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Review Article

A review on the association between gut microbiome and colorectal cancer

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SUMMARY

Colorectal cancer (CRC) represents one of the primary causes of cancer-related deaths across the globe. Research has identified an unhealthy diet as a significant factor contributing to the onset of CRC, alongside genetic and epigenetic alterations. Gut dysbiosis has been identified as a notable characteristic of CRC. Epigenetic modifications, which involve alterations to DNA that influence gene expression without changing the actual DNA sequence, play a critical role in the development of CRC. Additionally, factors including diet, lifestyle, and genetics, along with oncogenic infections, bacteria, or the entire microbiome, have been linked to this type of cancer. The precise role of the gut microbiome in CRC pathogenesis within the host remains unclear. In this review, we provide an overview of how gut microbiota contributes to colon carcinogenesis. The hypothesis linking gut microbiota to CRC illustrates the intricate and dynamic interactions among microbes that can initiate CRC development. In the complex mechanisms of colonic carcinogenesis, the progressive changes in microbiota, their surrounding environment, and the role of potential oncopathogenic microorganisms, which are infectious agents such as viruses, bacteria, and parasites that may play a role in the onset of cancer. in influencing cancer treatment and other aspects of microbiome dysbiosis leading to CRC are explored. Research indicates that therapeutic approaches such as probiotics, prebiotics, and postbiotics strengthen the intestinal immune response and enhance the effectiveness of immunotherapy agents, potentially serving as additional strategies in cancer treatment. This review summarizes the involvement of the microbiome in modulating CRC processes.

Introduction

Colorectal Cancer (CRC) refers to a type of gastrointestinal cancer that arises from either the colon or the rectum. Colon cancer (CC) and rectal cancer (RC) occur in the large intestine and are commonly grouped together as CRC (Alzahrani et al., 2021). CRC ranks as the second leading cause of cancer-related deaths and is the third most prevalent form of cancer. CRC can occur due to genetic factors (10%), family history (20%), or, in the majority of cases, as sporadic instances (70%). Hereditary CRC is classified into two categories: hereditary polyposis CRC and hereditary non-polyposis CRC (Boland and Goel, 2010). The hereditary polyposis type is further categorized into Familial Adenomatous Polyposis (FAP) and attenuated polyposis. FAP is marked by the formation of numerous polyps in the colon and rectum, which, if not treated, almost invariably progress to cancer. This condition arises from

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mutations in the APC gene, a tumor suppressor gene that typically plays a role in regulating cell growth. The advancement to cancer involves a sequence of genetic changes, referred to as the chromosomal instability pathway. This pathway includes mutations in the KRAS gene, which is crucial for cellular signaling, as well as mutations in the TP53 gene, another important tumor suppressor gene. The accumulation of these mutations contributes to the development of tumors (Nolano et al., 2022).

The majority of CRC cases are quite sporadic. The primary mechanism driving sporadic CRC involves the chromosomal instability pathway, which encompasses mutations in *APC*, *KRAS*, and *TP53* (Mármol et al., 2017). Various factors can contribute to the onset of sporadic CRC. One significant risk factor is age, with the typical diagnosis occurring around 50 years old, although it can present at much younger ages in individuals with hereditary CRC. Additionally, non-malignant conditions like colorectal polyps, adenomas, ulcerative colitis, and Crohn's disease heighten the risk of CRC development. Furthermore, environmental aspects such as lifestyle choices, dietary habits, and the microbial ecosystem can initiate tumor formation (Seesaha et al., 2020). Research has indicated that the gut microbiota may have a dual effect on CRC, offering protection against it while also potentially facilitating its progression under specific circumstances (Dougherty and Jobin, 2023). The gut microbiota, a complex community of microorganisms in the intestines, plays a significant role in the development and progression of CRC. Imbalances in the gut microbiota (dysbiosis) can influence inflammation, immune responses, and the production of metabolites, all of which can contribute to CRC pathogenesis (Kim and Lee, 2022).

Gut microbiome

The human microbiome comprises a wide array of bacteria, viruses, fungi, protozoa, and archaea that inhabit various parts of the human body. Estimates suggest that the bacteria associated with humans outnumber human cells in the body (Sender et al., 2016). Although most of these microorganisms may not pose a direct threat to humans, they can greatly influence human health. While it is estimated that trillions of organisms reside within the human microbiome, the International Agency for Research on Cancer (IARC) currently recognizes only 11 of them as directly carcinogenic (Group 1 carcinogens) to humans (de Martel et al., 2020).

The makeup of the human microbiota varies significantly among individuals. The impact of genetics on the composition of gut microbiota is relatively limited compared to environmental influences such as diet, lifestyle, and exposure to various microbial communities. The human gut microbiota begins to develop before birth. The maternal microbiota provides the initial microbial inoculum, which rapidly diversifies after birth, evolving into an adult-like gut microbiota by the end of the first 3–5 years of life. Factors occurring prenatally, including the method of delivery (vaginal vs. cesarean), dietary choices (breastfeeding or formula), genetics, and the glycosylation of intestinal mucin, have been shown to affect microbial colonization in the gut of newborns (Rodríguez et al., 2015). It is estimated that 10^{13} to 10^{14} microbes per milliliter, encompassing 500–1000 species, colonize the gastrointestinal tract during the first 3–5 years of life. Subsequently, a microbial profile is established for each individual, which is believed to impact the overall health of the human host (Al Bander et al., 2020).

Regarding genetic makeup, the number of bacteria found in the gut microbiota is over 25 times greater than in the host, with bacteria making up the majority of the gut microbiota (Skelly et al., 2019). This microbial community is capable of executing a broader array of metabolic functions compared to the human genome; however, accessing these metabolic functions through the human genome is challenging (Pascal Andreu et al., 2023). For this reason, researchers often refer to the gut microbiota as the "second genome".

Role of gut microbiota in tumorigenesis

The gut microbiota not only contributes to tumor formation but also plays an active role in several physiological functions within the human body, making significant impacts on human health (Shalon et al., 2023). They act as signaling molecules that are involved in the regulation of host physiological conditions, such as controlling systemic blood pressure,

moderating inflammatory responses, and maintaining the functionality of certain cells (Tang et al., 2022). Furthermore, the gut microbiota encourages the development of the host's immune system through various mechanisms, which in turn affects overall immune performance within the body (McCoy and Geuking, 2021). The gut microbiota influences the immune system, thereby affecting the effectiveness of cancer immunotherapy. The connection between cancer immunotherapy and the gut microbiota has gained considerable interest following a publication in 2015 by Science, which indicated that gut microbiota modulation could affect the immunosuppressive response (Sivan et al., 2015). Besides influencing the effectiveness of cancer immunotherapy, the gut microbiota also affects drug efficacy. Medications administered to the gut engage with the local gut microbiota. These medications can change the composition and quantity of the gut microbiota, while the enzymes they produce can alter drug structures, impacting drug activity and toxicity (Weersma et al., 2020). This area is being investigated as a possible target for enhancing drug therapy. There is considerable experimental and epidemiological evidence supporting the gut microbiota's influence on these cancer types. Changes in the gut microbiota's composition and its metabolites can alter cellular metabolism and immune function in humans, thus creating a plausible connection to cancer (Rubinstein et al., 2013). Despite the growing interest in this area, there is currently no unified framework for examining the relationship between gut microbiota and cancer occurrence, especially regarding the interpretation of research results (Sepich-Poore et al., 2021).

Dysbiosis of gut microbiota as a risk factor for CRC

The microbiome plays a crucial role in maintaining intestinal balance through a cooperative relationship with the host. The health of the host is significantly associated with the stability of the gastrointestinal tract barrier, which is partially upheld by the microbiome located in the outermost layer (Ghosh et al., 2021). Gut bacteria contribute to intestinal balance through various mechanisms. The microbiota influences the permeability and integrity of the epithelial layer. Interactions between gut bacteria and epithelial cells regulate permeability by affecting tight junctions (Allam-Ndoul et al., 2020). The gut microbiota engages with and supports the host's immune system throughout all phases of CRC (Wong and Yu, 2023). The role of gut microbiota in CRC has been established via the breakdown of dietary components, alteration of the tumor microenvironment, and antigen mimicry (Xing et al., 2022). The gut microbiota employs digested dietary components to enhance the host's immune resistance against CRC. As gut bacteria digest food, they ferment dietary fibers to produce secondary metabolites like Short-chain fatty acids (SCFAs), which are essential for the interaction between microbiota and the host's immune system (Wong and Yu, 2023). SCFAs attach to G-protein coupled receptors (GPCRs) located on dendritic cells (Hou et al., 2022). These interactions lead to a reduction in pro-inflammatory cytokine production and an increase in anti-inflammatory cytokine levels (Yoo et al., 2020). The microbiota can also combat CRC by reshaping the tumor microenvironment, enhancing programmed cell death (apoptosis) in tumors, and breaking down harmful tumor byproducts (Shakhpazyan et al., 2024).

Dysbiosis denotes a disruption in gut microbiota equilibrium, signified by alterations in microbial composition, bacterial distribution, or metabolic function. Changes in microbial balance have been linked to several health issues, including Inflammatory bowel disease (IBD), diabetes, autism spectrum disorders, and CRC. Dysbiosis has multiple contributing factors and is involved in a variety of physiological processes. Environmental influences such as diet, medications, and xenobiotics, along with host-related factors like genetics, health status, stress, and lifestyle, can cause dysbiosis (Hrncir, 2022). A balanced diet improves the gut microbiota, fortifies gut barrier function, and promotes the release of anti-inflammatory markers. Conversely, poor dietary choices have been associated with microbial imbalances, metabolic disorders, weakened intestinal barriers, and widespread inflammation (Thomas et al., 2022). Additionally, the consumption of food preservatives has been linked to gut microbiota dysbiosis. Xenobiotics including antibiotics, heavy metals, and pesticides can disrupt gut microbiota, leading to

antibiotic-induced dysbiosis. Antibiotics known to potentially cause dysbiosis encompass streptomycin, vancomycin, metronidazole, and ampicillin (Alcaire et al., 2024).

The progression of CRC is a complicated, multi-step process that transitions from normal epithelial cells to adenomas and finally to carcinoma. Research has indicated that dysbiosis can impact various stages of CRC development. Specific alterations in the microbiota, particularly an increase in pro-inflammatory bacteria, can change the colonic environment and lead to chronic inflammation, which subsequently facilitates cellular mutations and unchecked cell growth (Al Bander et al., 2020). Microbial metabolites, especially SCFAs, are crucial in modulating immune responses and preserving the integrity of gut epithelial cells. Nevertheless, an imbalance in the microbiome may diminish the production of beneficial metabolites while enhancing harmful ones that could encourage carcinogenesis (Kim et al., 2018). For example, certain bacteria create bile acid metabolites that can harm the DNA of colonocytes, resulting in mutations and tumor formation. Moreover, inflammation caused by microbes can modify gene expression and activate inflammatory pathways that foster cancer development (Arthur et al., 2014). Although the microbiota supports a healthy physiological gastrointestinal environment, it has the potential to spur the advancement of CRC under specific pathophysiological conditions, predominantly dysbiosis (Keku et al., 2015). Dysbiosis may exacerbate CRC progression in the presence of pathogenic and cancer-promoting bacteria such as *Fusobacterium nucleatum* and *Bacteroides fragilis* (Rye et al., 2022). These and other bacteria facilitate carcinogenic activities such as cell growth, angiogenesis, and apoptosis inhibition (Jahani-Sherafat et al., 2018). While the precise mechanisms remain unclear, several proposed pathways include chronic inflammation, DNA damage, and the production of carcinogenic metabolites. Chronic inflammation is recognized as a significant risk factor for CRC (Figure 1) (Artemev et al., 2022).

The dysbiotic microbiota creates a microenvironment conducive to tumor growth by disrupting mucosal barriers, modulating immune responses, and influencing metabolic pathways. On the other hand, some other gut bacteria are protective against the occurrence and progression of cancers. Examples include *Clostridium butyricum*, *Streptococcus thermophilus*, and *Lacticaseibacillus paracasei* (Qu et al., 2023).

To summarize, although not conclusively established, certain gut bacteria are significantly associated with the onset of tumors, especially regarding CRC. These bacteria may directly affect the genetic and epigenetic profiles of cells, promoting a carcinogenic environment through inflammation and toxin production. While some bacteria thrive in tumor-prone environments, leading to tumor progression, others can be protective against cancer. The relationship is complex and involves interactions with the host's immune system and metabolic pathways. The key CRC-associated bacteria and their mechanisms of action have been shown in Table 1.

Cancer treatment by gut microbiome modulation

The gut microbiome significantly influences the modulation of cancer treatments, such as immunotherapy and chemotherapy. New evidence shows its outcome on the effectiveness of therapies, immune reactions, and mechanisms of resistance. Microbial communities in the intestines play a role in shaping immune responses and drug metabolism, which directly influence the effectiveness and toxicity of treatment. Some bacterial species can enhance the activity of immune checkpoint inhibitors (ICIs), while microbial imbalances can lead to treatment resistance and negative side effects. In chemotherapy, microbial enzymes can activate or inactivate anticancer agents, thereby changing treatment outcomes. Metabolites produced by microbes, particularly SCFAs and compounds derived from tryptophan, further modulate immune responses that can influence treatment effectiveness. Additionally, the microbiome significantly affects drug metabolism, playing a role in chemotherapy resistance and influencing drug toxicity (Kim et al., 2025). Current studies emphasize strategies for modifying the microbiome in cancer treatment, such as fecal microbiota transplantation (FMT), probiotics, prebiotics, and postbiotics. These methods, when used alongside standard treatments, show promise in improving therapeutic responses

while minimizing side effects (Miller and Carson, 2020).

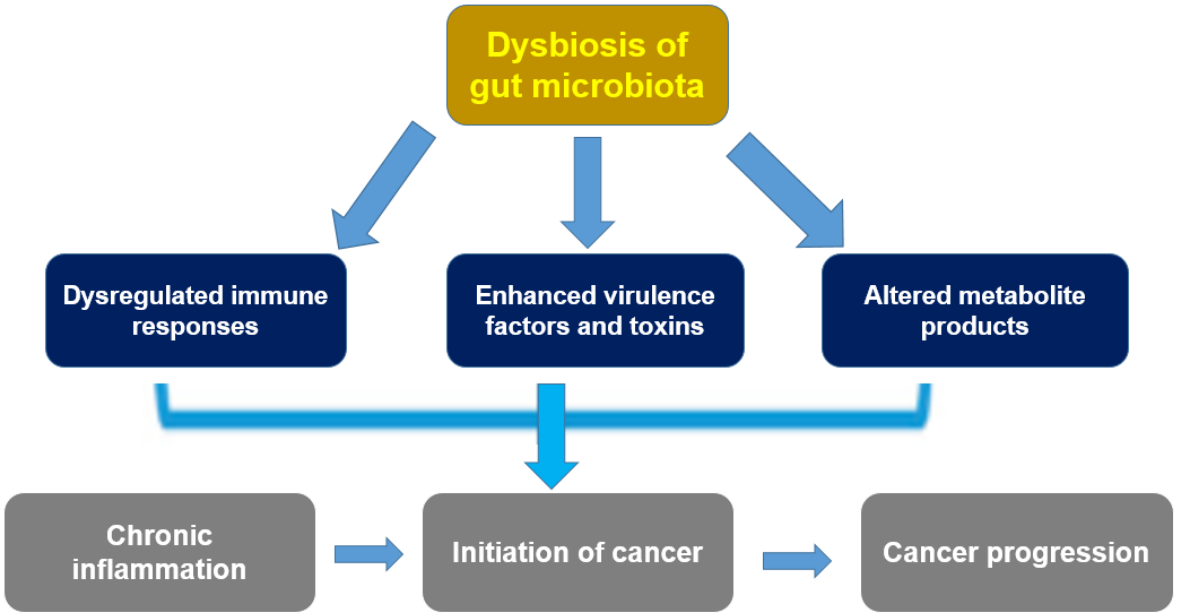

Figure 1. Changes in the gut microbiome and their connection to CRC involve three main mechanisms: the improper regulation of immune reactions, the existence of virulence factors or toxins, and the creation of metabolic byproducts. These elements can initiate chronic inflammation, potentially resulting in the development and progression of cancer due to dysbiosis in the gut microbiome and an increase in harmful bacterial populations.

Microbiome-modulating therapies, including FMT, probiotics, prebiotics, and symbiotic, are increasingly being investigated in clinical trials for various diseases. These therapies aim to alter the composition and function of the gut microbiome to potentially treat or improve outcomes in conditions ranging from infectious diseases to cancer. FMT involves transferring fecal matter from a healthy donor to a recipient to restore a healthy gut microbiome (Cao et al., 2025). Probiotic therapy shows promise in CRC management by potentially reducing treatment side effects and improving patient outcomes. Probiotics, beneficial bacteria, can modulate the gut microbiota, impacting immune responses, inflammation, and even cancer cell behavior (Zhao et al., 2023).

However, FMT faces challenges due to the variability in patient microbiota and potential safety risks. Donor screening is expensive and labor-intensive, and no method can definitively exclude the transfer of pathogens. Serious adverse events, including fatalities, have occurred after FMT due to the transmission of antibiotic-resistant bacteria. Furthermore, the long-term safety of FMT remains unclear.

The gut microbiome has a critical impact on metabolic and immune pathways necessary for maintaining host balance. In addition to promoting immune stability, it greatly affects both local and systemic immune responses against tumors (Velikova et al., 2021). This connection is especially evident in gastrointestinal (GI) cancers, where microbial imbalance—marked by the disruption of microbial populations—has been associated with decreased treatment effectiveness and worse clinical outcomes (de Castilhos et al., 2024).

Recent developments have revealed specific ways the gut microbiota affects immunotherapy. These include the regulation of immune checkpoints, alteration of the tumor microenvironment, and reduction of side effects associated with therapies (Zhao et al., 2024). Importantly, various clinical trials are currently testing microbiome-based strategies to improve immunotherapy effectiveness. Certain microbial species such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* have been recognized as important players in enhancing immune checkpoint inhibitors' (ICIs) efficacy

(Lin et al., 2025). Furthermore, metabolites produced by the microbiota, including SCFAs, are vital in lowering inflammation, promoting T-cell infiltration, and reprogramming metabolic pathways linked to tumors (Li et al., 2024). On the other hand, disruptions in the microbiome, often indicated by a loss of beneficial bacteria or an increase in pro-inflammatory species, have been connected to less effective immunotherapy results and a higher risk of Immune-related adverse events (irAEs) (Dai et al., 2024). Advances in microbiome research have created new opportunities for enhancing immunotherapy by improving its effectiveness and reducing related toxicities. This overview highlights the mechanisms involved, emphasizing the microbiome's role in precisely regulating immune checkpoint pathways, reshaping the tumor microenvironment, and boosting gut barrier function through SCFA production (Figure 2).

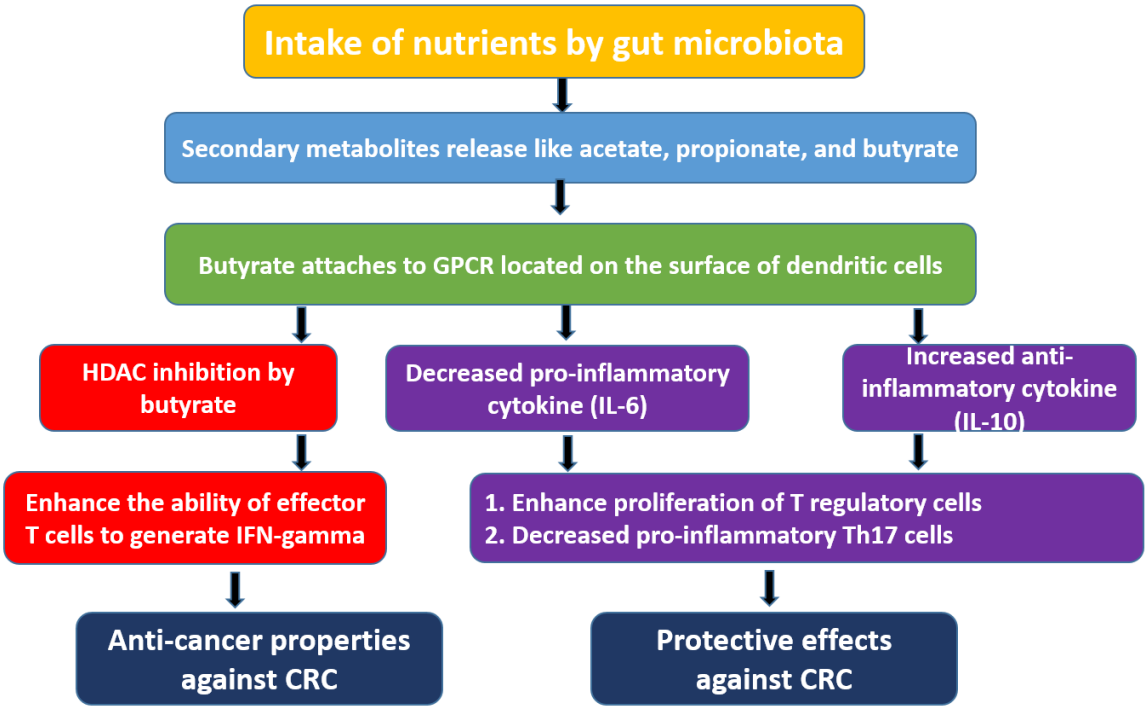

Figure 2: The gut microbiota plays a role in modulating the host's immune response to colorectal cancer. SCFAs like acetate, propionate, and butyrate are byproducts produced by gut microbiota after food intake. Butyrate interacts with G-protein coupled receptors (GPCR) found on dendritic cells, triggering various immune-modulatory responses. These responses include a reduction in the pro-inflammatory cytokine IL-6 and an elevation in the anti-inflammatory cytokine IL-10. Butyrate fosters the growth of regulatory T cells while inhibiting proinflammatory Th17 cells, thereby offering protective benefits against CRC. Additionally, butyrate acts as a histone deacetylase (HDAC) inhibitor, which enhances the capability of effector T cells to produce IFN-gamma and contributes to the anti-tumor effects against CRC.

Abbreviations: SCFAs: Short-chain fatty acids; GPCR: G-protein coupled receptors; IL-6: Interleukin-6; HDAC: Histone deacetylase; IFN: Interferon; CRC: Colorectal cancer.

Microorganisms populate various anatomical locations, with more than 90% found in the GI tract. Significant changes in the gut microbiota occur in CRC, such as a decrease in alpha diversity and disturbance of the microbial community structure (Sobhani et al., 2011). Comparable patterns of dysbiosis have been observed in other gastrointestinal malignancies. These changes have been associated with differences in the response to ICI, specifically anti–PD-1/PD-L1 therapies (Peng et al., 2020). SCFAs, especially butyrate, play a role in enhancing antitumor immunity by boosting T cell cytotoxicity (Bender et al., 2023). In mouse

models of CRC that are colonized with butyrate-producing bacteria such as *Roseburia intestinalis*, increased effectiveness of anti-PD-1 treatment has been noted. This phenomenon appears to be mediated by a rise in intratumoral $CD8^+$ T cell infiltration, leading to a decrease in tumor burden (Kang et al., 2023). Although these discoveries emphasize the immune-stimulating properties of SCFAs, recent research indicates that their effects are not consistently beneficial. In certain microbial and host environments, SCFAs may actually facilitate tumor development. For instance, in CRC models containing *Fusobacterium nucleatum*, butyrate stimulates Free fatty acid receptor 2 (FFAR2), which promotes the expansion of Th17 cells and IL-17-driven inflammation—an axis linked to immune remodeling that promotes tumors (Yang et al., 2023).

When considered collectively, SCFAs derived from gut microbiota, such as acetate, propionate, and butyrate, exhibit intricate and at times contradictory effects on host health. Although they are widely acknowledged for their beneficial roles in energy metabolism, inflammation, and gut health, aspects of their influence remain under exploration and yield mixed findings. For example, SCFAs, particularly butyrate, are recognized for their anti-inflammatory characteristics by inhibiting histone deacetylation, which can influence gene expression, along with modulating immune cell activities. Nevertheless, some research indicates that SCFAs, in specific situations or at elevated levels, might also play a role in promoting inflammation or displaying different results. Additionally, SCFAs have been associated with both protective and promoting functions in the development of cancer, as noted in studies from ScienceDirect. While certain research indicates that SCFAs can trigger apoptosis in cancer cells and boost the effectiveness of chemotherapy, other findings suggest that they might also promote the growth of cancer cells in particular scenarios (Liu et al., 2020).

Besides SCFAs, other microbial metabolites also play a role in immunomodulation. Inosine generated by *B. pseudolongum* enhances Th1 activation through the A2A receptor in murine CRC models, with its effects dependent on T cell co-stimulation, ultimately improving ICI efficacy (Mager et al., 2020). Microbial structural components like lipopolysaccharide (LPS) exhibit strain-specific immune impacts. LPS derived from *Fusobacterium periodonticum* elevated the production of IL-1β, IL-6, and IFN-γ, while LPS from *Bacteroides fragilis* and *Porphyromonas asaccharolytica* reduced cytokine levels (Sulit et al., 2023). These varied effects reflect the differences in the immune context of various CRC subtypes: consensus molecular subtypes 1 (CMS1) tumors display an abundance of immunostimulatory bacteria, while CMS4 tumors are linked to immunosuppressive taxa. Collectively, microbial diversity, compositional characteristics, and immunomodulatory metabolites significantly influence host responsiveness to ICI treatment across gastrointestinal cancers. The gut microbiota has been shown to influence cancer stem cells or quiescent cancer cells that are believed to be responsible for disease relapse (Artusa et al., 2023). The composition of gut microbiota can modify the tumor microenvironment and its relationship with the immune system, thereby affecting treatment predictions (Roy and Singh, 2024). The consumption of probiotics has been found to lower the risk of cancer, particularly CRC, by inducing immune responses and fostering balanced and healthy gut microbiomes to support various therapies (Pala et al., 2011).

Overall, therapeutic resistance and adverse effects continue to be significant challenges in cancer treatment management, even with high toxicity levels. Therefore, the future application of cancer-associated microbes in clinical settings is filled with both opportunities and challenges that must be acknowledged and addressed. Despite the obstacles that currently exist, the immense significance and potential of gut microbiota for developing new anti-cancer strategies cannot be overstated, necessitating a comprehensive approach that integrates microbial modulation therapy into the existing cancer management framework. While numerous microbial taxa have demonstrated the ability to enhance therapeutic efficacy, others might undermine treatment responses or contribute to tumor persistence. This dual nature of the microbiome underscores the need to consider both beneficial and detrimental microbial elements when devising microbiome-based therapies.

Conclusion:

In summary, this analysis emphasizes the connection between gut microbiota and CRC. The gut microbiota is essential for preserving the integrity of the colon barrier and regulating immune responses, both of which are vital for disease prevention. Besides CRC, disturbances in gut microbiota have also been associated with other intestinal disorders, such as inflammatory bowel disease (IBD), indicating common microbial pathways. Human cancer, known for being one of the most intricate, devastating, and least understood medical conditions, has been associated with specific microbial alterations and overall changes in microbiome community structure. Recent research highlights the significant impact of gut microbiota on the effectiveness of treatments, immune modulation, and management of toxicity. Certain microbial taxa and their metabolites have been demonstrated to improve the efficacy of immune checkpoint inhibitors and chemotherapy drugs, while dysbiosis has been linked to mechanisms of resistance and negative outcomes. Gut dysbiosis has been recognized as a significant characteristic of CRC. Modifications in diet and lifestyle can significantly reshape the composition of gut microbes and their metabolites, potentially playing a role in the initiation of CRC. Several key questions remain unresolved regarding the connection between the gut microbiome and CRC that need to be answered in the future. These include understanding the precise mechanisms by which specific bacteria influence CRC development, the impact of the microbiome on the tumor microenvironment, and how the microbiome might be targeted for therapeutic interventions? Moreover, can microbiome profiling predict CRC risk? And how do diet-microbiome interactions vary across populations?

Authors' contributions

Both authors wrote and reviewed the manuscript. The authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The author declares that he has no competing interests.

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149, 541-552.

Table 1: The key CRC-associated bacteria and their mechanisms of action.

NO.	Key CRC-associated bacteria	Mechanisms of action	Reference
1	*Fusobacterium nucleatum*	1. Modulating the tumor microenvironment. 2. Directly interacting with host cells. 3. Inducing inflammation.	(Li et al., 2022)
2	*Escherichia coli (pks + E. coli)*	These strains produce the genotoxin colibactin, which causes DNA damage in intestinal epithelial cells, promoting tumorigenesis.	(Jans and Vereecke, 2025)
3	*Bacteroides fragilis*	*Enterotoxigenic B. fragilis* (ETBF) produces a toxin called *B. fragilis** toxin (BFT), which can disrupt the intestinal barrier and activate signaling pathways that promote cancer development.	(Li et al., 2022)
4	*Enterococcus faecalis*	This bacterium can damage DNA through the production of free radicals, contributing to cancer development.	(Zhang et al., 2023)
5	*Streptococcus bovis*	This bacterium has been linked to CRC and can contribute to DNA damage and inflammation.	(Tsai et al., 2016)