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Cancer Immunotherapy COMMENTARY

How does the probiotic empower immunotherapy for colorectal cancer?

Wen-Di Liu,[1] Jielin Wang,[2] and Yi-Zhou Gao[1,*]

[1]Department of Environmental Hygiene, School of Public Health, Harbin Medical University, Harbin 150081, China

[2]Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200336, China

*Correspondence: gaoyizhou@yeah.net

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Colorectal cancer (CRC) is one of the most prevalent malignancies and a leading cause of cancer-related mortality worldwide. The advent of immune checkpoint blockade (ICB) therapy has revolutionized the treatment landscape of CRC. By targeting immune checkpoint molecules such as programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), this therapy relieves the immunosuppression exerted by tumor cells, yielding remarkable efficacy in CRC patients with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR). Currently, the combination of probiotics and immune checkpoint inhibitors in the treatment of colorectal cancer has become a research focus. Studies have confirmed that gut microbiota can regulate the tumor immune microenvironment (TIME), and probiotics can enhance the efficacy of immune checkpoint inhibitors by reshaping gut microbial structure and modulating immune cell functions. However, a core clinical dilemma persists: over 85% of CRC patients belong to the microsatellite-stable (MSS) subtype. Characterized by low mutation burden and insufficient immune cell infiltration, these "cold tumors" exhibit a response rate of less than 5% to current ICB therapies, posing a critical bottleneck hindering breakthroughs in CRC immunotherapy.

Against this backdrop, a 2025 study published in *Cancer Cell* by Xie et al.,[1] entitled "Tumor-resident probiotic *Clostridium butyricum* improves a PD-1 efficacy in colorectal cancer models by inhibiting IL-6-mediated immunosuppression," for the first time revealed the groundbreaking value of the human gut probiotic *Clostridium butyricum* in CRC immunotherapy. This probiotic can remodel the tumor immune microenvironment via specific molecular mechanisms while enhancing the sensitivity of both microsatellite instability-high (MSI-H) and microsatellite stable (MSS), the two core CRC subtypes, to PD-1 inhibitors. The study not only established a molecular model delineating the interactions among probiotics-tumor cells-immune cells but also provided an important paradigm for the clinical translation of microbe-assisted tumor immunotherapy.

The core innovation of this study lies in the identification of a specific interaction between SecD, a surface protein of *Clostridium butyricum*, and glucose-regulated protein 78 (GRP78), a surface receptor on colorectal cancer cells (Figure 1A). This binding abolishes the pro-tumorigenic function of GRP78 by directly blocking the PI3K-AKT-NF-κB core oncogenic signaling pathway in CRC cells (Figure 1B), thereby leading to a significant reduction in the secretion of the immunosuppressive cytokine interleukin-6 (IL-6). As a key molecule that inhibits $CD8^+$ T cell activity and induces M2 polarization of tumor-associated macrophages (TAMs), the reduction of IL-6 directly activates the function of cytotoxic $CD8^+$ T lymphocytes (CTLs) (Figure 1C).

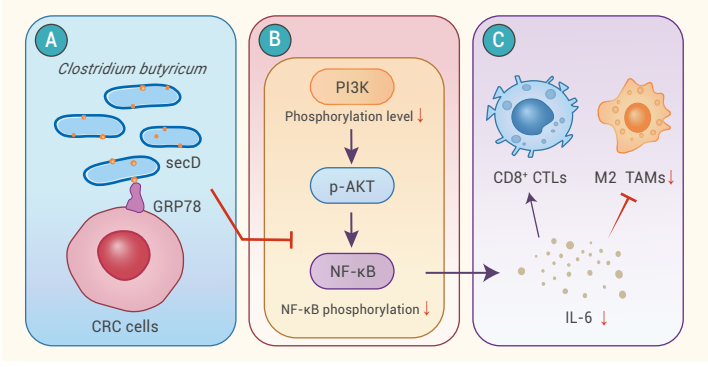

Figure 1. A molecular model of the direct interaction between probiotics and tumor cells (A) Specific binding of *Clostridium butyricum* surface protein SecD to CRC cell surface receptor GRP78. (B) Specific binding directly inhibits core oncogenic signaling in CRC cells. (C) Reduced IL-6 secretion directly alleviates immunosuppression and activates CTLs' function.

In addition, butyrate secreted by *Clostridium butyricum* can further activate CTLs, and its combination with ICB also enhances therapeutic efficacy. It is worth noting that *Clostridium butyricum* has already been approved for clinical application, Stoeva et al.[2] systematically summarized decades of clinical data on *Clostridium butyricum* and demonstrated that long-term administration (6-12 months) of this probiotic in patients with colorectal cancer did not cause significant adverse events, including gut dysbiosis, secondary intestinal infections, or immune dysfunction.

In contrast to traditional probiotic research that emphasizes the indirect "gut-tumor axis" effect, the "dual-pathway mechanism" of *Clostridium butyricum*—signal inhibition mediated by specific binding and immune activation mediated by metabolites—represents a theoretical breakthrough. Nevertheless, the study still has limitations: it only included two strains of *Clostridium butyricum* (the human-derived strain *Hkyucb11* and the commercial strain ATCC19398), and did not explore the functional heterogeneity of strains from different sources and with distinct genotypes. This makes it difficult to determine whether the therapeutic efficacy is dependent on specific strains, which may affect the universality of clinical application. Future efforts will be directed toward the establishment of a dedicated biobank of *Clostridium butyricum* isolates from different sources, integrated with high-throughput screening platforms to characterize the functional heterogeneity of strains at the genomic and functional levels, perform *in vitro* functional characterization, and conduct *in vivo* therapeutic assessment in preclinical animal models. Meanwhile, most CRC patients are elderly and often have comorbidities; key issues regarding the colonization efficiency and survival time of *Clostridium butyricum* in tumor tissues following long-term administration remain insufficiently investigated. Future research should expand the scope of strain screening, conduct long-term animal toxicity studies, and monitor dynamic changes in indicators including gut microbiota composition, hepatic and renal function, and immune function.

Beyond *Clostridium butyricum*, a variety of probiotics reported in recent years provide diversified supplementation for CRC treatment through differentiated mechanisms. These probiotics exert their effects via unique mechanisms such as epigenetic regulation, precise targeted delivery, and gut microbiota network remodeling, demonstrating distinct application values in different treatment scenarios. As a core member of gut commensal bacteria, *Bacteroides fragilis* was shown to secrete propionate that activates the Meox1-Cxcr6/Ccl5 axis through histone H3K14 acetylation, specifically promoting the infiltration of $CD8^+$ T cells into tumor tissues without relying on direct binding between probiotics and tumor cells.[3] This mechanism precisely compensates for the deficiency of immune infiltration in MSS CRC, forming a synergistic effect with the immunosuppression-relieving function of *Clostridium butyricum*.

Research on the genus *Lactobacillus* has focused on improvement of treatment tolerance. *Lactobacillus rhamnosus* GG significantly reduces the incidence of 5-FU chemotherapy-related diarrhea by repairing the gut barrier function and regulating the balance of inflammatory factors. Its intestinal protective function echoes that of butyrate from *Clostridium butyricum*, but with a greater focus on ensuring tolerance during chemotherapy.

The genus *Bifidobacterium* exhibits outstanding performance in microbiota restoration after chemotherapy. A recent study has confirmed that a selenium-fortified *Bifidobacterium* can rapidly restore the diversity of the gut microbiota in cancer patients following chemotherapy,[4] inhibit the expansion of pro-inflammatory microbiota, and indirectly ameliorate the tumor immune

microenvironment by regulating the balance of the gut microbial network, making it particularly suitable for patients with immunosuppression after chemotherapy.

Engineered neoantigen-presenting probiotics represent the cutting-edge application of synthetic biology in tumor microbial therapy. A 2024 study by a team from Columbia University engineered probiotics to express tumor neoantigens.[5] After entering the intestine, these probiotics can be recognized by gut-associated lymphoid tissue (GALT), activating humoral and cellular immunity to generate specific antibodies and cytotoxic T cells targeting tumor neoantigens, thereby achieving precise attacks on tumor cells. In mouse models, these engineered probiotics successfully eliminated primary colorectal tumors and lung metastases without causing damage to normal tissues. However, several critical challenges impede the clinical translation of engineered probiotics. Vector instability can lead to the loss of exogenous expression cassettes and disrupted expression of neoantigens or therapeutic proteins. Balancing immunogenicity is also challenging: either overexpression or insufficient expression of exogenous antigens triggers intestinal inflammation or fails to induce effective antitumor immunity. Moreover, genetic modification compromises intestinal colonization, while interindividual variations in the gut microbiota further limit their clinical application.

Based on their distinct metabolic traits and host interaction patterns, different strains exhibit divergent application values in the stratified intervention of colorectal cancer. *Clostridium butyricum* is suitable for synergistic therapy with immune checkpoint inhibitors in MSS subtype CRC; *Bacteroides fragilis* is conducive to improving the immune infiltration level of the tumor microenvironment; *Lactobacillus* is capable of balancing tumor chemoprevention and enhancement of chemotherapy tolerance; *Bifidobacterium* is appropriate for restoring the gut microbiota structure after chemotherapy. The functional complementarity of different probiotics provides a basis for their combined application. For MSS subtype CRC, a combination of *Clostridium butyricum* plus *Bacteroides fragilis* might be used in conjunction with immune checkpoint inhibitors. For MSI-H subtype CRC, *Clostridium butyricum* alone or combined with engineered probiotics may be applied to enhance immune activation.

Prospectively, with in-depth mechanistic investigations and accumulating clinical evidence, probiotics are anticipated to serve as a vital adjuvant modality in the multimodal management of colorectal cancer. Probiotics can be integrated with chemotherapy, radiotherapy, targeted therapy and immunotherapy to construct a multidimensional, patient-specific therapeutic paradigm. Future studies may prioritize probiotic combination regimens, to highlight the compatibility between strain specificity and the host's individual gut microbiota profile, and to advance the development of personalized microbiome-targeted therapies for CRC.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.