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The Role of the Gut Microbiome in Colorectal Cancer Development and Therapeutic Response

Kiren Mohammed Khalid Damodar[1], Ahmed Hashim Azeez[2]

[1]Department of Medicine, Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, Georgia.
[2]Department of Medicine, Faculty of Medicine, Tbilisi State Medical University, Georgia.

Corresponding Author: Kiren Mohammed Khalid Damodar

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ABSTRACT

Colorectal cancer (CRC) is a leading global malignancy (≈1.92–2.2 million new cases per year). Most CRCs (~85%) are microsatellite-stable (MSS), exhibit low tumor mutational burden, and respond poorly to immune checkpoint inhibitors (ICIs). Growing evidence links gut microbial dysbiosis to CRC pathogenesis, with oncogenic species (e.g. *Fusobacterium nucleatum, pks+ E. coli, enterotoxigenic Bacteroides fragilis)* promoting DNA damage, barrier disruption, chronic inflammation, and immune evasion. Conversely, depletion of beneficial commensals, including short-chain fatty acid (SCFA) producers such as *Faecalibacterium* and *Akkermansia*, reduces anti-inflammatory metabolite availability. These microbiota-driven processes intersect with oncogenic pathways, notably NF-κB/STAT3 and Wnt/β-catenin signaling. Distinct microbiome profiles are observed between MSI-High (dMMR) and MSS tumors, with dMMR tumors enriched in *Fusobacterium, Akkermansia,* and SCFA-producers, while MSS tumors show increased Proteobacteria (e.g. *Serratia*). The gut microbiota also modulates therapeutic response: certain commensals enhance anti-PD-1/CTLA-4 efficacy, whereas antibiotic-induced dysbiosis impairs ICI responses. Specific microbes can either sensitize or confer resistance to PD-1 blockade. Emerging strategies including fecal microbiota transplantation, probiotics, and dietary modulation aim to improve immunotherapy outcomes. Microbial biomarkers show diagnostic and prognostic potential in CRC.

Keywords: colorectal cancer; gut microbiome; microsatellite instability; immunotherapy; fecal microbiota transplantation; probiotics; biomarkers; inflammation.

INTRODUCTION

Colorectal cancer (CRC) is a major global health burden. It ranks as the third most common cancer and the second leading cause of cancer death worldwide[1]. In 2022 approximately 1.9–2.2 million new CRC cases and ~0.9 million deaths were reported globally[1]. This burden is projected to increase due to aging populations and Westernized lifestyles[1]. Despite advances in surgery, radiation, chemotherapy and targeted agents, 5-year survival for metastatic CRC remains poor. Notably, only 10–15% of CRCs exhibit deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) and high tumor mutational burden, making them susceptible to immune checkpoint blockade[1][5].Pembrolizumab (anti-PD-1) is now FDA-approved for MSI-H CRC, with median overall survival exceeding 77 months in KEYNOTE-177[12]. By contrast, ~85% of CRCs are microsatellite-stable (pMMR/MSS) with low

TMB and a "cold" immune phenotype (Wnt/β-catenin and TGF-β driven), and typically do not respond to single-agent ICIs[2]. Thus novel strategies are urgently needed to augment immune and other therapies for MSS CRC.

Emerging data implicate the gut microbiome as a critical modifier of CRC risk and therapy. Metagenomic studies have identified distinct dysbiosis in CRC patients compared to healthy controls, characterized by enrichment of pro-tumor taxa (e.g. *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides fragilis*) and depletion of beneficial fermenters (e.g. *Faecalibacterium*, *Roseburia*, *Bifidobacterium*)[2,3]. These microbes can drive oncogenesis via multiple mechanisms: generating DNA-damaging toxins, inducing chronic inflammation, disrupting the mucosal barrier, and modulating immune responses[3]. In parallel, the microbiome influences cancer therapy outcomes. Landmark studies showed that commensal microbes govern host anti-tumor immunity – for example, *Bifidobacterium* enhanced anti-PD-L1 efficacy in melanoma models, and *B. fragilis* potentiated anti-CTLA-4 through Th1 responses[6]. Clinically, antibiotic exposure often worsens ICI efficacy[6], whereas fecal transplants from ICI-responders can transfer sensitivity to non-responding hosts (in melanoma and RCC)[13]. Given this context, understanding the role of the gut microbiome in CRC development and therapy is of high translational importance. This review examines recent evidence (2015–2024) on microbial contributions to CRC pathophysiology and treatment response, emphasizing MSI-H vs MSS differences, mechanisms of ICI resistance, and translational applications (diagnosis, modulation, clinical trials). We critically analyze conflicting data, emphasize molecular pathways (e.g. bacterial genotoxins, immune signaling, microbial metabolites), and highlight how this knowledge informs emerging clinical strategies.

LITERATURE REVIEW

Pathophysiology and Mechanisms

Microbial dysbiosis and CRC pathogenesis: CRC patients consistently show a perturbed gut microbiome compared to healthy controls[3,14]. Dysbiosis is marked by overrepresentation of pro-carcinogenic bacteria and loss of commensal diversity. For example, meta-analyses demonstrate enrichment of genera *Fusobacterium*, *Parvimonas*, *Porphyromonas* and depletion of short-chain fatty acid (SCFA) producers (*Faecalibacterium*, *Roseburia*) in CRC tissue/stool[2,3]. Dysbiosis can promote oncogenesis via multiple mechanisms:

- **Genotoxic metabolites and toxins:** Certain bacteria produce direct DNA-damaging agents. Notably, *Escherichia coli* strains harboring the pks pathogenicity island synthesize the genotoxin colibactin, which induces DNA double-strand breaks and chromosomal instability in colonic epithelial cells[2]. Colibactin-exposed epithelium shows mutational signatures (e.g. mutational signature 96B) linked to CRC. Another example is *Helicobacter* spp. and *Salmonella* toxins (e.g. cytolethal distending toxin) that cause cell cycle arrest and DNA damage in epithelial cells (though less well studied in CRC). These genotoxic hits can drive oncogenic mutations early in carcinogenesis[2].
- **Bacterial effectors on signaling pathways**: *F. nucleatum* produces adhesins (FadA) and lectins (Fap2) that bind host E-cadherin or Gal-GalNAc, activating β-catenin and NF-κB signaling in colonocytes[22]. This upregulates proliferation and pro-inflammatory cytokines (e.g. IL-8/CXCL8). Similarly, enterotoxigenic *B. fragilis* (ETBF) secretes the metalloprotease BFT/fragilysin, which cleaves E-cadherin and activates NF-κB and Wnt pathways[2]. These interactions promote epithelial proliferation and survival signals. Moreover, lipopolysaccharide (LPS) from Gram-negative bacteria

engages TLR4, triggering MyD88/NF-κB–driven inflammation and STAT3 activation, fueling tumor-promoting inflammation.

- **Metabolic reprogramming:** Microbial metabolism influences host cell metabolism. SCFAs (butyrate, propionate, acetate) produced by fiber-fermenting bacteria are generally protective. Butyrate is a preferred fuel for colonocytes and a histone deacetylase (HDAC) inhibitor that induces apoptosis in CRC cells[4]. Loss of butyrate-producers in CRC reduces these protective effects. In contrast, dysbiotic microbiota can produce harmful metabolites: secondary bile acids (e.g. deoxycholic acid, DCA) accumulate in high-fat diets and are carcinogenic. DCA causes oxidative DNA damage and can activate Wnt/β-catenin in epithelium[3,14]. Other oncometabolites include polyamines and hydrogen sulfide, which can promote genotoxicity and inflammation. Microbial metabolism of tryptophan to kynurenine or indoles can modulate host immunity via the AhR pathway; physiologic AhR ligands (such as microbial indoles) have been shown to be essential for effective anti-PD-1 therapy by maintaining T-cell function[15].
- **Barrier disruption and inflammation:** Dysbiosis often compromises the gut mucosal barrier, allowing bacterial translocation and chronic inflammation. For example, ETBF also increases mucosal permeability, facilitating the penetration of other pathobionts. Chronic inflammation in turn promotes tumorigenesis via NF-κB, IL-6/STAT3, and immune-suppressive cell recruitment. In CRC models, persistent IL-6/STAT3 signaling (driven by microbial ligands and cytokines) accelerates malignant transformation. Conversely, beneficial SCFAs have anti-inflammatory effects: butyrate can enhance regulatory T cells and suppress pro-inflammatory cytokines[3,4]. Diet or polyphenol enrichment that boosts SCFA-producers restores anti-inflammatory macrophage phenotypes and reinforces barrier integrity[3].
- **Epigenetic modulation:** Some microbial products modify host gene expression epigenetically. Butyrate's HDAC inhibition also influences gene transcription in immune cells (promoting effector T-cell functions[16]). Conversely, microbial LPS can induce epigenetic silencing of tumor suppressor genes via inflammatory signaling. Microbial 'epigenetic toxins' (e.g. cyclomodulins) further reprogram host cell proliferation.

Collectively, these pathways illustrate how gut microbes can drive the "hallmarks of cancer" – sustaining proliferative signaling, resisting cell death, inducing angiogenesis, and evading immune destruction – in the colorectal mucosa[3].

MATERIALS & METHODS

We conducted a comprehensive literature review of peer-reviewed studies from 2015–2026. Databases searched included PubMed/MEDLINE, Web of Science, and Google Scholar, using combinations of keywords such as "colorectal cancer", "gut microbiome", "immunotherapy", "MSI", "Fusobacterium", "FMT", "probiotics", "dysbiosis", and "clinical trial". We also cross-referenced cited articles in key reviews. Inclusion criteria prioritized human studies, clinical trials, high-quality animal models or mechanistic studies, and recent comprehensive reviews. We included multicenter trials and high-impact publications where available. Older landmark studies were cited for foundational mechanisms as needed. Both narrative review and meta-analysis articles were used to contextualize trends. As this is a narrative review, no formal meta-analytic methods were applied, but we adhered to PRISMA-style principles (systematic search and selection) to ensure completeness and reproducibility.

RESULT

Key Microbial Species Involved

The following bacteria have been most consistently implicated in CRC (cancer-promoting species are noted first; beneficial/"protective" microbes follow):

- **Fusobacterium nucleatum:** Enriched in CRC tissues, Fusobacterium binds colon epithelial cells via FadA adhesin (engaging E-cadherin) and Fap2 lectin (Gal-GalNAc), activating β-catenin and NF-κB pathways[22]. Fn infection increases tumor inflammation (e.g. recruitment of IL-17-producing myeloid cells)[2] and can induce chemoresistance by upregulating anti-apoptotic autophagy. Notably, *F. nucleatum* appears to contribute to differences in CRC subtypes: it predominates in CMS1 (MSI-high, immune) tumors[2]. Paradoxically, recent data indicate Fn can enhance immunotherapy response in MSS CRC via production of butyrate, which inhibits HDAC in CD8+ T cells and reduces PD-1 expression[7], highlighting complex context-dependent roles. The impact of *F. nucleatum* on immunotherapy appears to be governed by its dominant metabolic output—sensitization via butyrate versus resistance via succinate, which may be determined by the co-occurrence of other microbial species.
- **Enterotoxigenic Bacteroides fragilis (ETBF):** A subset of *B. fragilis* produces Bacteroides fragilis toxin (BFT). ETBF colonizes many CRCs and triggers chronic colitis in animal models. BFT cleaves epithelial E-cadherin and activates NF-κB and STAT3, inducing pro-inflammatory cytokines (IL-17, IL-6) and promoting tumor growth[2]. ETBF can also drive Th17-mediated inflammation and myeloid infiltration. Preliminary data suggest that ETBF may influence immunotherapy; one report hints ETBF induces CD8+ IFN-γ+ cells, potentially synergizing with PD-1 blockade, but this requires further study.
- **pks+ Escherichia coli:** Strains of *E. coli* harboring the pks island synthesize colibactin, a potent genotoxin. These are overrepresented in CRC tissue[2]. Colibactin causes DNA double-strand breaks and cellular senescence with a secretory phenotype (SASP). In vivo, pks+ *E. coli* promote tumorigenesis. They also alter host immunity: pks+ *E. coli* expansion correlates with reduced CD8+ TILs and impaired response to PD-1 therapy[2]. Notably, German cohort data link seropositivity to colibactin and BFT with higher CRC incidence, suggesting cooperative action in tumor initiation[2].
- **Peptostreptococcus anaerobius:** An oral anaerobe enriched in CRC biopsies[2]. It binds epithelial α2β1 integrin and recruits myeloid-derived suppressor cells (MDSCs) via NF-κB–CXCL1 signaling[2]. MDSC infiltration driven by *P. anaerobius* promotes immunosuppression and chemoresistance[2]. A recent mouse study showed *P. anaerobius* colonization abolished anti-PD-1 efficacy by activating MDSCs via integrin signaling and Slamf4 engagement[8].
- **Streptococcus gallolyticus (formerly S. bovis):** Long linked epidemiologically to CRC, *S. gallolyticus* promotes tumor cell proliferation and inflammation. It adheres to colon tumors (via Pil3 pilus binding ECM) and can activate Wnt/β-catenin signaling. Animal data show *S. gallolyticus* accelerates tumor growth via IL-1β/COX-2–mediated inflammation[2]. Some clinical cohorts find *S. gallolyticus* DNA in blood/tumors as a CRC marker. (*S. gallolyticus* infection still prompts colonoscopic CRC screening in practice.)
- **Campylobacter and Helicobacter spp.:** *Campylobacter jejuni* and *Campylobacter concisus* have been detected at higher levels in CRC mucosa. *Campylobacter* delivers cytolethal distending toxin, causing DNA damage and inflammation. *Helicobacter hepaticus* (in mice) and *H. bilis* have

been shown to trigger colitis and colonic tumors. In humans, *Helicobacter* DNA or proteins are found in some CRCs, but causality is not established. These bacteria exemplify how chronic mucosal infection can promote dysplasia.

- **Beneficial commensals:** In contrast, certain microbiota appear protective. *Faecalibacterium prausnitzii*, *Roseburia*, *Bifidobacterium*, *Lactobacillus*, and *Akkermansia muciniphila* are often reduced in CRC patients[2,3]. These taxa produce SCFAs (like butyrate and propionate) that nourish colonocytes, strengthen barrier integrity, and exert anti-inflammatory effects[3,4]. For example, *A. muciniphila* (a mucin degrader) has been associated with improved barrier function and has shown synergy with anti-PD-1 therapy in other cancers[2]. *Bifidobacterium* spp. and *Lactobacillus* spp. are widely used probiotics; trials suggest they can reduce chemotherapy-induced toxicity and may enhance antitumor immunity[17,18].
- **Emerging and rare taxa:** Several other microbes have been implicated in CRC. *Klebsiella* spp., *Morganella morganii* and *Enterococcus faecalis* can produce toxins (colibactin-like peptides, superoxide) that may damage DNA. *Clostridium difficile* has been found near tumors, potentially via CDT toxin. *Fusobacterium varium* and *Peptostreptococcus stomatis* are occasionally enriched in tumor microbiomes. The intratumoral virome and mycobiome (e.g. certain bacteriophages, viruses like JC polyoma, and fungi like *Candida*) remain underexplored but could modulate CRC pathogenesis[2].

Collectively, these findings illustrate that CRC is not associated with a single "culprit" microbe but rather a complex shift in community structure.

Microbiome and Inflammation

Chronic inflammation is a well-established promoter of CRC. The gut microbiota plays a central role in modulating intestinal inflammation. Dysbiosis can trigger persistent NF-κB and inflammasome activation in the colon. For example, bacterial LPS and flagellin stimulate TLRs on epithelial and immune cells, inducing IL-6, TNF-α and IL-1β, which promote a tumorigenic milieu[3,14]. *Fusobacterium* and ETBF recruit IL-17–producing T cells and neutrophils into the tumor microenvironment[2,3]. In mouse models, *F. nucleatum* drives IL-17A and IL-11 expression via TLR4-MYD88 signaling, linking microbiota to Th17-mediated tumor promotion[2]. Conversely, beneficial metabolites like butyrate exert anti-inflammatory actions: butyrate enhances regulatory T cells and suppresses pro-inflammatory gene expression in macrophages[3,4]. One study showed that physiological activation of the aryl hydrocarbon receptor (AhR) by microbial indoles was essential for proper IFN-γ production by CD8+ T cells; loss of dietary AhR ligands led to PD-1–high T-cell exhaustion[15]. Thus, the microbiome influences inflammation and immune surveillance, shaping CRC risk and progression[3,14].

Gut barrier integrity is also critical. Dysbiotic communities (e.g. ETBF, *C. difficile*) degrade mucin and tight junctions, allowing bacterial products to incite colonic inflammation. In turn, inflammatory mediators (e.g. IL-1β from macrophages) disrupt epithelial homeostasis and promote mesenchymal transitions[3]. Notably, microbial metabolites modulate these effects: secondary bile acids like DCA inhibit CD8+ T-cell function[3], whereas dietary polyphenol–induced SCFAs restore macrophage balance and reduce colonic inflammation[3]. In summary, the gut microbiome forms a critical bridge between luminal environment, mucosal immunity and inflammation – a bridge that when dysregulated, fuels CRC development.

Microbiome and Immunotherapy Response

The gut microbiome has emerged as a key factor influencing cancer immunotherapy outcomes. Several lines of evidence underscore its importance:

- **Microbiome correlates of ICI response:** In multiple cancers, specific gut bacterial profiles associate with ICI efficacy. For instance, early studies showed that melanoma patients responding to anti-PD-1 had higher *Bifidobacterium*, *Collinsella* (Coriobacteriaceae) and *Enterococcus faecium* abundance, whereas non-responders had elevated *Bacteroidetes* species[6]. In gastrointestinal cancers, a study of metastatic CRC patients receiving adoptive cell therapy plus chemotherapy found that responders had higher circulating *Bifidobacterium*, *Lactobacillus* and *Enterococcus* species[6]. Conversely, broad-spectrum antibiotics administered before or during ICI treatment generally impair outcomes. Retrospective analyses in melanoma and lung cancer showed that antibiotic use (especially within one month of ICI) was associated with significantly reduced response rates and shorter progression-free survival[6]. This likely reflects loss of beneficial taxa or proliferation of resistant pathobionts.
- **Effects of FMT and probiotics:** Proof-of-concept trials in melanoma and renal cell carcinoma (RCC) have demonstrated that fecal microbiota transplantation (FMT) can transfer ICI sensitivity. Baruch *et al.* (Science 2021) treated anti–PD-1–refractory melanoma patients with donor FMT (from responders) followed by re-introduction of anti-PD-1; ~30% achieved objective responses (including one complete response)[19]. Similar success was reported in metastatic RCC: a live biotherapeutic *Clostridium butyricum* (CBM588) given with nivolumab/ipilimumab doubled objective response rates[13]. These findings illustrate that modifying the microbiome can overcome primary resistance.

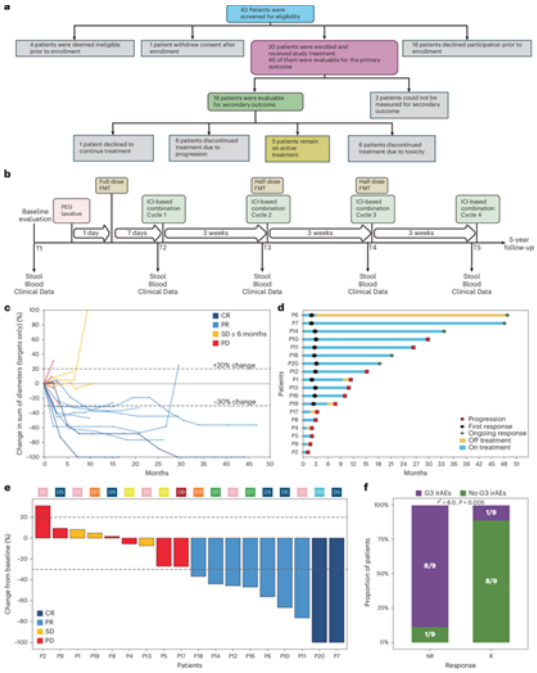

Figure 1: Trial Design and Clinical Activity of FMT plus ICI in Metastatic Renal Cell Carcinoma.

(a–b) In the PERFORM proof-of-concept trial (NCT03341143), 20 heavily pretreated patients with metastatic renal cell carcinoma received encapsulated healthy-donor Fecal Microbiota Transplantation (FMT) combined with PD-1 inhibitors [13]. The

protocol involved a full-dose FMT followed by subsequent half-doses alongside ICI cycles to sensitize otherwise resistant "cold" tumors[13].

(c–e) Clinical activity is illustrated via spider, swimmer, and waterfall plots. The waterfall plot (e) demonstrates that 8 patients achieved a Partial Response (PR, light blue) or Complete Response (CR, dark blue), defined by a tumor reduction of >30%. Several other patients maintained Stable Disease (SD, yellow) or experienced durable control[13].

(f) Safety analysis shows the distribution of Grade 3 immune-related adverse events (G3 irAEs). Notably, 88% (8/9) of non-responders (NR) experienced G3 irAEs compared to only 11% (1/9) of responders (R)[13]. This suggests that while microbiome augmentation can yield clinical responses in resistant tumors, the relationship between T-cell activation, systemic toxicity, and therapeutic efficacy remains complex [13].

Immune mechanisms: Preclinical models provide mechanistic insights. For example, *Bifidobacterium* augments dendritic cell function and CD8+ T-cell priming, synergizing with PD-1 blockade[6]. In CRC models, *Ruminococcus intestinalis* (a butyrate producer) has been shown to enhance radiotherapy response and possibly immunogenicity. Our group and others have demonstrated that microbial metabolites influence T-cell exhaustion: butyrate increases TBX21 (T-bet) expression in CD8+ cells and represses PD-1 via HDAC inhibition[7,16]. High intratumoral *F. nucleatum* correlates with better ICI responses in some cohorts, likely reflecting butyrate-mediated effects[7]. In contrast, other studies found that *F. nucleatum* generates succinate that suppresses STING signaling and CD8+ trafficking, causing resistance – an effect reversible with targeted antibiotics[2]. Thus, Fn may either potentiate or hinder immunotherapy depending on its metabolic output.

- **Resistance in MSS CRC:** MSS tumors often evade ICIs due to low neoantigen load and exclusion of effector T cells. Emerging evidence suggests the microbiome contributes to this resistance. For instance, *Peptostreptococcus anaerobius* colonization was shown to abolish anti–PD-1 efficacy in a mouse MSS CRC model by recruiting immunosuppressive MDSCs via TLR signaling[8]. Tumors with elevated TGF-β or Wnt signaling (common in MSS) may foster a microbiome that reinforces barrier integrity and immune exclusion; conversely, modulating the microbiome can partially “warm up” these tumors[2]. The interplay between MSS-specific pathways and microbial signals is an active research area.
- **Biomarkers of response:** Gut microbiome features may serve as predictive biomarkers. Higher α-diversity and presence of specific taxa (e.g. *Akkermansia*, *Faecalibacterium*) have been linked to better ICI outcomes across cancers[6]. Recently, spatial profiling of the tumor microbiome identified a “Colorectal Microbiome Score” based on the distribution of microbes like *Streptococcus* and *Acetivibrio*. Depletion of these intratumoral species in MSI-stable tumors was associated with diminished butyrate signaling and CD8+ T-cell exhaustion, stratifying patients by ICI resistance risk[20]. This highlights the potential of microbiome-informed stratification for immunotherapy.

In summary, the gut microbiome exerts profound effects on CRC immunotherapy. Enrichment of certain commensals can enhance antigen presentation and T-cell function, while pathobionts may induce immune suppression. Microbiota-based interventions (FMT, probiotics, dietary supplements) are being tested to overcome resistance in MSS CRC[6,21]. Understanding these dynamics is crucial for designing combined modality treatments that integrate microbiome modulation with ICIs.

DISCUSSION

Diagnostic and Prognostic Implications

The CRC-associated microbiome offers potential clinical biomarkers:

- **Noninvasive screening:** Fecal microbial signatures have been explored for early CRC detection. Studies show that CRC patients have higher stool levels of *Fusobacterium nucleatum*, *Peptostreptococcus*, and *Parvimonas*, and lower *Clostridium* spp. and *Bifidobacterium* compared to healthy controls. Meta-analyses indicate that fecal *F. nucleatum* alone can detect CRC with moderate accuracy (pooled sensitivity ~70%, specificity ~79%)[10]. Combining microbial markers with fecal immunochemical tests (FIT) significantly improves screening sensitivity. For example, one study reported that a panel of 4 bacterial markers identified ≥90% of CRCs when used alongside FIT[10]. Ongoing efforts are validating microbiome-based assays (16S rRNA or shotgun metagenomics) for CRC screening.
- **Adenoma risk:** Dysbiosis is evident even in early lesions. A 2025 report found that patients with adenomatous polyps (colorectal neoplasia) had an intermediate microbiome profile: increased *Bacteroidetes*, *Fusobacteria* and *Proteobacteria*, and decreased *Actinobacteria* versus normals[22]. At the species level, *Escherichia coli*, *Ruminococcus gnavus* and *Clostridium perfringens* were enriched in adenoma stool, while beneficial *Bifidobacterium longum* and *F. prausnitzii* were depleted[22]. These microbial shifts may eventually predict polyp progression or serve as biomarkers to triage patients for colonoscopy[22].
- **Prognosis:** Tumor-associated microbiota can influence survival. For instance, meta-analyses consistently show that high intratumoral *F. nucleatum* abundance portends poorer overall survival in CRC[11]. Similarly, serologic evidence of long-term exposure to *E. coli* colibactin or ETBF is associated with higher CRC incidence[2]. Conversely, some commensals (*Akkermansia*, *Bifidobacterium*) correlate with improved immune signatures and might predict better ICI outcomes, as seen in other cancers[6]. Investigational approaches include sequencing of the "blood microbiome" (bacterial DNA in plasma) as a noninvasive biomarker: one study found specific plasma bacterial signatures that distinguished ICI responders from non-responders in metastatic CRC[6].

While promising, microbiome biomarkers face challenges: geographic, dietary and technical variability necessitate rigorous validation. Large multicenter studies are underway to assess stool or plasma microbiota panels alongside clinical risk factors[23,24]. Ultimately, integrating microbial features with existing diagnostics (FIT, CEA levels, imaging) could yield more sensitive CRC screening and prognostic tools.

Therapeutic Modulation (Probiotics, FMT, Antibiotics, Diet)

Interventions targeting the microbiome hold therapeutic promise:

- **Probiotics:** Live beneficial bacteria (e.g. *Lactobacillus*, *Bifidobacterium*) have been studied in CRC prevention and treatment. Mechanisms include competitive exclusion of pathogens, production of SCFAs, enhancement of gut barrier, and modulation of host immunity[17]. In vitro and animal studies show that certain probiotics can reduce mutagenicity, bind carcinogens, and induce apoptosis in CRC cells via metabolites. Clinically, randomized trials (mostly in perioperative or chemotherapy contexts) suggest that probiotic mixtures can reduce postoperative infections, ameliorate chemotherapy-induced diarrhea/mucositis, and improve immune parameters[18,25]. For example, a recent meta-analysis found that probiotics halved the incidence of

chemoradiotherapy-associated diarrhea in CRC patients[18]. However, evidence for probiotics directly reducing tumor growth in humans is limited. Ongoing trials are testing specific strains or consortia (e.g. Bifidobacterium combinations) as adjuncts to chemotherapy or immunotherapy. Challenges include strain selection, dosing, and ensuring engraftment in the CRC-associated microbiome.

- **Prebiotics and Diet:** Dietary modulation is a practical way to alter the gut ecosystem. High fiber intake is epidemiologically linked to lower CRC risk[26]. Fiber-rich diets promote SCFA-producing bacteria, increase butyrate levels, and reduce secondary bile acids[4,26]. Polyphenol-rich foods (berries, tea, cruciferous vegetables) have prebiotic effects on commensals, suppress CRC-associated pathogens, and generate anti-inflammatory metabolites[3]. For instance, dietary indoles and other AhR ligands have been shown to sustain antitumor CD8+ T-cell activity during PD-1 therapy[15]. Conversely, Western diets high in fat and processed meat foster bile-tolerant, pro-inflammatory microbes (e.g. *Bilophila wadsworthia*, *Fusobacterium*)[26]. Clinical trials are evaluating structured diets or fiber supplements (e.g. inulin, resistant starch) to shift the microbiome in CRC patients.
- **Fecal Microbiota Transplantation (FMT):** FMT introduces a complete microbial community from a healthy donor. As noted, FMT has shown efficacy in restoring ICI responsiveness in melanoma/RCC[13,19]. In CRC, several early-phase trials are investigating FMT as an adjunct. A MD Anderson phase II trial (NCT04729322) is testing FMT plus pembrolizumab in refractory MSS CRC patients, with immune re-challenge[9]. Other studies are assessing FMT for chemotherapy modulation or toxicity reduction. FMT can drastically alter the microbiome; for example, after FMT the gut community resembles the donor's profile[9]. However, FMT carries risks (pathogen transfer) and batch variability. "Defined" microbial consortia (live biotherapeutic products) or sterilized fecal filtrates are being developed as safer alternatives.
- **Antibiotics and Targeted Killing:** Broad antibiotics can disrupt microbiome balance and have shown complex effects. While some antibiotics (e.g. *metronidazole*) can deplete CRC-associated pathogens, they also risk depleting beneficial flora. In mice, metronidazole targeting *F. nucleatum* improved chemotherapy response[2]. In the immunotherapy context, broad antibiotics generally diminish ICI efficacy[6]. Selective strategies, such as phage therapy or bacteriocins, are under exploration. Phage cocktails targeting *Fusobacterium* or *Peptostreptococcus* could theoretically reduce tumor-promoting bacteria while sparing commensals[27]. Indeed, phage therapy is an emerging approach: one review highlights that bacteriophages may be used to selectively modulate gut communities in CRC without disturbing overall diversity[27].
- **Engineered Microbiota:** Synthetic biology approaches aim to deliver beneficial functions via engineered microbes. For example, oral probiotics have been modified to produce anti-inflammatory cytokines or checkpoint-blocking peptides in situ. Preclinical work has shown that *E. coli* Nissle engineered to secrete IL-12 can elicit potent antitumor immunity in CRC models. Another approach is to use prebiotic drug carriers: a recent Nature Comm report created a capecitabine-loaded prebiotic nanoparticle (xylan-stearate) that both delivers chemotherapy and enriches SCFA-producing bacteria[21]. In CRC mice, this formulation increased intra-tumoral drug levels, boosted SCFA levels, and improved tumor control (tumor

inhibition rate 71.8% vs 5.3% with free drug)[21]. Such "two-in-one" strategies exemplify how dietary fibers can be combined with therapy to reshape the microbiome and enhance efficacy.

In summary, diverse microbiome-modulating strategies (probiotics, diet, FMT, phage, engineered vectors) are being pursued to boost antitumor immunity and suppress carcinogenic pathways. Early results are encouraging, but rigorous clinical trials are needed to determine which interventions meaningfully impact CRC outcomes.

Current Clinical Trials

Several clinical efforts are underway to translate microbiome science into CRC therapies. Most trials to date focus on augmenting immunotherapy in MSS CRC. For example, the MD Anderson Center is conducting a phase II trial (NCT04729322) of FMT followed by anti–PD-1 in refractory metastatic MSS CRC[9]. Similarly, investigators are exploring probiotic cocktails (live biotherapeutics) in combination with chemotherapy or immunotherapy in CRC. These efforts are informed by successes in other tumors: e.g., the PERFORM trial reported in Nature Medicine used encapsulated FMT to overcome TKI resistance in renal cancer[13]. Early-phase studies like this demonstrate proof-of-concept that microbiome adjuncts are feasible and may improve response rates. Beyond immunotherapy, microbiome interventions are being tested to mitigate treatment toxicity and improve general outcomes. Trials are evaluating probiotics or prebiotics to reduce postoperative infections and chemotherapy-related diarrhea (building on findings that probiotics cut such complications[18,25]). Other trials assess dietary fiber supplementation or polyphenol-rich diets during CRC treatment to promote beneficial bacteria.

Novel diagnostics are also being trialed: some groups are validating stool and blood microbiome panels for early CRC detection (e.g. combining microbial markers with FIT) or monitoring recurrence. While many studies are single-arm or small, multicenter consortia are emerging. Importantly, most microbiome-targeted CRC trials are in early phases or still recruiting; their outcomes will be crucial for demonstrating clinical utility.

Limitations of Existing Research

Current research on the CRC microbiome faces several limitations:

- **Correlative evidence:** Much of the literature is associative. While dysbiotic signatures in CRC are well-documented, causal proof in humans is lacking[14]. Most human studies are cross-sectional; longitudinal cohort studies (following patients from health to adenoma to carcinoma) are rare. Thus it is challenging to disentangle whether observed microbiota changes drive tumorigenesis or are consequences of the tumor environment.
- **Heterogeneity:** There is substantial variability across studies. Geographic, dietary, and genetic factors shape the microbiome, so findings from one population may not generalize[6,14]. Technical differences (sample collection, sequencing methods, bioinformatics pipelines) also impede comparison[2]. For example, 16S rRNA vs shotgun metagenomics or PCR bias can yield different apparent abundances. As a result, no single microbial "signature" is consistently reproducible across cohorts[6,14].
- **Confounders:** Patients with CRC often have bowel symptoms, antibiotics use, or concurrent treatments that alter the microbiome. Diet, medications (e.g. NSAIDs, proton pump inhibitors) and co-morbidities are seldom fully controlled for. In immunotherapy studies, factors like prior antibiotic use or steroid use can confound microbiome–response correlations[6].
- **Understudied domains:** Most research focuses on bacteria; fungal (mycobiome) and viral (virome) communities are underexplored in CRC[2]. Similarly, interactions with the host genome and

epigenome (multi-omics) have only begun to be addressed. The tumor-associated microbiome (bacteria within the tumor tissue) may differ from fecal communities, but tissue studies are fewer and technically challenging.

- **Small sample sizes and lack of controls:** Many studies involve tens of patients, limiting statistical power. Randomized controlled trials of microbiome interventions are sparse, and adverse event data (e.g. from FMT) are limited in oncology settings. Moreover, selection bias (e.g. only resectable tumors studied) can skew results.
- **Intervention standardization:** There is no consensus on optimal probiotic strains, FMT donor criteria, dosing or route of administration for CRC. FMT carries risks (transfer of pathogens or antibiotic resistance genes) that require stringent screening standards which are still evolving.

In sum, while the microbiome–CRC field is rich with intriguing findings, these limitations highlight the need for rigorous, standardized, and mechanistic studies.

Future Directions

To fully harness microbiome insights for CRC, future research should pursue the following directions:

- **Longitudinal and multi-omic studies:** Large prospective cohorts tracking individuals from healthy to adenoma to carcinoma (with serial stool and tissue sampling) are needed to establish causal relationships[14]. Integrating metagenomics, metatranscriptomics, metabolomics and host genomics will reveal functional interactions. Spatial mapping of microbes (e.g. in gut biopsy or surgical specimens) should elucidate localized niches (as in the recent spatial microbiome work[20]).
- **Mechanistic validation:** Key associations must be validated by experiments. For example, microbes enriched in MSS tumors (e.g. *P. anaerobius*) require further animal studies to confirm their roles in immune evasion[8]. Organoid and microfluidic gut-on-chip models can dissect microbe–epithelium interactions in a human context. Identification of bacterial gene products that drive resistance (such as *F. nucleatum* factors or colibactin) will offer targets for small-molecule inhibitors.
- **Personalized microbiome therapies:** Development of defined microbial consortia or next-generation probiotics tailored to CRC subtypes is a priority. Engineered strains (e.g. *E. coli* or *Lactococcus* secreting checkpoint modulators or cytokines) could be designed for precision delivery. Phage therapy or CRISPR-based antimicrobials targeting specific pathogens (e.g. *Fusobacterium* or *P. anaerobius*) offer an alternative strategy[27]. Clinical-grade manufacturing and safety testing of such biotherapeutics will be crucial.
- **Combination therapies:** Microbiome modulation should be tested synergistically with other treatments. For example, pairing FMT or probiotics with chemo/immunotherapy in MSS CRC could overcome primary resistance. Preclinical models suggest that combining dietary fibers or prebiotic nanoparticles with chemotherapeutics dramatically enhances efficacy[21]. Such strategies should be translated into clinical trials. Additionally, exploration of timing (e.g. perioperative vs maintenance therapy) and route (oral vs enema vs local injection) of microbiome interventions is needed.
- **Predictive biomarkers and AI:** Machine learning approaches on large datasets may identify complex microbial signatures predictive of therapy response[24]. Incorporating microbial features into existing clinical models (e.g. Immunoscore, MSI status) could refine patient stratification. Development of simple assays (qPCR panels or microarrays) for key microbial markers

(e.g. *F. nucleatum* levels) will facilitate clinical adoption.

- **Regulatory and standardization efforts:** Establishing guidelines for FMT and live biotherapeutic use in oncology is essential. This includes donor screening, manufacturing quality control, and monitoring protocols. Consensus frameworks (similar to those for probiotics) will enable reproducible research and clinical implementation[14].
- **Broader host–microbe interactions:** Future work should consider the microbiome's systemic effects. For instance, gut microbes influence systemic metabolites (bile acids, SCFAs) and immune cell trafficking. Understanding how the gut-liver axis or gut-brain axis affects CRC may open new therapeutic angles.

In summary, a concerted effort combining deep biology, engineering and clinical science is needed. Priorities include validating causative microbe–immune pathways, leveraging microbial metabolites as drugs, and integrating microbiome modulation into precision oncology. With appropriate interdisciplinary collaboration, the gut microbiome may become an exploitable "organ" in the fight against CRC.

CONCLUSION

The gut microbiome is emerging as a pivotal factor in colorectal cancer biology, influencing both tumor development and treatment responses. On one hand, dysbiotic communities rich in genotoxic and pro-inflammatory microbes promote CRC via DNA damage, barrier breach and chronic immune activation[3]. On the other hand, commensal microbes and their metabolites are essential for effective antitumor immunity; their depletion underlies resistance in MSS CRC. Translationally, these insights are yielding novel approaches: microbiome-based diagnostics for early detection, and microbiome modulation (probiotics, FMT, diet) to enhance chemotherapy and immunotherapy. Preliminary trials demonstrate feasibility (e.g. FMT restoring PD-1 sensitivity[13]) and probiotic regimens reducing treatment toxicity[18,25].

Despite remaining gaps, the field is rapidly advancing toward clinical applications. Future research must rigorously validate causal mechanisms, develop standardized microbial therapeutics, and incorporate microbiome analysis into personalized care pathways. Ultimately, by attenuating tumor-promoting bacteria and enriching immune-boosting taxa, microbiome-focused strategies may unlock durable therapy responses in CRC patients[14]. In this way, the gut microbiome may transition from a biomarker of disease to a targetable organ in colorectal cancer management.

Declaration by Authors

Ethical Approval: Not Applicable. (As this is a narrative review of previously published literature and does not involve original research on human or animal subjects, formal ethical approval was not required.)

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