

The Gut Microbiome and Its Multifaceted Role in Cancer Metabolism, Initiation, and Progression: Insights and Therapeutic Implications

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Abstract

This review summarizes the intricate relationship between the microbiome and cancer initiation and development. Microbiome alterations impact metabolic pathways, immune responses, and gene expression, which can accelerate or mitigate cancer progression. We examine how dysbiosis affects tumor growth, metastasis, and treatment resistance. Additionally, we discuss the potential of microbiome-targeted therapies, such as probiotics and fecal microbiota transplants, to modulate cancer metabolism. These interventions offer the possibility of reversing or controlling cancer progression, enhancing the efficacy of traditional treatments like chemotherapy and immunotherapy. Despite promising developments, challenges remain in identifying key microbial species and pathways and validating microbiome-targeted therapies through large-scale clinical trials. Nonetheless, the intersection of microbiome research and cancer initiation and development presents an exciting frontier for innovative therapies. This review offers a fresh perspective on cancer initiation and development by integrating microbiome insights, highlighting the potential for interdisciplinary research to enhance our understanding of cancer progression and treatment strategies.

Keywords

gut microbiome, cancer, mechanism, biomarker, therapy

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Introduction

The microbiome—which comprises bacteria, archaea, fungi, and viruses—inhabits diverse body sites (eg, gut, oral cavity, skin) and plays a critical role in regulating host physiology. Notably, the complex gut microbiome is localized to the gastrointestinal mucosa.¹ Currently, bacteria are the most studied microorganisms in the gut microbiome, consisting of phyla Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria.² These microorganisms convert the substances in the host GI tract into a variety of microbiome metabolites, such as short-chain fatty acids (SCFAs), metabolites of amino acids, vitamins, conjugated lipids, and secondary bile acids, to interact with host tissues and cells to affect host physiology.³ The gut microbiome shifts when the host suffers from diseases, such as autoimmune disease, type 2 diabetes, brain disease, inflammatory bowel disease, liver disease, etc.⁴ Thus, studying the gut microbiome's role in the host's physiological and pathophysiological state is critical.

One of the most important aspects that is affected by the gut microbiome is the host metabolism. The association between the gut microbiome and host metabolism is established through individuals who take antibiotics and have reduced weight compared to those who do not.⁵ Animal studies reveal that antibiotic-treated and germ-free models exhibit reduced body weight, while fecal transplantation restores normal weight—underscoring the gut microbiome's key role in energy

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homeostasis.⁵ This link is further supported by the differences in the gut microbiome between obese and lean preclinical models and individuals.^{5,6}

Building on these observations, subsequent studies have focused on how the gut microbiome communicates with host tissues to regulate energy intake, expenditure, and overall metabolic homeostasis. Currently, the gut microbiome regulates energy intake in two major ways. First, metabolites from the gut microbiome directly or indirectly participate in the caloric extraction from the food. One example is that the SCFAs, the fermented products from indigestible fiber, are involved in the different tissue energy metabolism, allowing the host to access the inaccessible calories without the gut microbiome. Butyrate is used as the energy source for colonocytes.^{7–9} Propionate is a substrate for gluconeogenesis in the intestine and liver.^{7,10} Astrocytes use acetate as an alternative energy source other than glucose.^{11–13} SCFAs also modulate incretin hormones to regulate appetite. Previous publications have shown that SCFAs regulate GLP-1 and PYY secretion from enteroendocrine cells via an FFAR2-mediated pathway, indirectly involving energy intake by controlling intestinal motility and appetite.^{14,15} Acetate, the most abundant SCFA, elevates the parasympathetic output, increasing food intake.¹⁶ Second, metabolites from the gut microbiome modulate energy expenditure through various mechanisms. Butyrate has been shown to increase energy expenditure in muscles, brown adipose tissue (BAT), and beige adipose tissue.^{17–19} Regarding increased BAT thermogenesis, butyrate has been shown to increase sympathetic output to BAT and BAT UCP1 expression, the key gene for thermogenesis.^{17–19} Butyrate enhances energy expenditure in beige adipose tissue and muscle by elevating fatty acid oxidation.^{17–19} These studies further reveal the gut microbiome's role in the host energy balance.¹⁷

The gut microbiome also plays important roles in carbohydrate, amino acid, and lipid metabolisms. Studies have shown that the gut microbiome regulates the insulin signaling pathway, enteroendocrine cell functions, and bile acid signaling via imidazole propionate, SCFAs, and FXR/TGR5 to maintain whole-body glucose metabolism homeostasis.^{5,20} Amino acids and their derivatives produced by the gut microbiome, especially tryptophan, and its metabolites, significantly affect intestinal permeability and immunity.^{21–23} The gut microbiome also impacts lipid metabolism by further processing the lipid. One example is that one bacterium can metabolize cholesterol into sterol, which is hardly absorbed by the intestine.²⁴ In addition, the gut microbiome can convert primary bile acids into secondary bile acids to regulate lipid metabolism.²⁵ This evidence further implies the complicated role of the gut microbiome in host metabolism.

Cancer, a disease that requires an adequate energy supply for proliferation, invasion, metastasis, and escape from the immune system censoring, has also been explored for its relationship with the microbiome. In this review, we elaborate on the correlation between cancer incidence and microbiome changes, which leads to searching for possible biomarkers for cancer diagnosis and treatment therapies. We also summarized the

major metabolic pathways and immune responses impacted by microbiome dysbiosis, which contribute to or impair carcinogenesis.

Microbiome Epidemiology and Epigenetic Alterations in Cancer

The first association of the gut microbiome with cancer was established in 1970 when germ-free mice subject to 1,2-dimethylhydrazine had less tumor load.²⁶ Later, studies have shown that cancer incidence is reduced in germ-free or antibiotic-treated mice, suggesting that the gut microbiome plays a role in tumorigenesis.^{27–30} With the ability to differentiate gut microbiome species using 16S ribosomal RNA sequencing, the correlation between the gut microbiome and cancer is stratified to the phylum level to order or class or even further to species. Etiology studies comparing the gut microbiome between healthy individuals and cancer patients, focusing on gut microbiome changes, have reached substantial results. The major characteristic present in cancer patients is gut microbiome dysbiosis, which includes a shift in the microbiome profile and reduced diversity and complexity of the gut microbiome in multiple cancers, including breast cancer, colorectal cancer (CRC), hepatocellular carcinoma (HCC), and pancreatic ductal adenocarcinoma (PDAC).^{31–34} Although confounded by multiple factors, such as diet, lifestyle, antibiotic usage, geometric location, and different detection methods, some common ground has been established for these cancers.^{31–34} Comparative studies reveal that breast cancer patients often exhibit an increased *Firmicutes* to *Bacteroidetes* ratio,^{35–37} along with elevated *Escherichia* levels in some cohorts.^{38,39} In human CRC gut microbiome studies, the increased abundance of *Fusobacterium nucleatum*,^{40,41} *Bacteroides fragilis*,^{42–45} *Escherichia coli*,^{46,47} *Streptococcus bovis*,⁴⁸ *Streptococcus gallolyticus*,⁴⁸ *Enterococcus faecalis*,^{49,50} and *Peptostreptococcus anaerobius*^{51,52} correlated with an increased risk of CRC. In gastric cancer, *Helicobacter pylori* is associated with peptic ulcers, chronic gastritis, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma.^{51,53,54}

Besides the gut microbiome, researchers have changed the perception of a sterile environment in tumors, realizing the associated risks and importance of the intertumoral microbiome's role in the initiation and progression of certain cancers.⁵⁵ In lung cancer, *Modestobacter*, *Aspergillus*, and *Agaricomycetes* are more abundant in tumor tissues than in normal tissue,^{56,57} suggesting that these microbes may play a role in lung cancer development. *Acidovorax*, *Klebsiella*, and *Anaerococcus* are relatively abundant in squamous cell carcinoma,⁵⁸ whereas *Acinetobacter*, *Brevundimonas*, and *Propionibacterium* increase in adenocarcinomas.⁵⁹ In PDAC, *Porphyromonas gingivalis*, a periodontitis pathogen, localizes to the pancreatic tissue and positively correlates with the risk of PDAC.^{60,61} *Fusobacterium nucleatum*, an oral cavity microbiome, presented with increased abundance in pancreatic tumors compared to the adjacent healthy tissue and was also positively correlated with the risk of PDAC.⁶² In HCC, a study

showed that *Gammaproteobacteria* is increased in the tumor tissue, and the presence of *Bacilli*, *Acidobacteriae*, *Parcubacteria*, *Saccharimonadia*, and *Gammaproteobacteria* in liver tissue can serve as an index for HCC prediction.⁶³ These discoveries provide insights into the function of specific microbiome taxa in cancer initiation and progression.

Dysbiosis of the microbiome influences cancer initiation and development through multiple mechanisms. Epigenetic modification is likely a key event affecting cancer initiation and progression through the gut microbiome's alteration of oncogene expression. The current literature lists various ways the microbiome can alter epigenetics, including DNA methylation, changes in DNA accessibility due to histone modification, and gene expression regulation by non-coding RNAs.⁶⁴ DNA methylation, specifically at CpG islands, involves attaching a methyl group to cytosine, followed by guanine in the DNA sequence.⁶⁵ The methylation status of a gene significantly affects its availability to transcription factors, thereby regulating gene expression.⁶⁵ In CRC, shifts in the gut microbiome profile correlate with the DNA methylation status of colorectal epithelial cells, suggesting that changes in the gut microbiome modify the DNA methylation profile.⁶⁶ This was further validated by introducing single- or mixed-species probiotics into colorectal cell cultures.⁶⁷ The most studied species in the gut microbiome that influences DNA methylation is *Fusobacterium nucleatum*. Research indicates that increased levels of *Fusobacterium nucleatum* or pan-*Fusobacterium* are associated with heightened CpG island methylation of tumor suppressor genes such as MLH1, CDKN2A, MTSS1, RBM38, PKD1, PTPRT, and EYA4, consequently reducing the expression of these genes.⁶⁸ *Hungatella hathewayi* also contributes to the methylation of SOX11, THBD, SFRP2, APC, GATA5, CDX2, ESR1, and EYA4 in CRC.⁶⁹ *Helicobacter pylori* is the primary cause of malignancy in gastric cancer and induces abnormal methylation through the CagA–Ras axis.⁷⁰

SCFAs, metabolites produced by the gut microbiome, modulate the activity of ten-eleven translocation methylcytosine dioxygenase enzymes, which can alter DNA methylation status.⁷¹ These correlations and mechanisms linking methylation to specific microbiome taxa underscore the role of specific microbiome species in cancer initiation and progression. The second mechanism involves histone post-translational modification. Histones are proteins that form nucleosomes with DNA. Modifying histones can regulate chromosomal accessibility to various transcription factors, thereby controlling gene expression.⁷² These modifications include acetylation, methylation, phosphorylation, ubiquitination, SUMOylation, and ADP-ribosylated citrullination.⁷² Acetylation is particularly relevant to the gut microbiome because of the high levels of acetate produced by it.⁷³ In CRC, gastric cancer, and pancreatic cancer, reduced levels of SCFAs, particularly butyrate, have been observed, leading to increased HDAC activity and contributing to histone deacetylation.^{74–76} Studies on overexpressed HDAC in the intestinal epithelium have revealed decreased production of antimicrobial peptides, which alters the gut microbiome profile,⁷⁷ disrupting the symbiosis between the gut

microbiome and the host, potentially leading to cancer. In addition to histone modifications, the gut microbiome also affects gene expression via non-coding RNAs, including miRNAs and long non-coding RNAs.⁷⁸ In CRC, both mouse models and patient samples have shown reduced miRNA expression in the gut compared to healthy samples.^{79–81} Tumors infected with *Fusobacterium nucleatum*, a species highly correlated with CRC risk, also correlated with certain miRNA expression.^{29,82,83} These epigenetic events contribute to alterations in oncogene expression, which drive cancer initiation and progression.

The gut microbiome and intertumoral microbiome play an important role in the initiation and progression of multiple cancers. The number of gut microbiome studies on CRC, gastric cancer, HCC, and pancreatic cancers is higher than other cancers, as these tissues are physically closer to the gut microbiome. Other cancers, such as breast cancer, correlate less with the gut microbiome. This may be due to the limitation of simply analyzing differences in the taxa of the gut microbiome. Transcriptome and metabolomic analyses of the microbiome may allow for a better understanding of functional changes in the microbiome during cancer initiation and development.

Effects of Microbiome Dysbiosis on Cancer Metabolic Pathways

Cancer cells require large amounts of energy to sustain rapid proliferation and metastasis, making the availability of nutrients—especially glucose—critical for tumor progression. Numerous studies have documented associations between gut microbiome alterations and systemic glucose homeostasis changes. For example, several reports have observed that levels of gut microbiome-derived short-chain fatty acids (SCFAs), known modulators of whole-body glucose metabolism, tend to be reduced in various cancers.^{84–87} Although reduced SCFA levels have been observed in various cancers, these findings remain correlational and do not prove that cancer cells directly alter insulin secretion or sensitivity through SCFA reduction.^{84–88}

Supporting these associations, Ye et al demonstrated that patients with leukemia exhibit systemic alterations in glucose metabolism—characterized by decreased insulin secretion and increased insulin resistance—concomitant with lower levels of gut-derived SCFAs.⁸⁹ Similarly, colorectal cancer (CRC) studies have shown that butyrate, a key SCFA, can interact with PKM2 to promote its tetramerization.⁹⁰ This interaction appears to diminish PKM2 enzymatic activity, leading to an accumulation of pyruvate and a reduction in glucose utilization. These findings, while suggestive, are correlative and underscore the need for further mechanistic studies.

In addition to SCFAs, other microbiome-derived metabolites, such as secondary bile acids, are also associated with glucose and lipid metabolism alterations in cancer. Some bile acids have been found to correlate positively with the risk of hepatocellular carcinoma (HCC). In contrast, others, such as

deoxycholic acid (DCA), have been linked to tumor suppression in gallbladder cancer via modulation of glucose metabolism through TGR5 and FXR receptor signaling.^{5,20} Given the complexity of bile acid profiles and their diverse biological activities, further studies are needed to clarify the roles of individual bile acids in cancer initiation and progression.

Furthermore, the interplay between the gut microbiome and cancer metabolism extends to several key nutrient pathways.

Nucleotide Synthesis: The pentose phosphate pathway is closely linked to glycolysis and supplies the nucleotides essential for rapid cancer cell proliferation.^{5,20}

Amino Acid Metabolism: In multiple myeloma, abnormal metabolism of amino acids—particularly serine, glycine, and glutamine—has been observed. Increased glutamine consumption by cancer cells may stimulate nitrogen-dependent gut microbes to produce additional glutamine.^{91,92}

Fatty Acid Metabolism: Tumors, including those in breast, renal, gastric, and colorectal cancers, often thrive in lipid-rich environments by acquiring fatty acids through uptake or *de novo* synthesis.⁹³ Secondary bile acids produced by the gut microbiome regulate lipid metabolism via TGR5 and FXR signaling.^{94,95} In colorectal cancer, *Fusobacterium nucleatum* has been implicated in promoting tumor development through formate production, thereby stimulating glutamine and fatty acid metabolism—a mechanism also noted in glioblastoma cells.^{96,97}

Serine-Glycine One-Carbon (SGOC) Pathway: This pathway supports the synthesis of nucleotides, proteins, and lipids, provides substrates for DNA and histone methylation, and supplies NADPH.^{98–100} Additionally, vitamins B6, B9, and B12 produced by gut microbes further support SGOC metabolism.¹⁰¹

Together, these findings indicate that the gut microbiome plays a crucial role in regulating cancer cell metabolism by influencing multiple nutrient pathways and modulating the availability of key metabolites. While strong correlations exist between microbiome dysbiosis, reduced SCFA levels, and altered cancer metabolism, definitive causal relationships have yet to be established. Future mechanistic studies are necessary to clarify the direct impact of microbiome-derived metabolites on cancer progression.

Immune Modulation and Carcinogenic Metabolites Arising from Microbiome Dysbiosis

As mentioned in the previous section, changes in microbiome profile or gut microbiome metabolites are associated with cancer risk. Efforts have been invested to explore possible ways the microbiome can affect physiology and pathophysiology. Studies have shown that the microbiome can affect cancer initiation and progression by modulating the immune system and producing carcinogens and genotoxic agents,¹⁰² in addition to the previously mentioned role in altering cancer metabolism. We describe each of these in the following paragraphs.

The microbiome can affect multiple aspects of the immune system, which either facilitates or impedes the initiation or progression of cancer.¹⁰² It is well documented that multiple cancers are induced by prolonged inflammation; for example, unmanaged inflammatory bowel disease, colitis, pancreatitis, and hepatitis virus infection have all been shown to increase cancer risk.¹⁰³ Specific bacterial species are responsible for developing certain cancers, such as *Helicobacter pylori* infection in gastric cancer and *Schistosoma haematobium* infection in bladder cancer.^{104,105} Obesity and type 2 diabetes, characterized by chronic low-grade inflammation, are associated with an increased cancer risk.¹⁰³ Inflammatory environments in cancer can be triggered by a range of factors, including microbial infections, immune dysregulation, and other stimuli, all of which may contribute to a milieu that promotes cancer progression. Apart from fostering an inflammatory environment, the gut microbiome induces certain immune cell populations that modulate cancer progression and initiation. For example, vancomycin/neomycin-aerosolized mice show reduced regulatory T cells and increased activation of T and NK cells, leading to reduced metastasis.¹⁰⁶

SCFAs enhance intestinal barrier function and mucus production, thereby limiting the invasion of harmful pathogens that can trigger systemic inflammation.¹⁰⁷ Tryptophan metabolism is enhanced in most cancers, and the metabolites produced in the kynurenine and indole pathways can activate Ahr signaling, resulting in increased inflammation.¹⁰⁸ Molecules in the microbiome can serve as antigen epitopes to create a pool that potentially affects cancer initiation and progression. These antigens either promote or inhibit cancer initiation and progression through molecular mimicry, which mimics the antigen that inhibits or potentiates the immune cells that identify these cancer cells.¹⁰⁹ For instance, an antibody generated specifically using the *Enterococcus hirae* TMP1 epitope can react with a sarcoma-specific peptide that enhances antitumor treatment with cyclophosphamide.¹¹⁰

Apart from changing the immune response, the gut microbiome can produce genotoxic or carcinogenic metabolites. Secondary bile acids and their metabolites at high concentrations can be carcinogenic, which promotes CRC development.¹¹¹ Another example is that formate released by *Fusobacterium nucleatum* can increase CRC cancer invasion.⁹⁶ Meanwhile, the microbiome also produces genotoxic substances, such as N-butyl-N-(3-carboxypropyl)-nitrosamine (BCPN), from nitrosamine and N-nitroso compounds, causing DNA damage and inducing carcinogenesis.¹¹²

Microbial-Host Signaling in Cancer: Contact-Dependent and -Independent Mechanisms

Due to the significant variable concentration of the microbiome metabolites and location of certain microbiome species, the interaction of these components of the microbiome and host consequently affects oncogenesis differently. Here, we briefly

describe these different interactions (Figure 1). Microbial-host interactions contribute to cancer initiation through two primary routes: direct (contact-dependent) and indirect (contact-independent) mechanisms.

Contact-Dependent Mechanism

The contact-dependent mechanism requires the direct contact of microbiome species with the site that undergoes oncogenesis, and this process is well studied (Figure 1). One example is *Helicobacter pylori* infection-induced gastric cancer. *Helicobacter pylori* releases enzymes that degrade the mucus layer in the intestinal lumen, exposing the intestinal epithelial cells. CagA toxin produced by *Helicobacter pylori* generates reactive oxygen species that damage DNA. Prolonged exposure to CagA toxin increases the resistance and risk of malignancy.¹¹³ Certain *Escherichia coli* strains can alkylate DNA using colibactin in a contact-dependent manner, significantly increasing the risk of CRC.¹¹⁴ Due to the low oxygen level and abundant vasculature in the intratumoral environment, the anaerobic microbiome likely exists; for example, *Bacteroides fragilis* and *Enterococcus faecalis* are found in CRC tumors.¹¹⁵ Meanwhile, bacteria localized in the cytosol of the tumor are likely to be positively associated with metastatic ability, and the detection of *Enterococcus* and *Streptococcus* in breast cancer cells is likely to lead to a higher chance of metastasis.¹¹⁶ In CRC, the presence of *Fusobacterium nucleatum* can also increase tumor stemness and invasion ability.¹¹⁶

Contact-Independent Mechanism

Compared with contact-dependent interactions, contact-independent interactions are more complicated (Figure 1). This contact-independent interaction is mainly achieved by metabolites produced by the gut microbiome and outer membrane vesicles.¹¹⁶ SCFAs, the major metabolites the gut microbiome produces from indigestible carbohydrates, can reach considerably high concentrations (in mM for acetate or μ M for propionate and butyrate) in the systemic circulation.¹¹⁷ They can serve as ligands for multiple GPCRs, such as FFAR2, FFAR3, and HCA2, to regulate cellular events.¹¹⁷ Among these SCFAs, propionate, and butyrate are HDAC inhibitors that significantly affect gene expression patterns.^{71,76,90} Secondary bile acids, such as DCA, can directly activate the PI3K-AKT/ I κ B/ NF κ B pathway in HM3 colon cancer cells. In CRC cells and a mouse model, DCA activated the Wnt/ β -catenin pathway, potentiating tumor growth and reducing apoptosis.⁴⁸

The gut microbiome can metabolize tryptophan to indole and kynurenine, which activates AHR-dependent or -independent signaling to modulate immune reactions to increase apoptosis.^{102,118} In the AHR-dependent mechanism, indole and kynurenine alter the T cell differentiation profile by increasing the population of T regulatory cells.^{102,118} Indole can also compete with kynurenine to activate AHR to boost anti-PD-1 therapy.¹¹⁸ In the AHR-independent method,

3-Indolepropionic acid (IPA) increased $\Gamma\delta$ T cell cytotoxicity and B cell granzyme and perforin release to increase anti-cancer immunity.¹¹⁸ IPA also increases the population of CD8 T cells, boosting the efficacy of immune checkpoint blockade inhibitors.¹¹⁸

Multiple vitamin Bs produced by the gut microbiome, such as B6, B9, and B12, can feed into the SGOC pathways to participate in cancer cell metabolism in a contact-independent way.¹⁰¹ Vitamin B9, after being converted into the tetrahydro-folate form, can participate in the one-carbon metabolism, which can provide a methyl group to DNA or histone methylation events.¹⁰¹ Vitamin B6 and B12 are cofactors in one-carbon metabolism,¹⁰¹ and Vitamin B6 is also involved in the production of cysteine.¹⁰¹

Another way the gut microbiome interacts with the host in a contact-independent manner is through bacteria-produced outer membrane vesicles.¹¹⁶ Engevik et al showed that outer membrane vesicles produced by *Fusobacterium nucleatum* and *polymorphum* activate TLR4 signaling, increasing local inflammation and forming an environment with precancerous conditions.¹¹⁹ The abundant metabolites from the gut microbiome have been extensively studied; however, low-concentration metabolites and microbiome species with low abundance still require attention.

Microbiome-Based Biomarkers in Cancer Diagnosis and Prognosis

Previous sections have described distinct microbiome diversity, species, and mechanism differences between cancer patients and healthy individuals. Thus, searching for potential microbiome profiles and distinct species as biomarkers for cancer initiation and prognosis would be logical. Ongoing research suggests that finding unique gut microbiome species or patterns is associated with a high probability of certain cancers, including CRC, PDAC, and oral squamous cell carcinoma.¹²⁰ As collecting fecal samples is a non-invasive approach and the sequencing price drops, analyzing the fecal microbiome can be promising for diagnosing these cancers. For cancers that do not have a distinct species or pattern, the intratumoral microbiome, a rising star in invasive microbiome cancer research, can also serve as a potential biomarker because the intratumoral microbiome profile is usually specific to cancers.¹¹⁶

Microbial signatures have been shown to have remarkable potential for the prediction of CRC. *Fusobacterium nucleatum* is one of the most widely studied microbes associated with CRC.^{119,121–124} Multiple studies have shown that *Fusobacterium nucleatum* plays a role in the initiation and progression of CRC, indicating its ability to serve as a biomarker.^{119–124} In precancerous adenomas before progression into CRC, Gao et al conducted cross-cohort analyses to identify adenoma-associated microbial multimodal signatures, showing that fungal species, especially select fungal species, may outperform bacterial species as biomarkers to distinguish precancerous adenomas from controls.¹²⁵ In PDAC, a multinational

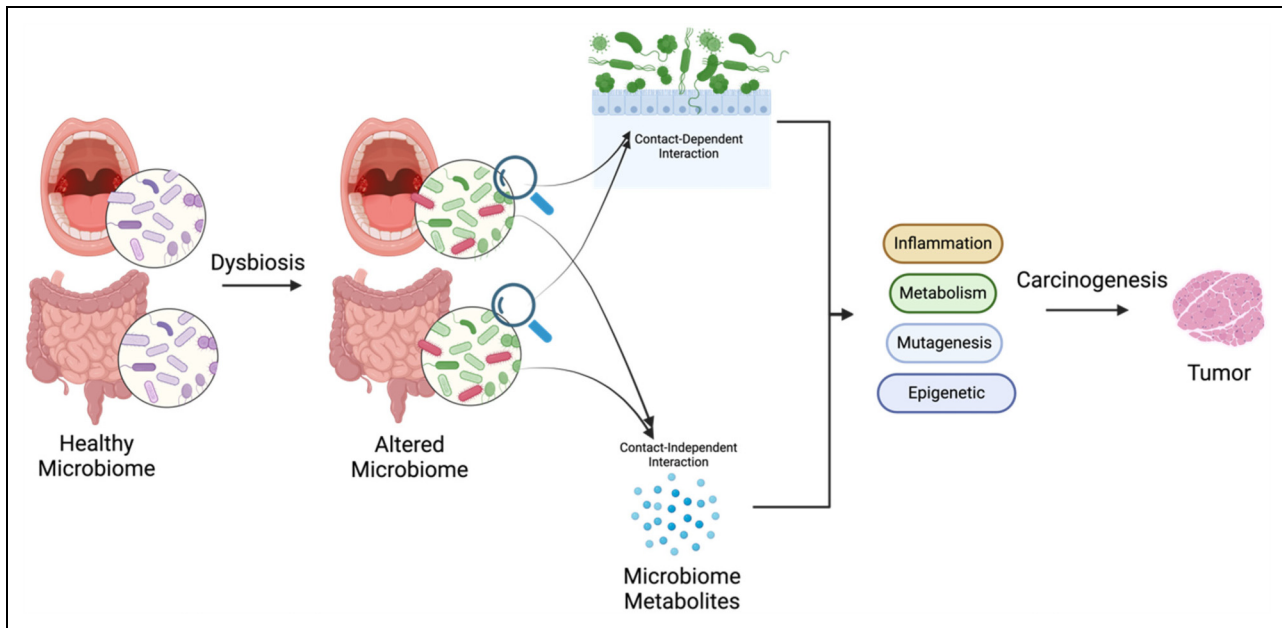


Figure 1. From Dysbiosis to Tumorigenesis: Microbiome-Mediated Inflammation, Metabolism, Epigenetics, and Mutagenesis: Microbiome Dysbiosis Leads to an Altered Microbiome, Subsequently Modulating Inflammation, Metabolism, and Epigenetics and Causing Mutagenesis Through Contact-Dependent or Contact-Independent Interactions to Elicit Carcinogenesis.

study revealed a significant increase in *Streptococcus* and *Veillonella* species and depletion of *Faecalibacterium prausnitzii* in PDAC patient samples in Japan, Germany, and Spain.^{120,126} Wei et al also showed increased oral *Streptococcus* species in PDAC patients,¹²⁷ providing a potential biomarker reservoir for PDAC. In oral squamous cell carcinoma, studies showed a decrease in *Streptococcus pneumoniae* and an increase in *Fusobacterium nucleatum*, the main microbial changes in the cancer environment compared to healthy control.^{120,128} Other studies have also shown a correlation between an increase in *Fusobacterium nucleatum* and oral cancer,^{129–132} suggesting that *Fusobacterium nucleatum* may also be a biomarker for detecting oral squamous cell carcinoma.

Other cancers showed less consistent microbiome species changes across different studies. Human papillomavirus infection has been linked to the development of cervical cancer and is being used for screening at-risk patients.^{133–135} Recent microbiome studies, although still preliminary, may facilitate cervical cancer diagnosis. *Prevotella* was significantly more abundant in the invasive cervical cancer group and *Clostridium* in the healthy control group in fecal samples. Another study with a considerably small sample number but analysis of the vaginal microbiome showed completely different results. In HCC, early forms are enriched in the phylum *Actinobacteria* and genera *Gemmiger* and *Parabacteroides*.¹³⁶ In clear cell renal cell cancer (ccRCC), five genera, *Blautia*, *Streptococcus*, *Ruminococcus torques*, *Romboutsia*, and *Eubacterium hallii*, were noticeably over-represented in fecal samples. *Prevotella*, *Lachnospira*, *Lachnoclostridium*, and *Roseburia* were the most prevalent microbiota in healthy

controls.¹³⁷ Further studies are needed to refine (CRC, PDAC, and oral squamous cell carcinoma) and identify (cervical cancer, HCC, and clear cell renal cell cancer) the use of microbiota as biomarkers for the early diagnosis of malignancies.

Treatment

Multiple microbiome-related treatments have been described in the literature, with a prime focus on modifying the microbiota, ranging from pharmacological agents such as antibiotics to the use of probiotics and postbiotics. Certain biotherapeutic modalities, such as fecal microbiota transplantation, have also gained widespread attention and require special mention.

Antibiotics as Adjuncts in Cancer Therapy

Antibiotics are well-accepted as intercalating treatments in cancer therapy.¹³⁸ Beyond altering the microbiome, certain antibiotics synergize with chemotherapy by directly affecting cancer cell survival pathways.¹³⁸ Ciprofloxacin, a common class of broad-spectrum antibiotics, can overcome the ABCB1 overexpressing cancer cell efflux of chemotherapy drugs, leading to apoptosis.¹³⁹ Besides allowing chemotherapeutic drug retention in cells, ciprofloxacin also potentiates M1 macrophage polarization.¹⁴⁰ Cytokines produced by polarized macrophages synergize with the anticancer effect of ciprofloxacin.¹⁴⁰ Doxycycline can alter the tumor environment by affecting immune response and activation of metalloproteinase, resulting in impaired mitochondria function, potentiating apoptosis, and reduced invasion.¹⁴¹ Doxycycline also increases the production

of reactive oxygen species, which likely leads to DNA double-strand breaks in cancer cells.¹³⁸ Other antibiotics, like macrolides, can reduce the autophagy and mitophagy in cancer cells, and chloramphenicol can reduce HIF-1-induced cancer survival.^{142–144} Preclinical studies have also identified that antibiotics can synergize with immunotherapy and tyrosine kinase inhibitors to enhance cytotoxicity.¹³⁸

Probiotics, Postbiotics, and Nutritional Interventions

Probiotics are beneficial, ingestible microbes that colonize the gastrointestinal tract and exert protective effects.^{145,146} These probiotics are non-pathogenic, cannot be killed by the harsh environment of the digestive system, and can colonize the GI tract.^{145,146} Most importantly, they benefit the host through contact-dependent or independent interactions. Currently, the most used probiotic species belong to the genera *Lactobacillus* or *Bifidobacterium*.^{145,146} In cancer therapy, probiotics can affect cancer treatment in multiple ways. Probiotics can stop carcinogenesis at the very beginning of mutagenesis by detoxifying it.^{145,146} For example, *Lactobacillus rhamnosus* can detox the mutagen aridine orange.¹⁴⁷ Probiotics can also reduce carcinogenesis by regulating oncogene expression and influencing epigenetics or essential signaling molecules.^{148,149} These genes include tumor suppressor genes and oncogenes.^{118,149} Studies have shown that metabolic extracts of *Bifidobacterium longum* influence key tumor suppressor genes by increasing the expression of miRNAs.¹⁵⁰ Probiotics were able to affect important kinases and pathways, including the bax-bcl2, c-Jnk, and MAPK-PTEN pathways, to modulate apoptosis.¹⁴⁵ Studies have shown that *Lactobacillus acidophilus* and *Bifidobacterium bifidum* increase apoptosis by inducing the expression of cytokines, such as IFN- γ and TNF- α , and reducing the expression of bcl-2, leading to apoptosis.¹⁵¹ Autophagy has been detected in cancer cells to overcome nutrition or oxygen shortages. For example, lactic acid-producing bacteria activate autophagy through the Beclin1/GRP78 pathway.¹⁵² Probiotics can also prevent metastasis by altering cell-cell adhesion, epithelial-mesenchymal transition, the tumor microenvironment, and cancer stemness.¹⁵³ Studies have shown that secretes from *Lactobacillus* can decrease metalloproteinase activity and increase tight junction gene expression. Probiotic treatment also decreased the expression of EMT markers Snail and ZEB-1.¹⁵⁴

The mechanism of how probiotics exert beneficial effects in preventing cancer progression has been widely studied, including modifying the immune response, intestinal barrier function, and out-competing the harmful microbiome, which has been mentioned in the previous section. These important mechanisms are through the secretion of beneficial metabolites called postbiotics.¹¹⁸ SCFAs are the most studied postbiotics.¹¹⁸ In the previous section, we described how glucose metabolism in cancer cells is affected by the modulation of available nutrients in the systemic circulation and immune response through different mechanisms. Studies providing probiotics show butyrate and propionate to suppress cancer proliferation, invasion,

and metastasis through HDAC or SCFAs receptor-mediated signaling.^{102,118} Butyrate has also been demonstrated to promote apoptosis and reduce the expression of oncogenes.¹⁵⁵ The beneficial concentration of butyrate usually requires a millimolar range.¹¹⁸ Propionates have been shown to increase tight junction protein and mucin expression.¹⁵⁶ The tryptophan metabolites kynurenine and indoles are also postbiotics. In addition to the immune regulatory function mentioned in the previous section, indole reduces SREBP2 expression and increases oxidative stress to increase anticancer function in liver and breast cancer.¹⁵⁷ Ursodeoxycholic acid (UDCA) is a hydrophilic secondary bile acid that provides greater protection than DCA.¹¹⁸ UDCA has been shown to prevent cholestasis and protect against oxidative damage, which confers hepatocyte protection.¹⁵⁸ UDCA can also inhibit NF- κ B to inhibit the development of CRC.¹⁵⁹ However, similar to DCA, UDCA has cancer-promoting properties at high concentrations.¹¹⁸ Urolithin, a bacterial metabolite derived from ellagitannin, has been shown to suppress Wnt/ β -catenin signaling and phosphorylation of AKT and P70S6 K to stop HCC and pancreatic cancer progression.¹⁶⁰ Urolithin can also induce P53-dependent senescence in CRC to exert its anticancer function.¹⁶¹

FMT: Emerging Therapeutic Applications in Cancer

As an environmental factor, the gut microbiome plays an important role in cancer initiation and progression. Thus, approaches to changing the microbiome profile that processes the anticancer effect would benefit cancer treatment. Fecal microbial transfer (FMT) is one such approach.¹⁶² In anti-cancer therapy, FMT is given fecal material from healthy or treatment-responding donors to non-responders.¹⁶² This is proven to be effective in conjunction with immunotherapy and chemotherapy. Immune checkpoint blockade therapy has shown variations in treatment efficacy.¹⁶² Studies have provided evidence that differences in the gut microbiome between responders and non-responders are one of the reasons for immunotherapy variation.^{163–165} This has also been proven in preclinical models in which germ-free or antibiotic-treated mice showed increased immune checkpoint blockade therapy^{166,167} efficacy. Clinical studies are underway to validate the promising data obtained from preclinical models (NCT03353402, NCT03772899, NCT03819296, NCT04577729, NCT04116775, and NCT04758507).¹⁶² In chemotherapy, FMT not only increases the effectiveness of chemotherapy but also confers protection against its side effects of chemotherapy.¹⁶⁸ Thus, FMT represents a promising therapeutic approach; however, its clinical application requires rigorous recipient screening and standardization to avoid potential adverse outcomes. However, caution needs to be taken because there are unknown aspects of FMT. Owing to the complexity of the fecal microbiome, it is important to screen recipients and exclude immune-deficient patients. In addition, a detailed analysis of the fecal microbiome to eliminate feces containing possible drug-resistant pathogens is paramount. There is a reported death caused by drug-resistant *Escherichia coli* after FMT.¹⁶⁹

Standardizing the procedure of FMT from collection, analysis, and screening would ensure the safety and consistent performance of FMT.

Lifestyle Determinants Shaping Gut Microbiome-Cancer Interactions

Environmental factors significantly influence the gut microbiome's composition and function, thereby indirectly affecting cancer risk.¹⁷⁰ Diet, physical activity, and psychological stress are key factors that shape microbial communities and their metabolic outputs.¹⁷¹ Diets high in fat and low in fiber have been linked to a reduction in beneficial short-chain fatty acid (SCFA) producers, contributing to microbial dysbiosis. In contrast, a fiber rich diet promotes the growth of SCFA-producing bacteria, which are associated with anti-inflammatory effects and improved metabolic health.¹⁷² Additionally, high consumption of red and processed meats has been correlated with shifts in the gut microbiome that may favor inflammatory pathways involved in carcinogenesis.¹⁷³

Physical activity is another important modulator of the gut microbiome.¹⁷⁴ Regular exercise enhances microbial diversity and fosters the production of metabolites that support an anti-inflammatory environment, which may lower cancer risk.¹⁷⁴ Conversely, chronic psychological stress has been shown to disrupt the intestinal barrier and alter the gut microbiome, leading to systemic inflammation—a condition that may further predispose individuals to cancer.

By focusing on these modifiable environmental factors—diet, exercise, and stress—we underscore the potential for lifestyle interventions to modulate the gut microbiome in ways that could reduce cancer risk.^{175,176} Future research should aim to clarify the mechanisms by which these factors influence microbial composition and function, ultimately contributing to strategies that leverage the microbiome for cancer prevention and treatment.^{177,178} Overall, these findings suggest that lifestyle interventions—such as adopting a high-fiber diet, engaging in regular exercise, and managing stress—could favorably modulate the gut microbiome and potentially reduce cancer risk.

Discussion

This review summarizes the complex relationship between the gut microbiome and cancer, highlighting how dysbiosis influences metabolic pathways, immune responses, and gene expression. We also discuss current therapeutics that target the microbiome to improve cancer treatment outcomes. However, there is still much research to be conducted on these topics. Individual variability in diet, genetics, lifestyle, and environment complicates the generalization of these findings across different cancer types.^{179,180} Currently, the complex interplay of factors that predispose an individual to cancer remains elusive. While many studies have established correlations between gut microbiome alterations and cancer development, the precise molecular and cellular mechanisms—especially those relevant to treatment—remain unclear.¹⁷⁹ This necessitates more

in-depth studies at the molecular level to elucidate the exact mechanism. Most studies have been performed on animal models, particularly mice, which may not fully replicate human physiology, and their relevance to humans is questionable. This is due to the inherent difference between the human and murine gut microbiomes. Translating from animal to human clinical studies requires careful validation to ensure strict adherence to ethical standards.¹⁸¹

Future research using advanced metagenomic and metabolomic techniques will be essential to elucidate the relationship between the gut microbiome and cancer development.^{182,183} This will aid in identifying specific microbes and their metabolites involved in causing cancer. In vitro and in vivo experiments focusing on these microbes and their metabolite effects on cancer cells must be conducted to understand the underlying mechanism better.¹⁸⁴ In addition, it is important to understand the temporal relationship between gut microbiota and cancer development, for which large-scale, longitudinal cohort studies would be required.¹⁸⁵ We need to reach a stage where we can develop a personalized microbiome-based treatment regimen tailored to the individual's microbiome and cancer type, possibly using custom-designed probiotics or specific microbiota transplantation.^{186,187} Further progress in cancer treatment requires well-designed clinical trials to evaluate the efficacy and safety of microbiome-targeted cancer treatment. Such a holistic approach will help the scientific community combat cancer and improve overall patient outcomes.

Abbreviations

GI	gastrointestinal
BAT	brown adipose tissue
BCPN	N-butyl-N-(3-carboxypropyl)-nitrosamine
ccRCC	clear cell renal cell cancer
CRC	colorectal cancer
DCA	deoxycholic acid
FMT	Fecal Microbiota Transplantation
HCC	hepatocellular carcinoma
IPA	3-Indolepropionic acid
MM	multiple myeloma
PDAC	pancreatic ductal adenocarcinoma
SCFAs	short-chain fatty acids
SGOC	serine-glycine one-carbon
UDCA	Ursodeoxycholic acid

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