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GUT DYSBIOSIS IN THE ADENOMA-CARCINOMA SEQUENCE: A COMPREHENSIVE REVIEW OF CLINICAL AND PRECLINICAL EVIDENCE

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ABSTRACT

Background: Colorectal cancer (CRC) is a major oncological challenge increasingly linked to gut microbiota dysbiosis. Microbial alterations are believed to drive the progression from benign precursor lesions to invasive cancer along the adenoma-carcinoma sequence.
Aim: The aim of this review is to summarize current knowledge about the role of microbial alterations in the adenoma-carcinoma sequence, focusing on specific pro-tumorigenic pathogens - specifically Fusobacterium nucleatum, enterotoxigenic Bacteroides fragilis (ETBF), and pks+ Escherichia coli and their pathogenic mechanisms.
Material and methods: A literature review was conducted using PubMed and Google Scholar, focusing on articles published in English within the last eight years with a particular focus on recent evidence from 2019 to 2025. The search prioritized metagenomic analyses and preclinical studies regarding CRC, dysbiosis, and specific bacterial drivers using terms such as 'colorectal cancer', 'adenoma-carcinoma sequence', and 'gut microbiota'.
Results: Dysbiosis appears early in carcinogenesis, characterized by the depletion of beneficial butyrate-producers and expansion of pathobionts. Key pathogens drive tumorigenesis through distinct mechanisms, including toxin production (e.g., BFT, colibactin), DNA damage, and immune modulation. Functional evidence from murine models confirms a causal link, demonstrating that dysbiotic microbiota actively accelerates tumor growth and inflammation.
Conclusions: Intestinal dysbiosis is a fundamental, early driver of CRC pathogenesis, not merely a passive consequence. Identifying oncogenic bacteria offers new perspectives for early non-invasive diagnosis and therapeutic strategies to inhibit disease progression.

KEYWORDS

Colorectal Cancer, Gut Microbiota Dysbiosis, Adenoma-Carcinoma Sequence, Pro-Tumorigenic Bacteria, Murine Models

CITATION

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1. Introduction

Colorectal cancer (CRC) is one of the most common types of cancer. Based on 2022 WHO data, CRC is the third most frequently diagnosed malignancy and the second leading cause of cancer mortality worldwide (Bray et al., 2024). By 2030, CRC will be the leading cause of cancer mortality among adults aged 20–49 (Rahib et al., 2021). The alarming rise in CRC incidence and mortality among individuals younger than 50 years (Rahib et al., 2021; Siegel et al., 2024) emphasizes the urgent need to identify new etiological factors and establish better diagnostic strategies.

The development of CRC is a multistep process lasting several years, classically described as the adenoma-carcinoma sequence. While some cases are hereditary and associated with syndromes such as Lynch syndrome and familial adenomatous polyposis (FAP**)** (Valle et al., 2019), the majority of CRC cases are sporadic and have a complex etiology. The malignancy rarely arises *de novo* in healthy tissue; instead, it typically evolves from benign precursor lesions (adenomatous polyps)**.** The primary risk factors for sporadic CRC include age, a low fiber diet, obesity, smoking, alcohol consumption and sedentary lifestyle (Montalban-Arques & Scharl, 2019; Song & Chan, 2019). Healthy intestinal microbiota plays an important role in fermenting food, protecting against pathogens, stimulating the immune system, and producing vitamins in the human body (Alum et al., 2025). Dysbiosis, characterized by significant shifts in microbial population and composition, establishes a pro-tumorigenic microenvironment. This imbalance drives carcinogenesis by triggering a cascade of pathological events, including chronic inflammation, oxidative stress, and metabolic dysfunction (Wong & Yu, 2023). According to current literature, dysbiosis is detectable in the early stages of carcinogenesis and adenoma development (Xiang et al., 2024). Specifically, metagenomic analyses have

identified a distinctive global microbial signature associated with CRC, characterized by the enrichment of pro-carcinogenic species including oral pathobionts (e.g., *Fusobacterium nucleatum*, *Peptostreptococcus stomatis*) and gut-resident opportunists (e.g., *Bacteroides fragilis*, *Escherichia coli*) as well as the depletion of beneficial butyrate-producing commensals such as *Faecalibacterium prausnitzii, Roseburia intestinalis and Eubacterium rectale* (Thomas et al., 2019; Wirbel et al., 2019).

A number of studies have suggested that the gut microbiota as a major environmental factor capable of modulating host immunity and genomic stability (Park et al., 2022). Although the gut ecosystem also includes viruses, fungi, and archaea (Liu et al., 2022), this review focuses on the bacterial component, with a particular focus on *Fusobacterium nucleatum*, a pathogen commonly identified in the tumor microenvironment. The aim of this study is to examine the role of gut dysbiosis in the progression of the adenoma-carcinoma sequence, specifically focusing on the enrichment of pro-tumorigenic pathogens (*F. nucleatum*, ETBF, *pks+ E. coli*), their pathogenic mechanisms, and evidence from preclinical murine models confirming the causal link between dysbiosis and malignant transformation.

2. Methodology

2.1. Literature Search Strategy

A comprehensive literature search was conducted using major electronic databases, including PubMed, Google Scholar, Scopus, and Web of Science. The search strategy combined Medical Subject Headings (MeSH) terms with relevant free-text keywords associated with colorectal carcinogenesis and gut microbiology. Boolean operators (AND, OR) were applied to refine the search results (e.g., “dysbiosis AND colorectal cancer”, “microbiota AND adenoma”), ensuring a balance between comprehensiveness and specificity. The focus was on retrieving peer-reviewed articles published from 2017 to 2025, with particular emphasis on recent evidence from 2019 to 2025 to ensure the inclusion of the latest genomic and functional data.

2.2. Inclusion and Exclusion Criteria

To maintain scientific rigor and relevance, the inclusion criteria encompassed peer-reviewed original research articles, systematic reviews, meta-analyses, and comprehensive reviews published in English. The review specifically prioritized studies that provided metagenomic data on human cohorts or functional insights from preclinical (murine) models regarding the bacterial drivers of CRC. Studies were excluded if they lacked available full texts, were published in languages other than English, or focused exclusively on non-bacterial components of the microbiome (e.g., virome, mycobiome) without addressing bacterial dysbiosis. An initial screening of titles and abstracts was undertaken to remove irrelevant records and duplicates, followed by a full-text evaluation aligned with the predefined research objectives.

2.3. Types of Evidence Included

This review synthesizes evidence from high-level medical research, including clinical observational studies, metagenomic analyses, and preclinical *in vivo* models, focusing on the causal role of gut dysbiosis in the adenoma-carcinoma sequence.

2.4. Timeframe and Language

Only articles published in the English language within the timeframe of 2017 to 2025 were included in the final analysis, ensuring that the review reflects the most current state of knowledge in the rapidly evolving field of gut microbiota and colorectal cancer research.

3. Research Results

3.1. Microbiota Alterations Along the Adenoma-Carcinoma Sequence: Mechanisms and Methodological Context

The fundamental hypothesis underlying colorectal cancer (CRC) development is the "adenoma-carcinoma sequence," representing the stepwise progression from benign precursor lesions to invasive cancer (Dekker et al., 2019). The initiating event of this classic cascade is generally believed to be the inactivation of the APC (*adenomatous polyposis coli*) tumor suppressor gene, leading to the formation of adenomatous polyps, which are the most common premalignant lesions of sporadic CRC detected frequently in the aging population (Liang et al., 2020). Research indicates that the inactivation of APC is directly correlated with specific microbial shifts, including a reduction in beneficial species such as *Faecalibacterium prausnitzii* and *Bifidobacterium*, and an enrichment of opportunistic pathogens like *Fusobacterium mortiferum* (Liang et al.,

2020). This highlights the important 'gut-tumor connection', where dysbiosis not only promotes chronic inflammation but also induces the genetic and epigenetic alterations necessary for malignant transformation (Wei et al., 2025).

Colorectal cancer (CRC) develops as a result of a profound transformation of the gut microsystem that occurs prior to the development of the tumor's clinical appearance. However, in contrast to inflammatory bowel disease (IBD), where the loss of biodiversity (α-diversity) is typically observed, the situation in CRC is more nuanced and method dependent (Abdel-Rahman & Morgan, 2023; Song et al., 2024). Specifically, recent analyses have revealed that the factor 'study' often has a predominant impact on species composition, sometimes outweighing the biological effects of CRC itself. This heterogeneity is largely driven by differences in DNA extraction protocols between cohorts (Wirbel et al., 2019). Furthermore, results differ depending on the sequencing technology utilized. While earlier studies that used 16S rRNA amplicon sequencing frequently reported reduced α-diversity as a result of the loss of dominant commensals (W. Liu et al., 2020), deep metagenomic analyses (shotgun sequencing) show a more complex picture. Species richness can be paradoxically higher in CRC samples than in healthy controls. A major reason for this phenomenon is the massive infusion of oral pathobionts (oral-gut translocation) and the creation of a novel ecological niche by the tumor, which increases the total number of species detected despite the ongoing dysbiosis (Thomas et al., 2019).

3.1.1 Early Adenomatous Polyps

Despite technical variations, predictable patterns have emerged across populations, confirming that dysbiosis is not only a late-stage consequence but can already be detected early in adenomatous polyps (Wong & Yu, 2023). Detailed metagenomic analyses have revealed specific microbial profiles characteristic of the adenoma stage. The microbiome at this stage exhibits intermediate characteristics; however, a significant decline in beneficial commensals has already been observed. In a recent systematic meta-analysis of adenoma-carcinoma sequences, the presence of *Firmicutes*, particularly those belonging to the families *Lachnospiraceae* and *Ruminococcaceae*, was significantly reduced (Wu et al., 2024).

The taxa in this group are the primary producers of butyrate, a short-chain fatty acid (SCFA) that has anti-inflammatory function and maintains the integrity of intestinal barriers. Studies of patients with adenomatous polyps confirm that the loss of these protective populations creates a vacant niche (Hale et al., 2017). Some evidence suggests that this permissive environment is colonized by pro-inflammatory species from the phyla *Proteobacteria* and *Fusobacteriota* (Pop et al., 2020), although the findings vary across cohorts (Hale et al., 2017).

3.1.2 Advanced Adenomas (AA) and Metabolic Shifts

An important insight into the next phase of progression is provided by stage-specific analyses of patients with advanced adenomas (AA). Analysis of global community structure (β-diversity) demonstrated that the microbial profile of these advanced precursor lesions is significantly distinct from that of healthy controls, accompanied by a reduction in species richness (α-diversity) (Xiang et al., 2024). At the species level, this dysbiosis manifested as an enrichment of pathobionts, including *Escherichia coli* and unclassified *Enterobacteriaceae*, accompanied by a significant depletion of major butyrate-producers and beneficial commensals such as *Faecalibacterium prausnitzii* and multiple commensal *Bacteroides* species. This shift towards a pro-inflammatory profile and the loss of protective taxa reflects the dysbiotic patterns described in global meta-analyses of patients with established CRC (Wirbel et al., 2019). Functionally, these taxonomic shifts translate into profound metabolic alterations within the gut microenvironment. An analysis of metabolomic profiles of patients with adenomatous colon polyps (ACP) revealed high levels of bioactive lipids, including polyunsaturated fatty acids, sphingolipids, and secondary bile acids (Kim et al., 2020). The microbiome of AA exhibited upregulated degradation of aromatic compounds and tryptophan metabolism (Xiang et al., 2024). This metabolic shift is critical, as independent studies confirm that enhanced tryptophan catabolism plays a significant role in the development of CRC, directly linked to local immunosuppression and disease progression (Yachida et al., 2019; Zhang et al., 2019). A comprehensive summary of these metabolic alterations and their functional impact is presented in Table 1. These findings indicate that dysbiosis occurs early at the adenoma stage, driven by distinct metabolic and ecological shifts.

Table 1. Metabolic alterations and microbial drivers in colonic adenomas.

Metabolite Class	Trend in Adenoma/AA	Associated Bacterial Shift	Biological Consequence	Ref.
Short-Chain Fatty Acids (Butyrate)	Decrease (↓)	Depletion of *Firmicutes*, specifically families *Lachnospiraceae*, *Ruminococcaceae* (e.g., *F. prausnitzii*)	Loss of epithelial barrier integrity, reduced anti-inflammatory protection, potentially creating a microenvironment permissive for tumorigenesis	(Liang et al., 2020; Xiang et al., 2024)
Secondary Bile Acids (SBAs)	Increase(↑)	Enrichment of SBA-producing bacteria (e.g., specific *Clostridium* spp., *Bacteroides*)	Cytotoxicity to colonocytes, DNA damage, promotion of a pro-inflammatory microenvironment favorable for tumorigenesis	(Kim et al., 2020; Yachida et al., 2019)
Tryptophan Metabolites	Altered / Increase (↑) in progression	Upregulation of enzymatic pathways in specific taxa like *Peptostreptococcus*	Induction of local immunosuppression, facilitating immune evasion by early tumor cells.	(Yachida et al., 2019; Zhang et al., 2019)

3.2. Key Pro-Tumorigenic Pathogens

The human intestinal microbiota is dominated by four main phyla: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria* (W. Liu et al., 2020). However, during CRC development, this homeostatic balance is disrupted, allowing for the overgrowth of specific opportunistic pathogens. According to current research, a distinct pro-tumorigenic group is driving this process. This group includes enterotoxigenic *Bacteroides fragilis* (ETBF), *pks+ Escherichia coli*, *Fusobacterium nucleatum.*

3.2.1. Fusobacterium nucleatum: From Oral Commensal to Oncogenic Driver

Fusobacterium nucleatum is a Gram-negative, non-spore-forming anaerobic bacterium that is naturally present in the oral cavity. As an oral commensal, it plays a key role in the development and structural maturation of dental biofilms due to its unique ability to coaggregate with diverse bacteria (Brennan & Garrett, 2019). Current evidence suggests that it reaches the colon through the digestive tract and by hematogenous spread (Abed et al., 2020). Although traditionally considered a periodontal pathogen, recent studies have linked it to various extra-oral conditions, such as adverse pregnancy outcomes, cardiovascular disorders, inflammatory bowel disease (IBD), however it is most strongly associated with CRC at every stage of the disease (even metastases) (Brennan & Garrett, 2019; Bullman et al., 2017). A 2025 meta-analysis involving a large cohort of CRC patients estimated the global prevalence of *F. nucleatum* at 38.9% (Sameni et al., 2025).

The presence of *F. nucleatum* in the gut promotes the expression of tumor-associated cytokines and triggers an inflammatory response. However, recent genomic analyses have revealed that not all *F. nucleatum* strains are equally carcinogenic. Zepeda-Rivera et al. demonstrated that the *Fn* subspecies *animalis* (*Fna*) is actually divided into two distinct groups (*Fna* C1 and *Fna* C2). Of these, only the *Fna* C2 clade (which encompasses diverse pathogenic strains) dominates the CRC tumor niche, while *Fna* C1 is restricted to the oral cavity (Zepeda-Rivera et al., 2024). The pathogenicity of these tumor-associated strains is driven by specific virulence factors.

The carcinogenic potential of these strains is mediated by adhesins like FadA and Fap2, which target epithelial and endothelial cells. By engaging these cells, *F. nucleatum* alters signaling cascades and induces local inflammatory cytokines (including IL-1β, IL-6, IL-17, TNF-α, IFN-γ) and COX-2, while also activating the STAT3 pathway and promoting CD4+ T cell proliferation and Th1/Th17 differentiation (Bostanghadiri et al., 2023; H. Liu et al., 2020). These alterations occur within the tumor microenvironment (TME) and can promote crucial stages of CRC development (Bhat et al., 2022). The abundance of Fusobacterium nucleatum in CRC significantly increases from precancerous adenomatous lesions to carcinoma, suggesting that

Fusobacterium nucleatum is an important factor in the progression of CRC (Yachida et al., 2019). Many recent reports and meta-analyses confirmed that the abundance of *F. nucleatum* in CRC tissues is a strong independent predictor of worse prognosis and reduced overall survival (Kim et al., 2022). It has also been proven that its presence promotes resistance to chemotherapy (5-FU and oxaliplatin) by activating autophagy pathways (Ayabe & White, 2024).

F. nucleatum is recognized as a key bacterium promoting metastasis. Recent studies link this pathogen to the induction of specific signaling pathways, particularly the epithelial-to-mesenchymal transition (EMT), which actively promotes cancer progression (Wong & Yu, 2023).

Latest findings highlight the role of bacterial extracellular vesicles (BEVs) - nanoscale vesicles produced by Gram-positive and Gram-negative bacteria. BEVs carry a diverse cargo of biomolecules, including proteins, lipids, nucleic acids, and metabolites, and play an important role in host–microbe interactions. BEVs derived from Fusobacterium nucleatum promote metastasis of CRC by creating an immunosuppressive microenvironment. Immune evasion is enabled by polarizing macrophages into a tumor-supporting M2 phenotype, inhibiting dendritic cell maturation, and modulating T-cell responses. Furthermore, these vesicles promote cell proliferation and vascularization by delivering pro-angiogenic factors and oncogenic miR-21 (Bhanu et al., 2025).

3.2.2. Escherichia coli and Bacteroides fragilis

Other pathogens strongly linked to colorectal carcinogenesis are enterotoxigenic *Bacteroides fragilis* (ETBF) and *pks+ Escherichia coli.* Some types of *Escherichia coli*, such as *pks+* strains expressing polyketide synthases, produce colibactin - a genotoxin capable of alkylating DNA, inducing double-strand breaks, and promoting tumor growth (Yang et al., 2020). Moreover, *E. coli* releases extracellular vesicles (BEVs) that serve as carriers of bioactive factors. This role is strain-dependent: while BEVs from *pks+* strains carry toxic cargo and ABC transporters that reduce chemotherapy effectiveness (Bhanu et al., 2025), vesicles derived from laboratory strains (EcEVs) show therapeutic potential by repairing the intestinal epithelium and selectively destroying tumor cells (Liang et al., 2024). *Bacteroides fragilis* is typically an intestinal commensal, estimated to be present in 42.5% of CRC patients (Sameni et al., 2025). However its enterotoxigenic subtype (ETBF) acts as a distinct driver of colorectal carcinogenesis. ETBF promotes tumorigenesis through the secretion of *B. fragilis* toxin (BFT), which cleaves E-cadherin, disrupting mucosal barriers and activating signaling pathways that promote inflammation and cancer proliferation (Sameni et al., 2025). Research by Dejea *et al.* demonstrated that co-colonization of toxigenic *E. coli* and ETBF in mice caused increased production of pro-inflammatory IL-17 and subsequent DNA damage, resulting in an accelerated development of CRC (Dejea et al., 2018).

3.3. Functional Validation in Murine Models

3.3.1. Overview of Experimental Models

Although metagenomic studies in humans have shown strong links between dysbiosis and colorectal cancer (CRC), they do not allow us to conclusively determine whether these changes are the cause or merely the effect of the disease. Functional studies in murine models have played an important role in providing compelling evidence that the microbiota actively promotes carcinogenesis. Murine models enable researchers to observe and control the progression of complex diseases like CRC. These models are valued not only for their cost-effectiveness, manageability, and close anatomical resemblance to humans, but also for their genetic amenability (Neto et al., 2023). Two types of mouse models are primarily used in research on colon carcinogenesis: chemically induced (e.g., AOM/DSS) and genetically modified.

The most commonly used chemicals to induce CRC are 1,2-dimethylhydrazine (DMH) and its metabolite azoxymethane (AOM). In addition to being potent carcinogens, they cause mutations in a variety of cellular signaling genes. Frequently, these are combined with Dextran Sodium Sulfate (DSS). DSS is a non-genotoxic pro-inflammatory agent used to model acute and chronic colitis in rodents (Neto et al., 2023).

The second major category includes Genetically Engineered Murine Models (GEMMs), which are designed to mimic the spontaneous mutations found in human CRC. The malignant phenotype is frequently associated with mutations in multiple genes such as *KRAS*, *p53*, and *APC* (Valle et al., 2019). Therefore, models targeting these mutations are essential**.** Among these, mice with defects in the Adenomatous Polyposis Coli (*APC*) gene are particularly relevant. This is because *APC* inactivation is the initiating event in approximately 90% of human colorectal cancers. As a result, the $Apc^{min/+}$ mouse has become the gold standard for studying early genetic interaction with environmental factors (Neto et al., 2023).

3.3.2. Evidence from Fecal Microbiota Transplantation (FMT)

Early evidence of a causal link to CRC development was provided by Wong et al., who conducted experiments involving fecal microbiota transplantation (FMT) from CRC patients into germ-free mice and antibiotic-treated mice (to induce microbiota depletion), followed by exposure to azoxymethane (AOM). The authors used an AOM-alone model to avoid the overly inflammatory effects of DSS, thereby ensuring that the transplanted microbiota were responsible for tumor promotion. Results showed that animals receiving microbiota from cancer patients developed significantly more high-grade dysplastic lesions and macroscopic polyps compared to controls receiving microbiota from healthy individuals. Complementary analyses revealed the molecular basis for this phenomenon: inoculation with oncogenic microbiota led to the upregulation of genes associated with the Th17 inflammatory response (including *Il17a*, *Il22*, and *Il23a*) and increased proliferation of intestinal epithelial cells. This confirms that the dysbiotic bacterial community itself has oncogenic potential capable of driving tumor initiation (Wong et al., 2017).

These results were partially confirmed and expanded upon by Song et al. (2024) using a pseudo-germ-free, colitis-associated CRC model (AOM/DSS). Unlike previous studies focusing solely on the risk posed by dysbiosis, this research highlighted the dual nature of gut microbial interactions. The authors demonstrated that while mice colonized with stool from CRC patients (CRC-FMT) exhibited inflammation and a higher tumor burden, transplantation from healthy controls (HC-FMT) exerted a protective effect.

In support of the adenoma-carcinoma hypothesis, the study demonstrated that the microbiota of patients with premalignant adenomas (CRA-FMT) also promoted carcinogenesis. Although phenotypic severity (number and volume of tumors) was most marked in the CRC group.

The fact that microflora derived from CRA already accelerated disease progression confirms that dysbiosis is an early factor promoting its development.

At the molecular level, these cancer-promoting phenotypes (CRC, CRA, and IBD) shared common features characterized by increased expression of the proliferation marker *Ki-67* and inflammatory mediators (*TNF-α, COX-2, Th1/Th17 cells*). In contrast, HC-FMT downregulated these factors, likely due to the enrichment of beneficial taxa such as *Faecalibacterium* and *Ruminococcus*. Consequently, this protection was linked to the restoration of intestinal barrier integrity and the effective suppression of pro-inflammatory signaling cascades. This finding suggests that re-establishing a eubiotic microbial community does not only neutralize risk but can actively suppress tumor development (Song et al., 2024).

To further investigate the role of dysbiosis in tumor progression, Li et al, used the *Apc* $^{min/+}$ genetic model, mimicking the hereditary predisposition observed in humans. It was observed that oral administration of stool samples from CRC patients significantly accelerated the progression of benign adenomas to invasive carcinomas. Microbiological analysis revealed that the levels of opportunistic pathogens, including *Escherichia coli*, *Helicobacter*, and *Prevotella*, increased, while the abundance of short-chain fatty acid (SCFA)-producing bacteria, such as *Ruminococcus* and *Roseburia*, was significantly lower in the group receiving samples from CRC patients. This dysbiosis led to impaired gut barrier function and chronic low-grade inflammation, evidenced by the upregulation of pro-inflammatory markers (*NLRP3*, *IL-1β*, and *TNF-α*). Mechanistically, this effect was linked to the hyperactivation of the *Wnt/β-catenin* signaling pathway and the subsequent upregulation of target genes like *Cyclin D1* and *c-Myc*, thereby promoting cell proliferation and inhibiting apoptosis. This suggests that even in a genetically susceptible host, the gut microbiota acts as a critical accelerator of neoplastic transformation (Li et al., 2019).

3.3.3. Host Genetics and Bacterial Invasion: The ZEB2 Model

Further analyses by Slowicka et al. demonstrated a new significant relationship between host genetics and bacterial invasion. In their study, the authors used a mouse model with epithelial-specific overexpression of ZEB2 (*Zeb2*$^{IEC\text{-}Tg/+}$), a transcription factor that interacts with the TGF-β signaling pathway. It has been shown that ZEB2 expression induces epithelial-mesenchymal transition (EMT), leading to loss of intestinal barrier integrity. This structural disruption allows the commensal microbiota to infiltrate deeper layers of the intestinal wall, triggering a strong inflammatory response driven by myeloid cells, including macrophages and neutrophils (recruited, among others, by the chemokine CXCL1). Important evidence for the key role of bacteria in this process is the fact that in *Zeb2*$^{IEC\text{-}Tg/+}$ mice, cancerous lesions developed exclusively in the large intestine, while the epithelium of the small intestine remained normal. The authors attribute this to the significantly lower number of bacteria in the small intestine, which is insufficient to cause pathological inflammation. Furthermore, while *Zeb2*$^{IEC\text{-}Tg/+}$ mice with preserved microbiota spontaneously developed invasive cancer, the removal of bacteria (using broad-spectrum antibiotics) completely prevented

carcinogenesis. Interestingly, selective depletion of Gram-positive bacteria (using vancomycin) was sufficient to inhibit tumorigenesis, suggesting a key role for this group of microorganisms in driving pathology in this model. Molecularly, this process was characterized by the activation of the oncogenic factor STAT3 and the TGF-β pathway, as well as the overexpression of CD44, a stem cell marker associated with tumor aggressiveness. Importantly, targeted sequencing analyses did not reveal the presence of hot-spot mutations in key CRC genes such as *APC, KRAS,* or *TP53* in these tumors. The authors of the study indicate that the $Zeb2^{IEC\text{-}Tg/+}$ mouse model is a new, unique tool that not only allows for the study of the mechanisms through which the microbiota drives cancer development, but also for the validation of new microbiota-based therapeutic strategies in the treatment of invasive forms of the disease (Slowicka et al., 2020).

In summary, these findings highlight the important interdependence between host genetics and the microbiome. While genetic predisposition initiates the process, dysbiotic microbiota acts as a necessary environmental trigger that induces inflammation and drives the transition to invasive cancer.

4. Discussion

Understanding the role of gut microbiota in the adenoma-carcinoma sequence represents a fundamental change in our view of colon carcinogenesis. Unlike traditional models focusing solely on host genetics, current evidence points to dysbiosis as a key environmental driver of malignant transformation. Microbial alterations are detectable as early as the adenoma stage, characterized specifically by the depletion of butyrate-producing *Firmicutes* and an enrichment of oral pathobionts. Therefore, these distinct signatures could serve as sensitive, non-invasive biomarkers for early detection, potentially complementing existing screening methods such as colonoscopy or immunochemical Fecal Occult Blood Test (iFOBT).

However, diagnostic potential is only one aspect; recent genomic studies have also refined our understanding of the pathogenic mechanisms. It appears that CRC is driven by specific virulent strains, such as the F. nucleatum animalis C2 clade, rather than by bacterial species in general. The distinct pathogenicity of these strains is mediated by specific adhesins (e.g., FadA, Fap2), which facilitate adherence to the epithelium and evasion of the immune system.

Beyond *F. nucleatum*, other key pathogens demonstrate direct genotoxic capabilities**.** For instance, *pks+ E. coli* produces colibactin to induce DNA double-strand breaks, while the BFT toxin from *ETBF* cleaves E-cadherin to disrupt the mucosal barrier. These diverse virulence factors - whether through immune modulation or direct DNA damage - contribute to the creation of a microenvironment conducive to tumor growth, which drives disease progression and can cause resistance to chemotherapy.

Despite consistent preclinical findings, translating this knowledge into clinical practice remains challenging. While murine models (e.g., *Zeb2*-overexpressing or *Apc*-mutant mice) demonstrate a clear cause-and-effect relationship, human data are primarily based on observational studies susceptible to confounding factors such as diet and geography.

The dual nature of the microbiota - where commensals can inhibit tumor growth while pathogens promote it - complicates therapeutic interventions. Simple eradication with broad-spectrum antibiotics is potentially harmful; instead, precise modulation strategies, such as targeted bacteriophages, next-generation probiotics, or rigorous FMT protocols, require validation in controlled clinical trials.

5. Conclusions

Intestinal dysbiosis is not just a secondary effect of disease but plays a fundamental and early role in the pathogenesis of colorectal cancer. Imbalances in the intestinal ecosystem are detectable as early as the precancerous stage, manifesting as a loss of beneficial butyrate-producing bacteria and the progressive expansion of pathobionts. *Fusobacterium nucleatum* (specifically the C2 clade), enterotoxigenic *Bacteroides fragilis* (ETBF), and *pks+ Escherichia coli* are key drivers of this process. These microorganisms drive cancerous transformation by producing genotoxins, degrading epithelial barriers, and modulating immune responses, which promotes genomic instability and chronic inflammation.

Functional studies on preclinical models confirm that the dysbiotic bacterial profile itself possesses carcinogenic potential, capable of activating proliferative pathways such as Wnt/β-catenin. Moreover, modern genetic models provide compelling evidence that even with strong host genetic predisposition, the microbiota may act as a necessary environmental trigger for the development of invasive cancer. Future research should focus on large - scale longitudinal studies to validate microbial biomarkers and on the development of targeted therapeutic strategies aimed at restoring microbial homeostasis to inhibit progression along the adenoma-carcinoma sequence.

Disclosures

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REFERENCES

1. Abdel-Rahman, L. I. H., & Morgan, X. C. (2023). Searching for a Consensus Among Inflammatory Bowel Disease Studies: A Systematic Meta-Analysis. *Inflamm Bowel Dis*, *29*(1), 125-139. https://doi.org/10.1093/ibd/izac194
2. Abed, J., Maalouf, N., Manson, A. L., Earl, A. M., Parhi, L., Emgård, J. E. M., Klutstein, M., Tayeb, S., Almogy, G., Atlan, K. A., Chaushu, S., Israeli, E., Mandelboim, O., Garrett, W. S., & Bachrach, G. (2020). Colon Cancer-Associated Fusobacterium nucleatum May Originate From the Oral Cavity and Reach Colon Tumors via the Circulatory System. *Front Cell Infect Microbiol*, *10*, 400. https://doi.org/10.3389/fcimb.2020.00400
3. Alum, E. U., Uti, D. E., Ugwu, O. P., Alum, B. N., Edeh, F. O., & Ainebyoona, C. (2025). Unveiling the microbial orchestra: exploring the role of microbiota in cancer development and treatment. *Discov Oncol*, *16*(1), 646. https://doi.org/10.1007/s12672-025-02352-2
4. Ayabe, R. I., & White, M. G. (2024). Metastasis and the Microbiome: The Impact of Bacteria in Disseminated Colorectal Cancer. *Front Biosci (Landmark Ed)*, *29*(4), 152. https://doi.org/10.31083/j.fbl2904152
5. Bhanu, P., Godwin, A. K., Umar, S., & Mahoney, D. E. (2025). Bacterial Extracellular Vesicles in Oncology: Molecular Mechanisms and Future Clinical Applications. *Cancers (Basel)*, *17*(11). https://doi.org/10.3390/cancers17111774
6. Bhat, A. A., Nisar, S., Singh, M., Ashraf, B., Masoodi, T., Prasad, C. P., Sharma, A., Maacha, S., Karedath, T., Hashem, S., Yasin, S. B., Bagga, P., Reddy, R., Frennaux, M. P., Uddin, S., Dhawan, P., Haris, M., & Macha, M. A. (2022). Cytokine- and chemokine-induced inflammatory colorectal tumor microenvironment: Emerging avenue for targeted therapy. *Cancer Commun (Lond)*, *42*(8), 689-715. https://doi.org/10.1002/cac2.12295
7. Bostanghadiri, N., Razavi, S., Shariati, A., Talebi, M., Mirkalantari, S., Emami Razavi, A., & Darban-Sarokhalil, D. (2023). Exploring the interplay between *Fusobacterium nucleatum* with the expression of microRNA, and inflammatory mediators in colorectal cancer. *Front Microbiol*, *14*, 1302719. https://doi.org/10.3389/fmicb.2023.1302719
8. Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, *74*(3), 229-263. https://doi.org/10.3322/caac.21834
9. Brennan, C. A., & Garrett, W. S. (2019). Fusobacterium nucleatum - symbiont, opportunist and oncobacterium. *Nat Rev Microbiol*, *17*(3), 156-166. https://doi.org/10.1038/s41579-018-0129-6

10. Bullman, S., Pedamallu, C. S., Sicinska, E., Clancy, T. E., Zhang, X., Cai, D., Neuberg, D., Huang, K., Guevara, F., Nelson, T., Chipashvili, O., Hagan, T., Walker, M., Ramachandran, A., Diosdado, B., Serna, G., Mulet, N., Landolfi, S., Ramon Y Cajal, S.,…Meyerson, M. (2017). Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer. *Science*, *358*(6369), 1443-1448. https://doi.org/10.1126/science.aal5240
11. Dejea, C. M., Fathi, P., Craig, J. M., Boleij, A., Taddese, R., Geis, A. L., Wu, X., DeStefano Shields, C. E., Hechenbleikner, E. M., Huso, D. L., Anders, R. A., Giardiello, F. M., Wick, E. C., Wang, H., Wu, S., Pardoll, D. M., Housseau, F., & Sears, C. L. (2018). Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria. *Science*, *359*(6375), 592-597. https://doi.org/10.1126/science.aah3648
12. Dekker, E., Tanis, P. J., Vleugels, J. L. A., Kasi, P. M., & Wallace, M. B. (2019). Colorectal cancer. *Lancet*, *394*(10207), 1467-1480. https://doi.org/10.1016/S0140-6736(19)32319-0
13. Hale, V. L., Chen, J., Johnson, S., Harrington, S. C., Yab, T. C., Smyrk, T. C., Nelson, H., Boardman, L. A., Druliner, B. R., Levin, T. R., Rex, D. K., Ahnen, D. J., Lance, P., Ahlquist, D. A., & Chia, N. (2017). Shifts in the Fecal Microbiota Associated with Adenomatous Polyps. *Cancer Epidemiol Biomarkers Prev*, *26*(1), 85-94. https://doi.org/10.1158/1055-9965.EPI-16-0337
14. Kim, M., Vogtmann, E., Ahlquist, D. A., Devens, M. E., Kisiel, J. B., Taylor, W. R., White, B. A., Hale, V. L., Sung, J., Chia, N., Sinha, R., & Chen, J. (2020). Fecal Metabolomic Signatures in Colorectal Adenoma Patients Are Associated with Gut Microbiota and Early Events of Colorectal Cancer Pathogenesis. *mBio*, *11*(1). https://doi.org/10.1128/mBio.03186-19
15. Kim, Y., Cho, N. Y., & Kang, G. H. (2022). Prognostic and clinicopathological significance of Fusobacterium nucleatum in colorectal cancer: a systemic review and meta-analysis. *J Pathol Transl Med*, *56*(3), 144-151. https://doi.org/10.4132/jptm.2022.03.13
16. Li, L., Li, X., Zhong, W., Yang, M., Xu, M., Sun, Y., Ma, J., Liu, T., Song, X., Dong, W., Liu, X., Chen, Y., Liu, Y., Abla, Z., Liu, W., Wang, B., Jiang, K., & Cao, H. (2019). Gut microbiota from colorectal cancer patients enhances the progression of intestinal adenoma in $Apc^{min/+}$mice. *EBioMedicine*, *48*, 301-315. https://doi.org/10.1016/j.ebiom.2019.09.021
17. Liang, A., Korani, L., Yeung, C. L. S., Tey, S. K., & Yam, J. W. P. (2024). The emerging role of bacterial extracellular vesicles in human cancers. *J Extracell Vesicles*, *13*(10), e12521. https://doi.org/10.1002/jev2.12521
18. Liang, S., Mao, Y., Liao, M., Xu, Y., Chen, Y., Huang, X., Wei, C., Wu, C., Wang, Q., Pan, X., & Tang, W. (2020). Gut microbiome associated with APC gene mutation in patients with intestinal adenomatous polyps. *Int J Biol Sci*, *16*(1), 135-146. https://doi.org/10.7150/ijbs.37399
19. Liu, H., Hong, X. L., Sun, T. T., Huang, X. W., Wang, J. L., & Xiong, H. (2020). Fusobacterium nucleatum exacerbates colitis by damaging epithelial barriers and inducing aberrant inflammation. *J Dig Dis*, *21*(7), 385-398. https://doi.org/10.1111/1751-2980.12909
20. Liu, N. N., Jiao, N., Tan, J. C., Wang, Z., Wu, D., Wang, A. J., Chen, J., Tao, L., Zhou, C., Fang, W., Cheong, I. H., Pan, W., Liao, W., Kozlakidis, Z., Heeschen, C., Moore, G. G., Zhu, L., Chen, X., Zhang, G.,…Wang, H. (2022). Multi-kingdom microbiota analyses identify bacterial-fungal interactions and biomarkers of colorectal cancer across cohorts. *Nat Microbiol*, *7*(2), 238-250. https://doi.org/10.1038/s41564-021-01030-7
21. Liu, W., Zhang, R., Shu, R., Yu, J., Li, H., Long, H., Jin, S., Li, S., Hu, Q., Yao, F., Zhou, C., Huang, Q., Hu, X., Chen, M., Hu, W., Wang, Q., Fang, S., & Wu, Q. (2020). Study of the Relationship between Microbiome and Colorectal Cancer Susceptibility Using 16SrRNA Sequencing. *Biomed Res Int*, *2020*, 7828392. https://doi.org/10.1155/2020/7828392
22. Montalban-Arques, A., & Scharl, M. (2019). Intestinal microbiota and colorectal carcinoma: Implications for pathogenesis, diagnosis, and therapy. *EBioMedicine*, *48*, 648-655. https://doi.org/10.1016/j.ebiom.2019.09.050
23. Neto, Í., Rocha, J., Gaspar, M. M., & Reis, C. P. (2023). Experimental Murine Models for Colorectal Cancer Research. *Cancers (Basel)*, *15*(9). https://doi.org/10.3390/cancers15092570
24. Park, E. M., Chelvanambi, M., Bhutiani, N., Kroemer, G., Zitvogel, L., & Wargo, J. A. (2022). Targeting the gut and tumor microbiota in cancer. *Nat Med*, *28*(4), 690-703. https://doi.org/10.1038/s41591-022-01779-2
25. Pop, O. L., Vodnar, D. C., Diaconeasa, Z., Istrati, M., Bințințan, A., Bințințan, V. V., Suharoschi, R., & Gabbianelli, R. (2020). An Overview of Gut Microbiota and Colon Diseases with a Focus on Adenomatous Colon Polyps. *Int J Mol Sci*, *21*(19). https://doi.org/10.3390/ijms21197359
26. Rahib, L., Wehner, M. R., Matrisian, L. M., & Nead, K. T. (2021). Estimated Projection of US Cancer Incidence and Death to 2040. *JAMA Netw Open*, *4*(4), e214708. https://doi.org/10.1001/jamanetworkopen.2021.4708
27. Sameni, F., Elkhichi, P. A., Dadashi, A., Sadeghi, M., Goudarzi, M., Eshkalak, M. P., & Dadashi, M. (2025). Global prevalence of Fusobacterium nucleatum and Bacteroides fragilis in patients with colorectal cancer: an overview of case reports/case series and meta-analysis of prevalence studies. *BMC Gastroenterol*, *25*(1), 71. https://doi.org/10.1186/s12876-025-03664-x
28. Siegel, R. L., Giaquinto, A. N., & Jemal, A. (2024). Cancer statistics, 2024. *CA Cancer J Clin*, *74*(1), 12-49. https://doi.org/10.3322/caac.21820
29. Slowicka, K., Petta, I., Blancke, G., Hoste, E., Dumas, E., Sze, M., Vikkula, H., Radaelli, E., Haigh, J. J., Jonckheere, S., Taminau, J., Vandamme, N., Wullaert, A., Tulchinsky, E., Nittner, D., Van Vlierberghe, P., De Hertogh, G., Baldin, P., Etlioglu, E.,…van Loo, G. (2020). Zeb2 drives invasive and microbiota-dependent colon carcinoma. *Nat Cancer*, *1*(6), 620-634. https://doi.org/10.1038/s43018-020-0070-2

30. Song, M., & Chan, A. T. (2019). Environmental Factors, Gut Microbiota, and Colorectal Cancer Prevention. *Clin Gastroenterol Hepatol*, *17*(2), 275-289. https://doi.org/10.1016/j.cgh.2018.07.012
31. Song, Q., Gao, Y., Liu, K., Tang, Y., Man, Y., & Wu, H. (2024). Gut microbial and metabolomics profiles reveal the potential mechanism of fecal microbiota transplantation in modulating the progression of colitis-associated colorectal cancer in mice. *J Transl Med*, *22*(1), 1028. https://doi.org/10.1186/s12967-024-05786-4
32. Thomas, A. M., Manghi, P., Asnicar, F., Pasolli, E., Armanini, F., Zolfo, M., Beghini, F., Manara, S., Karcher, N., Pozzi, C., Gandini, S., Serrano, D., Tarallo, S., Francavilla, A., Gallo, G., Trompetto, M., Ferrero, G., Mizutani, S., Shiroma, H.,…Segata, N. (2019). Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. *Nat Med*, *25*(4), 667-678. https://doi.org/10.1038/s41591-019-0405-7
33. Valle, L., Vilar, E., Tavtigian, S. V., & Stoffel, E. M. (2019). Genetic predisposition to colorectal cancer: syndromes, genes, classification of genetic variants and implications for precision medicine. *J Pathol*, *247*(5), 574-588. https://doi.org/10.1002/path.5229
34. Wei, Z., Gao, G., He, Q., Kwok, L. Y., & Sun, Z. (2025). The gut-tumor connection: the role of microbiota in cancer progression and treatment strategies. *J Adv Res*. https://doi.org/10.1016/j.jare.2025.08.038
35. Wirbel, J., Pyl, P. T., Kartal, E., Zych, K., Kashani, A., Milanese, A., Fleck, J. S., Voigt, A. Y., Palleja, A., Ponnudurai, R., Sunagawa, S., Coelho, L. P., Schrotz-King, P., Vogtmann, E., Habermann, N., Niméus, E., Thomas, A. M., Manghi, P., Gandini, S.,…Zeller, G. (2019). Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. *Nat Med*, *25*(4), 679-689. https://doi.org/10.1038/s41591-019-0406-6
36. Wong, C. C., & Yu, J. (2023). Gut microbiota in colorectal cancer development and therapy. *Nat Rev Clin Oncol*, *20*(7), 429-452. https://doi.org/10.1038/s41571-023-00766-x
37. Wong, S. H., Zhao, L., Zhang, X., Nakatsu, G., Han, J., Xu, W., Xiao, X., Kwong, T. N. Y., Tsoi, H., Wu, W. K. K., Zeng, B., Chan, F. K. L., Sung, J. J. Y., Wei, H., & Yu, J. (2017). Gavage of Fecal Samples From Patients With Colorectal Cancer Promotes Intestinal Carcinogenesis in Germ-Free and Conventional Mice. *Gastroenterology*, *153*(6), 1621-1633.e1626. https://doi.org/10.1053/j.gastro.2017.08.022
38. Wu, Y. J., Xiong, J. F., Zhan, C. N., & Xu, H. (2024). Gut microbiota alterations in colorectal adenoma-carcinoma sequence based on 16S rRNA gene sequencing: A systematic review and meta-analysis. *Microb Pathog*, *195*, 106889. https://doi.org/10.1016/j.micpath.2024.106889
39. Xiang, J., Chai, N., Li, L., Hao, X., & Linghu, E. (2024). Alterations of Gut Microbiome in Patients with Colorectal Advanced Adenoma by Metagenomic Analyses. *Turk J Gastroenterol*, *35*(11), 859-868. https://doi.org/10.5152/tjg.2024.24294
40. Yachida, S., Mizutani, S., Shiroma, H., Shiba, S., Nakajima, T., Sakamoto, T., Watanabe, H., Masuda, K., Nishimoto, Y., Kubo, M., Hosoda, F., Rokutan, H., Matsumoto, M., Takamaru, H., Yamada, M., Matsuda, T., Iwasaki, M., Yamaji, T., Yachida, T.,…Yamada, T. (2019). Metagenomic and metabolomic analyses reveal distinct stage-specific phenotypes of the gut microbiota in colorectal cancer. *Nat Med*, *25*(6), 968-976. https://doi.org/10.1038/s41591-019-0458-7
41. Yang, Y., Gharaibeh, R. Z., Newsome, R. C., & Jobin, C. (2020). Amending microbiota by targeting intestinal inflammation with TNF blockade attenuates development of colorectal cancer. *Nat Cancer*, *1*(7), 723-734. https://doi.org/10.1038/s43018-020-0078-7
42. Zepeda-Rivera, M., Minot, S. S., Bouzek, H., Wu, H., Blanco-Míguez, A., Manghi, P., Jones, D. S., LaCourse, K. D., Wu, Y., McMahon, E. F., Park, S. N., Lim, Y. K., Kempchinsky, A. G., Willis, A. D., Cotton, S. L., Yost, S. C., Sicinska, E., Kook, J. K., Dewhirst, F. E.,…Johnston, C. D. (2024). A distinct Fusobacterium nucleatum clade dominates the colorectal cancer niche. *Nature*, *628*(8007), 424-432. https://doi.org/10.1038/s41586-024-07182-w
43. Zhang, H. L., Zhang, A. H., Miao, J. H., Sun, H., Yan, G. L., Wu, F. F., & Wang, X. J. (2019). Targeting regulation of tryptophan metabolism for colorectal cancer therapy: a systematic review. *RSC Adv*, *9*(6), 3072-3080. https://doi.org/10.1039/c8ra08520j