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From dysbiosis to oncogenesis; the evolving role of the gut microbiome in cancer pathogenesis and treatment

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Abstract

The gut microbiome significantly influences cancer pathogenesis, progression, and treatment outcomes. Dysbiosis, an imbalance in gut microbial communities, can lead to tumorigenesis and is implicated in approximately 20% of all cancers. The gut microbiota contributes to cancer development through various mechanisms, including inducing chronic inflammation, producing genotoxic metabolites, and modulating signaling pathways. Numerous studies found that, *Helicobacter pylori* is a known microbial risk factor for gastric cancer. In esophageal cancer, accumulating evidence suggests a crucial role for gut microbiota in its development and progression. Specific microbes like *Fusobacterium nucleatum* can contribute to aggressive tumor behavior in esophageal squamous cell carcinoma by activating chemokines. Similarly, in colorectal cancer, distinct metagenomic and metabolomic shifts, including an abundance of *F. nucleatum*, have been identified across various stages of pathogenesis. Beyond pathogenesis, the gut microbiome also affects cancer therapies, particularly immune checkpoint inhibition (ICI). Studies have shown that gut microbiota composition and diversity can predict ICI responses. For instance, certain microbial species like *Bifidobacterium* spp., have been linked to improved efficacy of anti-PD-L1 antibodies in murine models. The microbiome can also influence the efficacy and toxicity of chemotherapy. Consequently, manipulating the gut microbiome through approaches such as dietary modification, probiotics, and fecal microbiota transplantation is being explored as a potential therapeutic strategy. Fecal microbiota transplantation has shown promise in modulating immune cell infiltrates and gene expression profiles in melanoma patients receiving immune checkpoint inhibitors.

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Introduction

The human intestinal tract harbors over 100 trillion microorganisms, collectively forming microbiomes in individual organs. This complex community, often referred to as the last undiscovered human organ, significantly affects human health and immune function due to its proximity to the immune environment within the gastrointestinal tract (1). The normal gut microbiota performs specific functions in host nutrient metabolism, xenobiotic and drug metabolism, maintaining the structural integrity of the gut mucosal barrier, immunomodulation, and protection against pathogens (2). The gut microbiome's composition is established early in life, with maternal microbiota forming the initial inoculum, then diversity increasing to an adult-like state by age 3 to 5 years. This colonization is influenced by factors such as delivery mode, perinatal antibiotic exposure in mothers and infants, and feeding methods (3). Once established, the gut microbiota typically remains relatively stable throughout adulthood, although it can be altered by bacterial infections, antibiotic treatment, smoking, disease states, medical and surgical interventions, and long-term dietary changes (3). In this narrative review, we sought to study the evolving role of gut microbiome in cancer pathogenesis and treatment.

Key point

By transitioning from dysbiosis to oncogenesis, gut microbiome profoundly influences cancer pathogenesis. A dysbiotic shifts in microbial composition promote chronic inflammation, genotoxic metabolite production and impaired immune surveillance, promoting tumorigenesis across colorectal, gastric, hepatic, and extra-gastrointestinal cancers like breast and pancreatic. These microbes modulate host epigenetics, DNA damage responses, and tumor microenvironment dynamics, exacerbating oncogenic signaling by pathways such as Wnt/β-catenin and NF-κB.

Search strategy

For this narrative review, a comprehensive literature search was conducted across major scientific databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase. The search strategy incorporated a broad range of relevant keywords to capture the evolving evidence based on microbiome–cancer interactions, including 'gut microbiome', 'dysbiosis', 'oncogenesis', 'cancer pathogenesis', 'neoplasm', 'tumor microenvironment', 'microbial metabolites', 'inflammation', 'immune modulation', and 'carcinogenesis'.

Definition of dysbiosis

The human gut microbiome, comprising trillions of microorganisms including bacteria, fungi, viruses, and archaea, maintains a delicate symbiotic balance that profoundly influences host physiology, from metabolism and immunity to barrier integrity (4). Dysbiosis, defined as a shift in microbial composition characterized by reduced diversity, enrichment of pathobionts, and depletion of beneficial taxa, disrupts this equilibrium and has emerged as a pivotal driver in the pathogenesis of numerous diseases, including cancer. This progression from dysbiosis to oncogenesis unfolds through interconnected mechanisms like chronic inflammation, genotoxic damage, metabolic reprogramming, and immune evasion that, transforming the gut into a tumor-permissive niche that extends its influence by distant pathways like gut-liver, gut-lung, and gut-tumor microenvironments (5). Recent multi-omics studies reveal conserved dysbiotic signatures across malignancies such as expansion of Proteobacteria such as *Escherichia coli, Shigella* and depletion of *Firmicutes/Bacteroidetes* producers of short-chain fatty acids (SCFAs) like butyrate, underlining the microbiome's causal role in carcinogenesis (6). Several studies found that, dysbiosis initiates through multifactorial triggers that converge on microbial imbalance. Dietary patterns exert the most immediate influence (6). Given that, western diets high in processed foods, saturated fats, and sugars diminish SCFA-producing genera like *Faecalibacterium prausnitzii* and *Roseburia* while promoting bile-tolerant pathobionts such as *Bilophila wadsworthia*, whose hydrogen sulfide production erodes the mucus layer (7). Moreover, high-fat intake elevates lipopolysaccharide from gram-negative bacteria, inducing low-grade endotoxemia by leaky gut, whereas fiber-rich Mediterranean diets foster *Bifidobacterium* and *Lactobacillus*, enhancing barrier function through IgA secretion and Treg differentiation (8). On the other hand, smoking enriches *Bacteroides-Prevotella* clusters, stress disrupts the gut-brain axis favoring pro-inflammatory Enterobacteriaceae, and antibiotics like broad-spectrum ciprofloxacin decimate *Actinobacteria*, with recovery timelines varying from weeks to months depending on exposure duration (9). Geographical variances underscore environmental modulation; rural African cohorts exhibit Prevotella dominance from polysaccharide-rich diets, conferring resilience against colorectal cancer compared to urban Western profiles skewed toward *Bacteroidetes* fragility (10). In cancer-prone states, these perturbations reduce alpha-diversity, enabling pathobiont overgrowth (11). Previous studies demonstrated that, *Fusobacterium nucleatum* invades by FadA adhesin binding E-cadherin, activating beta-catenin/Wnt signaling for epithelial proliferation or *E. coli*'s polyketide synthase island produces colibactin, a genotoxin causing DNA double-strand breaks and mutagenesis akin to APC mutations in sporadic colorectal cancer (12). The inflammatory cascade represents dysbiosis's primary oncogenic conduit. Pathobiont-derived lipopolysaccharide engages Toll-like receptor 4 (TLR4) on epithelial and myeloid cells, triggering NF-κB/STAT3 activation and cytokine storms that foster a Th17-skewed milieu (13). In colorectal cancer, *Peptostreptococcus anaerobius* adheres by PCWBR2 to α2/β1 integrin, amplifying ROS/cholesterol biosynthesis and IL-10/IFN-γ release (14), while *Bacteroides fragilis* toxin cleaves E-cadherin, delivering beta-catenin for c-Myc/ cyclin D1 transcription (15). *Helicobacter pylori* exemplifies gastric oncogenesis. It has been detected that CagA and VacA effectors phosphorylate host kinases, hijacking Crk adaptor protein for IL-8/NF-κB induction, progressing from gastritis to metaplasia by epigenetic CpG methylation of tumor suppressors (16). Chronicity ensues as dysbiosis impairs resolution; since, butyrate deficiency stemming from *Faecalibacterium/Roseburia* loss fails to inhibit HDAC, allowing unchecked histone acetylation that sustains pro-survival genes (17). In the next step, tryptophan catabolites like kynurenine from IDO1 exacerbate Th17 suppression (18), while *Enterococcus*-derived phenylethylamine shreds epithelia, potentiating translocation (18,19). This hit model posits dysbiosis as the initiator, with genetic/epigenetic second hits (20). Furthermore, *F. nucleatum*'s FadAc homolog similarly engages TLR4/2 for chromosomal instability (21). Porphyromonas gingivalis-derived gingipains degrade tight junctions, facilitating systemic spread (22), while *Streptococcus gallolyticus* pilots biofilm formation shielding adenomas from immunosurveillance (23). In extraintestinal sites, the gut-liver axis transmits harm; while, dysbiosis elevates deoxycholic acid by *Clostridium scindens* (24). Likewise, ovarian cancer links gut-vaginal

dysbiosis; as β-glucuronidases reactivate estrogens, fueling NF-κB/STAT3 and DNA methyltransferases silence suppressors through microbial folate analogs (25).

Impact of gut microbiome on cancer pathogenesis

The mechanisms by which the gut microbiome influences cancer pathogenesis are diverse. These include damaging DNA, activating oncogenic signaling pathways, producing tumor-promoting metabolites, and suppressing the antitumor immune response (26). The gut mucosal barrier's structural integrity is crucial, and its dysfunction has been implicated in colorectal carcinogenesis through the induction of epithelial-to-mesenchymal transition and increased gut permeability. This can lead to the translocation of bacteria and pathogenic metabolites, increasing the risk of local and systemic inflammation and subsequent carcinogenesis (27). The fermentation of dietary fibers into SCFAs by the gut microbiota is another important mechanism. Colonocytes use acetate, propionate, and butyrate as energy sources, while transformed colorectal cancer cells primarily undergo aerobic glycolysis (27). In fact, colorectal cancer cells show increased sensitivity to SCFAs, suggesting their vital role in cell homeostasis. Manipulation of SCFA levels through changes in the gut microbiome has emerged as a potential preventive or therapeutic strategy for colorectal cancer (28). Mechanistically, microbes promote oncogenesis through several overlapping pathways. One major route is chronic inflammation. Certain bacteria trigger persistent mucosal immune activation, recruiting myeloid cells and producing cytokines such as IL-6, TNF-α, and IL-17 that create a pro-tumorigenic microenvironment (29). Inflammatory mediators increase cellular proliferation, inhibit apoptosis, and generate reactive oxygen (ROS) and nitrogen species that damage DNA (30). Microbial components like lipopolysaccharide and flagellin engage pattern recognition receptors (TLRs, NLRs) on epithelial and immune cells, sustaining a feed-forward loop of inflammation and tissue remodeling (31). In the colon, for instance, biofilms formed by polymicrobial consortia adhere to the mucosal surface and amplify local inflammation, promoting epithelial barrier disruption and facilitating direct microbe-host interactions that favor neoplastic progression (32). The second mechanism is direct genotoxicity. Some bacteria produce toxins or metabolites that damage host DNA or interfere with repair pathways (33). The pks genomic island in certain strains of *E. coli* encodes colibactin, a genotoxin that induces DNA double-strand breaks and a mutational signature found in colorectal tumors (34). Enterotoxigenic *B. fragilis* secretes *B. fragilis* toxin, which cleaves E-cadherin, activates β-catenin signaling, and promotes epithelial proliferation and DNA damage (15). *Fusobacterium nucleatum*, enriched in many colorectal cancers, expresses FadA adhesin that binds E-cadherin and stimulates oncogenic signaling, and it can modulate local immune responses to favor tumor growth. These microbe-derived genotoxins and adhesins create a microenvironment in which mutation accumulation and clonal expansion are more likely (35). It should remember that, metabolic reprogramming by the microbiome is the third mechanism, which is an equally important axis. Importantly, gut microbes metabolize dietary components and host molecules into a vast array of small molecules that influence epithelial biology and systemic physiology (36). Short-chain fatty acids such as butyrate, produced by fiber-fermenting bacteria, generally exert anti-inflammatory and anti-neoplastic effects by serving as an energy source for colonocytes, reinforcing barrier function, and acting as histone deacetylase inhibitors that modulate gene expression (37). Conversely, microbial conversion of primary bile acids into secondary bile acids can be carcinogenic: since deoxycholic acid and lithocholic acid promote DNA damage, oxidative stress, and epithelial proliferation in the colon and liver (38). Accordingly, microbial metabolism of choline and carnitine yields trimethylamine N-oxide, which has been linked to inflammation and cancer risk in some studies. The balance of protective versus harmful metabolites is therefore a critical determinant of whether a given dysbiotic state will favor tumorigenesis (39).

Interplay of microbiome and chemotherapy

The interplay between microbiome and chemotherapy is complex and bidirectional. Chemotherapeutic agents can disrupt the gut barrier and microbiota, precipitating mucositis, infection, and systemic inflammation that limit dosing and compromise outcomes (40). Conversely, microbes can metabolize drugs into active or inactive forms, altering pharmacokinetics and toxicity profiles. Besides, bacterial β-glucuronidases can reactivate irinotecan metabolites in the gut, causing severe diarrhea (41). Hence, the gut microbiome plays a role in chemotherapy efficacy and toxicity. Recent findings showed that, in germ-free or antibiotic-treated tumor-bearing mice, responses to oxaliplatin were inefficient compared to those with an intact gut microbiome (42). Commensal microbiota are hypothesized to regulate Toll-like receptors agonists, which promote a rise in reactive oxygen species and subsequent tumor cell death. Conversely, a combination of cisplatin with probiotics like *Lactobacillus* has shown improved response to therapy, potentially through the induction of pro-apoptotic genes and enhanced immunosurveillance (43). The gut microbiome has also been implicated in chemotherapy-induced neurological toxicities, such as peripheral neuropathy and cognitive impairment. Previous authors found that, paclitaxel can decrease the abundance of beneficial *Akkermansia muciniphila*, impairing mucosal barrier integrity and allowing the translocation of pro-inflammatory and neuromodulatory metabolites (44).

Treatment modalities

Interventions to modulate the microbiome are diverse.

Antibiotics can transiently suppress harmful taxa but also deplete beneficial organisms and reduce diversity, often with unpredictable consequences (45). Probiotics and prebiotics aim to restore beneficial functions; some strains have shown synergy with chemotherapy in animal models, enhancing chemosensitivity and reducing toxicity, nevertheless human data are mixed and strain-specific effects complicate general recommendations (46). Fecal microbiota transplantation has emerged as a powerful tool to transfer complex microbial communities; whilst, small clinical trials have demonstrated that fecal microbiota transplantation from immune checkpoint inhibition (ICI)-responding donors can convert some refractory melanoma patients into responders, accompanied by shifts in immune parameters (47). Yet fecal microbiota transplantation carries risks pathogen transmission, unpredictable engraftment, and regulatory challenges, since its long-term oncologic safety is not fully established. Defined microbial consortia rationally selected combinations of cultured strains seek to reproduce the beneficial immune-modulating effects of responder microbiomes while minimizing variability and safety concerns (48). On the other hand, bacterial engineering offers the possibility of programming microbes to deliver therapeutic payloads, degrade immunosuppressive metabolites, or produce anti-tumor cytokines locally within the gut or tumor microenvironment (49). Small molecules that inhibit microbial enzymes implicated in drug inactivation or carcinogen activation represent another targeted approach. Dietary interventions and fiber supplementation can shift microbial metabolism toward SCFA production and away from harmful bile acid transformations, offering a low-risk adjunct to other therapies (50). Each of these strategies requires rigorous clinical testing to define efficacy, dosing, timing relative to cancer therapy, and patient selection criteria (50).

Conclusion

In summary, the microbiome is no longer a passive bystander but an active co-conspirator and modulator in cancer pathogenesis and treatment response. Compelling evidence now delineates how dysbiotic communities drive carcinogenesis through chronic inflammation, genotoxin production, metabolic reprogramming, and immune evasion, establishing direct mechanistic links beyond mere correlation. The microbiome's influence extends profoundly into the therapeutic modalities. It acts as a double-edged sword, capable of both diminishing the efficacy of conventional chemotherapies and immunotherapies while simultaneously exacerbating treatment-related toxicities, yet also holding the potential to enhance therapeutic success when favorably modulated. This evolving understanding necessitates a fundamental re-evaluation of cancer prevention, diagnosis, and management strategies. Targeting the microbiome by precision probiotics, prebiotics, dietary interventions, fecal microbiota transplantation, or engineered microbial therapeutics emerges not as a fringe concept but as a tangible translational imperative.

Authors' contribution

Conceptualization: Naeem Nikpour and Simin Zeinadini.
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Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

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