relatlimab, anti-TIGIT mAbs	75
Immunosuppressive myeloid cells	CSF1R, CCR2/CCL2, CXCR2, IL-6	Deplete or reprogram TAMs/MDSCs	CSF1R inhibitors, CCR2 antagonists, CXCR2 inhibitors, anti-IL-6	76
Tregs	CD25, CTLA-4, IL-2 pathway	Treg depletion/modulation	Anti-CD25, low-dose cyclophosphamide, anti-CTLA-4 strategies	77
Tumor vasculature/ immune exclusion	VEGF/VEGFR	Vascular normalization to enable infiltration	Bevacizumab, VEGFR TKIs	78
Stromal/CAF/ TGF-β barrier	TGF-β, CAF signaling, CXCL12	Stromal modulation/ ECM remodeling	Anti-TGF-β agents, CAF targeting, CXCR4/CXCL12 blockers	79
Wnt/β-catenin signaling	Wnt pathway, PORCN, β-catenin	Inhibit Wnt signaling to improve T-cell recruitment	PORCN inhibitors, β-catenin pathway modulators	80
Lactate/acidosis	LDH, MCT1/4, proton pumps	Reduce lactate production/ transport; buffer pH	LDH inhibitors, MCT inhibitors, alkalinizing strategies	81
Tryptophan catabolism	IDO1, TDO2, kynurenine	Block tryptophan→kynurenine pathway	Epacadostat, navoximod	82
Glutamine/methionine metabolism	GLS, MAT2A, SLC43A2	Inhibit tumor nutrient metabolism; restore T-cell access	GLS inhibitors, MAT2A inhibitors, SLC43A2 targeting	52
NETs	PAD4, NET formation	Inhibit NETs to reduce protumor inflammation	PAD4 inhibitors, DNase therapies	83
IL-33/ST2 axis	IL-33/ST2 signaling	Block pro-tumor alarmin signaling	Anti-IL-33 or anti-ST2 biologics	84
Microbiome dysbiosis	Gut microbial composition/metabolites	Microbiome modulation to boost systemic & local immunity	FMT, defined probiotics, dietary interventions	85
Adoptive & cellular therapies	Tumor antigens, TCR/CAR targets	Supply or engineer effector cells	TIL therapy, CAR-T, engineered TCRs	86
Combination metabolic + ICI	Multi-node metabolic targeting	Combine metabolic inhibitors with ICIs	MCT1/4 + anti-PD-1; GLS + ICI; IDO1 + ICI	87
Immune-priming local therapies	Tumor antigen release	Local therapy to increase antigen availability	SBRT, thermal ablation, intratumoral oncolytic viruses	88
Biomarker-guided MRD	ctDNA, immune signatures	Use MRD to select adjuvant/ early intervention	ctDNA-guided trials + ICI	89

CAF, cancer-associated fibroblast; CAR, chimeric antigen receptor; CCL2, C-C motif chemokine ligand 22; CCR2, C-C motif chemokine receptor 2; CRC, colorectal cancer; CSF1R, colony-stimulating factor 1 receptor; ctDNA, circulating tumor DNA; CTLA-4, cytotoxic t-lymphocyte–associated protein 4; CXCL12, C-X-C motif chemokine ligand 12; CXCR2, C-X-C chemokine receptor 2; DC, dendritic cell; ECM, extracellular matrix; FMT, fecal microbiota transplantation; GLS, glutaminase; ICI, immune checkpoint inhibitor; IDO1, indoleamine 2,3-dioxygenase 1; IL, interleukin; LAG-3, lymphocyte-activation gene 3; LDH, lactate dehydrogenase; MAT2A, methionine adenosyltransferase 2A; MCT, monocarboxylate transporter; MDSCs, myeloid-derived suppressor cells; MHC I, major histocompatibility complex class I; MRD, minimal residual disease; MSS, microsatellite stable; NET, neutrophil extracellular trap; PAD4, peptidylarginine deiminase 4; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; PORCN, porcupine O-acyltransferase; SBRT, stereotactic body radiation therapy; SLC43A2, solute carrier family 43 member 2; TAMs, tumor-associated macrophages; TAP, transporter associated with antigen processing; TCR, T-cell receptor; TDO, tryptophan 2,3-dioxygenase; TGF-β, transforming growth factor-beta; TIGIT, T-cell Immunoreceptor with Ig and ITIM domains; TKI, tyrosine kinase inhibitor; TLR, Toll-like receptor; TMB, tumor mutational burden; Tregs, regulatory t cells; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

microbiome analysis) to elucidate mechanisms of response and resistance. Finally, for microbiome-based interventions in particular, safety, donor screening, and regulatory compliance remain significant barriers to large-scale deployment. Taken together, we recommend adopting a "mechanism–biomarker–stratified" paradigm, prioritizing combinations that have demonstrated clear immunologic effects in preclinical or window-phase clinical settings and that maintain a controllable safety profile, while embedding phar-

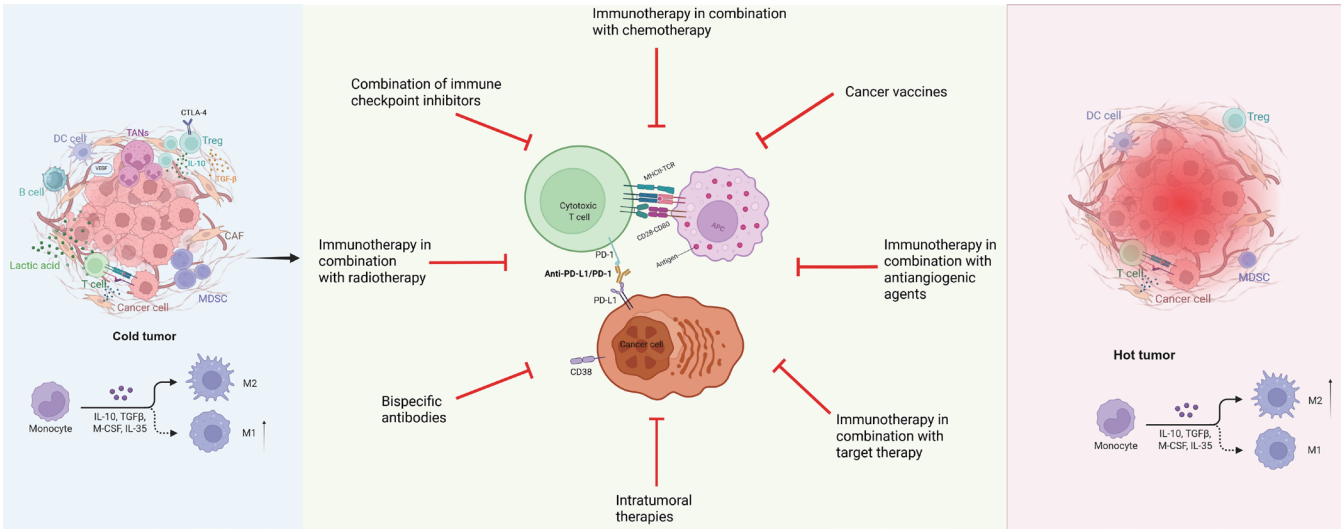

Fig. 2. Strategies to convert immunologically "cold" MSS CRC into "hot" tumors. Chemotherapy, cancer vaccines, anti-angiogenic agents, dual immune checkpoint blockade, radiotherapy, bispecific antibodies, targeted therapies, and intratumoral therapies—each aiming to perturb distinct resistance mechanisms to convert "cold" MSS CRC into an immune-responsive or "hot" tumor. CAF, cancer-associated fibroblast; CRC, colorectal cancer; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; DC, dendritic cell; IL, interleukin; M-CSF, macrophage colony-stimulating factor; MDSC, myeloid-derived suppressor cell; MSS, microsatellite stable; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; TAN, tumor-associated neutrophil; TGF-β, transforming growth factor-beta.

macodynamic and biomarker validations early in development to elevate the success rate of subsequent randomized trials and accelerate translation of feasible combinations into clinical practice.

Future prospects

Future immunotherapeutic strategies for MSS CRC must embrace multi-targeted combination approaches to overcome the multifaceted resistance mechanisms. One promising direction is targeting immunosuppressive cell populations within the TME. In addition to well-established immunosuppressive cell populations such as Tregs, MDSCs, and TAMs, emerging targets like the IL-33/ST2 axis, NET formation, and the Wnt/β-catenin signaling pathway also exhibit significant regulatory potential.[95–97] Small-molecule inhibitors or monoclonal antibodies directed at these pathways, if effective in reprogramming the TME, hold promise for enhancing T-cell infiltration and function. For instance, blocking CCL2 can inhibit MDSC recruitment, while targeting IL-33 may suppress Treg activation or reprogram their function to relieve local immunosuppression.[98] Metabolic reprogramming is another crucial avenue—therapies that inhibit lactate transporters (MCT1/4) may alleviate TME acidification, and combining IDO inhibitors can disrupt the tryptophan catabolism pathway, thereby restoring effector T-cell cytotoxicity.[99] Inhibiting the Wnt/β-catenin pathway using small molecules such as PORCN inhibitors has the potential to reinstate DC–mediated antigen presentation and enhance T-cell infiltration.[100] Although modulation of the gut microbiota has shown early promise for augmenting ICI responses, its safety, standardization, and personalized application remain key priorities for future research. Rigorous donor screening protocols and regulatory frameworks must be established, and mechanistic studies are needed to elucidate how microbiome interventions synergize with CRC immunotherapy. Meanwhile, targeting metabolic nodes such as lactate metabolism, amino acid uptake, and catabolism can alleviate nutrient competition and metabolic suppression within the TME, thereby helping to restore effector T-cell function.[101] Additionally, combining anti-angiogenic agents with ICIs may normalize tumor vasculature and improve immune cell trafficking into the tumor core. Integrating advances from basic immunology and translational oncology holds great promise for overcoming the current therapeutic bottlenecks in MSS CRC, ultimately leading to more durable clinical benefits and prolonged survival for patients.

Conclusions

Immunotherapy resistance in MSS CRC arises from a complex interplay between intrinsic tumor characteristics and the immunosuppressive TME. The low TMB of MSS CRC limits neoantigen production, impairs T-cell recognition and activation, and creates a "cold tumor" phenotype. Immunosuppressive populations, such as Tregs, MDSCs, and TAMs, secrete IL-10 and TGF-β, compete for essential metabolites like arginine and tryptophan, and expand regulatory networks that directly inhibit effector T-cell function. CAFs and NETs reinforce immune exclusion by remodeling the extracellular matrix, promoting angiogenesis, and blocking lymphocyte infiltration. Metabolic reprogramming also plays a central role in resistance mechanisms. Overactivation of Wnt/β-catenin signaling impairs recruitment of $CD103^+$ DCs and CCL3 secretion, further hindering T-cell trafficking into tumors. VEGF not only drives neovascularization but also subverts antitumor immunity by blocking DC differentiation, inducing T-cell exhaustion, and recruiting suppressive cell subsets, resulting in a multidimensional immune-escape network. A variety of combination and next-generation immunotherapeutic strategies, including chemotherapy- or targeted therapy–based regimens, anti-angiogenic and radiotherapy combinations, dual checkpoint blockade, cancer vaccines, bispecific antibodies, and intratumoral immune-activating approaches, are being developed to remodel the TME, enhance antigen presentation, and overcome immune resistance in MSS CRC (Fig. 2). A deeper mechanistic understanding of these intertwined

pathways will be critical for devising combination therapies that convert "cold" MSS CRC into "hot" tumors amenable to durable immunotherapeutic responses.

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Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

Study concept and design (JD, XZ), acquisition of data (JD, XZ), drafting of the manuscript (JL, XZ), critical revision of the manuscript for important intellectual content (XZ), administrative, technical, or material support (XZ), and study supervision (XZ). All authors have made significant contributions to this study and have approved the final manuscript.

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