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**EDITORIAL**

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**Yang SH, Ren HF, Chen X, Wang R, Zhang MG.** Refractory esophageal stenosis after endoscopic submucosal dissection for esophageal cancer managed with multiple dilations: A case report. *World J Gastrointest Oncol* 2025; 17(11): 110828 [DOI: [10.4251/wjgo.v17.i11.110828](https://doi.org/10.4251/wjgo.v17.i11.110828)]

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### LETTER TO THE EDITOR

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**Demirli Atici S.** Innovative insights into gut microbiota modulation in colorectal cancer: From microbial dysbiosis to therapeutic strategies. *World J Gastrointest Oncol* 2025; 17(11): 108747 [DOI: [10.4251/wjgo.v17.i11.108747](https://doi.org/10.4251/wjgo.v17.i11.108747)]

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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGO* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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## Innovative insights into gut microbiota modulation in colorectal cancer: From microbial dysbiosis to therapeutic strategies

Semra Demirli Atici

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### Abstract

Colorectal cancer (CRC) is increasingly recognized as a multifactorial disease influenced by hereditary, environmental, and microbial factors. This article explores recent insights into the role of gut microbiota dysbiosis in CRC pathogenesis and progression. Key differences in microbial composition, characterized by enrichment of pro-carcinogenic species such as *Fusobacterium nucleatum* and *Bacteroides fragilis* and depletion of beneficial commensals like *Faecalibacterium prausnitzii*, have been identified alongside changes in microbial metabolites such as short-chain fatty acids and secondary bile acids. We discuss immune system modulation by the microbiota, formation of bacterial biofilms, and the activation of host pathways such as the urea cycle during tumorigenesis. Special attention is given to therapeutic innovations, including microbiota-informed precision modelling, synthetic biology-based engineered probiotics, and evolving alternatives to fecal microbiota transplantation. These integrative strategies represent promising tools in the era of personalized oncology for CRC.

**Key Words:** Colorectal cancer; Fecal microbiota transplantation; Gut oncomicrobiome signatures; Gut oncology index; Gut microbiota; Microbiota-informed risk stratification

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**Core Tip:** This article clarifies the complex involvement of the gut microbiota in colorectal cancer (CRC), emphasizing the influence of microbial metabolites, immunological interactions, biofilm formation, and the therapeutic potential of fecal microbiota transplantation. It also presents innovative future directions, including engineered probiotics and microbiota-informed risk stratification models, which may advance precision oncology in CRC care.

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## TO THE EDITOR

Colorectal cancer (CRC) is the third most common cancer worldwide. Although diet, genetic predisposition, and lifestyle variables have historically been considered important contributors to CRC risk, recent developments have suggested that the gut microbiota plays a significant role in tumor initiation and progression. The importance of microbial dysbiosis in CRC pathophysiology was recently highlighted by Liu *et al*[1]. This letter to the editor emphasizes recent research on microbiota-derived metabolites, immune system interactions, and therapeutic applications, including fecal microbiota transplantation (FMT), engineered probiotics, and predictive modeling strategies that could transform CRC diagnosis and treatment.

## MICROBIAL DYSBIOSIS IN COLORECTAL CARCINOGENESIS

Patients with CRC frequently demonstrate significantly distinct gut microbial patterns compared to healthy individuals. The condition, also known as microbial dysbiosis, is defined by an excess of procarcinogenic bacteria and a reduction of beneficial defensive germs. Several taxa – most notably *Fusobacterium nucleatum* (*F. nucleatum*), *Bacteroides fragilis* (*B. fragilis*), and *Escherichia coli* (*E. coli*) strains harboring the *pks* island – have been implicated in CRC pathogenesis due to their ability to promote inflammation, release genotoxins, and evade immune detection mechanisms[2–4]. Recent studies have further underscored the pathogenicity of these bacteria. For example, *F. nucleatum* has been linked to increased tumor invasiveness, immune suppression *via* programmed death ligand-1 (PD-L1) upregulation, and poor clinical outcomes in patients with CRC[5]. *B. fragilis* has been shown to drive pro-inflammatory cytokine production and epithelial barrier disruption through its enterotoxin *B. fragilis* toxin, while colibactin-producing *E. coli* directly induces DNA damage and genomic instability, particularly in early stages of tumor development[4]. Beneficial microbes such as *Faecalibacterium prausnitzii* (*F. prausnitzii*), *Akkermansia muciniphila* (*A. muciniphila*), and *Clostridium butyricum* (*C. butyricum*) are typically depleted in patients with CRC. These taxa contribute to mucosal homeostasis by producing short-chain fatty acids (SCFAs) such as butyrate, enhancing T-regulatory cell function and maintaining epithelial integrity[6–8]. In particular, *F. prausnitzii* has demonstrated anti-inflammatory properties and tumor-inhibitory effects in preclinical studies[9], whereas *A. muciniphila* is now under investigation as a next-generation probiotic with demonstrated CRC-suppressive activity[10]. *C. butyricum* has also gained attention for its ability to inhibit CRC cell proliferation and enhance gut barrier function[11]. *Bifidobacterium* plays a dual role by contributing to mucosal health and by degrading urea in the intestinal lumen. Its depletion leads to urea accumulation, which impairs macrophage function and disrupts mucosal immunity, thereby creating a permissive environment for tumor progression[12].

Emerging data suggests that intestinal flora imbalance in CRC is associated with disruptions in host metabolic pathways, particularly the urea cycle. High urea load, resulting from the absence of urea-degrading symbionts such as *Bifidobacterium*, interferes with intestinal immune balance by impairing phosphorylated STAT1 binding to the SAT1 promoter in macrophages[12]. This leads to skewed differentiation toward immunosuppressive macrophage subtypes, thus promoting tumor immune evasion and growth[12]. Studies integrating single-cell transcriptomics, metabolomics, and microbial sequencing confirm that activation of the urea cycle is a key feature of the adenoma–adenocarcinoma sequence. The relationship between pathogenic and commensal bacteria plays an important role in the etiology of CRC and underscores the therapeutic significance of microbiome modification. The structure of the gut microbiota is highly individualized and shaped by a complex interaction of genetics, food, environment, antibiotic exposure, and geographic location[13,14]. Heterogeneity among individuals is a considerable obstacle in the creation of standardized microbiome-based therapies and highlights the necessity for precision techniques customized to the host's distinct microbial environment. With advances in microbiome science, there is increasing potential to utilize microbial signatures for early detection and prevention of CRC, as well as for risk stratification and therapy optimization. Future efforts may encompass tailored prebiotic/probiotic protocols, FMT, or targeted manipulation of bacterial communities to restore microbial equilibrium and diminish tumor-promoting activity.

## MICROBIAL METABOLITES AND TUMOR MICROENVIRONMENT

Microbial metabolites are pivotal in the association between the microbiome and CRC development. Butyrate, a SCFA, is among the most extensively studied compounds generated during dietary fiber fermentation. Butyrate enhances colonocyte vitality, triggers neoplastic cell death, modulates gene expression *via* histone deacetylase inhibition[15,16] and plays a role in epigenetic regulation and immune modulation by enhancing T-regulatory cell activity and maintaining mucosal barrier integrity[6]. These properties highlight its dual function as both an energy source for healthy colonocytes and a tumor suppressor agent through the induction of cell cycle arrest and apoptosis in malignant cells[15,16]. High-fat,

high-protein diets promote microbial communities that produce harmful substances such as secondary bile acids and hydrogen sulfide. These metabolites are linked to chronic inflammation, DNA damage, and conditions favorable for tumorigenesis[17-19]. The findings underscore the significance of nutrition in shaping the gut microbial composition to promote or impede carcinogenesis.

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## IMMUNOLOGICAL INTERACTIONS BETWEEN HOST AND MICROBIOTA

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The gut microbiota is essential for immune system regulation. Engagement with host pattern recognition receptors, specifically toll-like receptors (TLRs) and NOD-like receptors, can facilitate immunological homeostasis or promote cancer[20,21]. *F. nucleatum* stimulates TLR4 signaling, resulting in nuclear factor-kappa B activation, interleukin-6 synthesis, and a biased T helper type 17 response[22,23]. It also diminishes cytotoxic T-cell activity *via* PD-L1 overexpression[20-23]. In addition, microbial extracellular vesicles have been shown to affect macrophage polarization and modify the tumor immune microenvironment, indicating an additional mechanism by which the microbiota influences tumor growth and treatment efficacy[23].

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## BACTERIAL BIOFILMS IN CRC

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Biofilms, which are organized bacterial populations that adhere to the intestinal mucosa, are significant contributors to colorectal carcinogenesis. These forms, especially in the right colon, promote chronic inflammation and compromise epithelial integrity. Dejea *et al*[24] identified a significant incidence of mucosal biofilms in patients with hereditary and sporadic CRC, indicating their potential as early disease indicators.

### Opportunities and difficulties of FMT

FMT, the transplantation of fecal matter from a healthy donor to a recipient, has demonstrated potential in reestablishing microbial diversity and decreasing tumor burden in preclinical CRC models[20]. Preliminary clinical investigations have indicated that FMT may improve responses to immune checkpoint inhibitors in certain patients with CRC[25]. Nonetheless, safety issues, such as risk of disease transfer and variable microbial engraftment, persist. While FMT has shown promise, it is no longer considered novel. Ongoing research is now focusing on next-generation strategies such as bacteriophage therapy, engineered commensals, and targeted microbial consortia that offer improved specificity and safety profiles. Researchers are investigating more regulated alternatives, such as specified microbial consortia and synthetic postbiotics, to harness the advantages of FMT with enhanced safety and precision[26,27].

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## TARGETED PROBIOTICS AND RISK EVALUATION

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Recent advances in synthetic biology have facilitated the creation of engineered probiotics, genetically modified bacteria capable of colonizing the gut, and detection of specific tumor-associated microenvironment signals, including hypoxia, elevated lactate, reactive oxygen species, and inflammatory cytokines. In response to these signals, engineered microorganisms can be programmed to administer therapeutic drugs, such as interleukins, immune checkpoint inhibitors (*e.g.*, anti-PD-L1), or apoptosis-inducing compounds, to specific locations as required[28,29]. This focused on-site methodology holds considerable potential to overcome the constraints of systemic medicines by diminishing off-target effects, lowering toxicity, and enhancing treatment specificity. Numerous preclinical investigations have established the viability of employing synthetic probiotic strains to deliver anticancer agents into the tumor microenvironment, resulting in decreased tumor burden and enhanced immune infiltration. As these platforms advance, the integration of biosensor circuits, safety switches, and logic gates will enhance their controllability and biosafety, thereby expediting their translation into clinical applications. The synthesis of multi-omics data, including microbiome profiles, microbial metabolite signatures (*e.g.*, butyrate and deoxycholate), host genetic mutations (*e.g.*, adenomatous polyposis coli, tumour protein 53, and MLH1), and dietary variables, facilitates the development of individualized CRC risk models. The gut oncomicrobiome signatures system is intended to categorize individuals based on microbiota-related oncogenic risk[30, 31]. It would be very useful to create a model such as the "gut oncology index" using machine learning algorithms that can identify complex, nonlinear patterns across datasets to predict CRC susceptibility with higher accuracy than traditional risk models[30,31]. This predictive modeling method will also play a role in therapeutic decision-making by identifying patients who are more likely to respond to microbiome-modifying treatments, such as FMT, prebiotic supplementation, or engineered microbiota-based therapies. The gut oncology index or analogous predictive parametric indices that are developed can be integrated into standard screening methods, offering a noninvasive, microbiome-informed approach to evaluate CRC risk in both average-risk and high-risk populations. It can be used to track risk advancement or treatment efficacy and may pave the way for dynamic, individualized cancer prevention. Recent findings suggest that microbiota residing within tumor tissue (intratumoral microbiota) also exert significant effects on CRC progression. These microbial communities influence tumor immunity and therapeutic responsiveness and may differ from luminal gut populations. For example, *Fusobacterium* and *Peptostreptococcus* have been isolated from tumor tissues and linked to immune exclusion and chemotherapy resistance. Future research must distinguish luminal and intratumoral ecosystems to develop fully effective microbiota-based interventions[32].

## CONCLUSION

In conclusion, the gut microbiota affects almost every phase of CRC progression, including the regulation of immune responses and alteration of the tumor microenvironment. Liu *et al*[1] established the foundation by emphasizing the significance of dysbiosis and further investigated the therapeutic potential of microbiome manipulation by FMT, tailored probiotics, and predictive modeling. As research advances in elucidating host-microbiome interactions, the incorporation of microbiota-based techniques into CRC prevention and therapy may become a standard approach in precision oncology.

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