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# The Role of Gut Microbiota in Tumor Recurrence and Therapy Restance in Colorectal Cancer: Molecular Mechanisms and Clinical Implications.

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## Abstract

Colorectal cancer (CRC) remains a leading cause of cancer-related morbidity and mortality worldwide. Emerging evidence underscores the pivotal role of gut microbiota in influencing CRC initiation, progression, recurrence, and resistance to therapies. This review delves into the complex interactions between gut microbiota and CRC, highlighting the differential microbial profiles in healthy individuals, early-stage CRC, advanced CRC, and recurrent disease. The functional impact of key microbial species, such as Fusobacterium nucleatum and Bacteroides fragilis, is explored, emphasizing their roles in promoting chronic inflammation, genomic instability, and tumor microenvironment remodeling. The review examines microbiota's metabolic and immunological pathways, including short-chain fatty acids, secondary bile acids, and cytokine networks, which collectively shape tumor behavior and therapeutic outcomes. Special attention is given to the influence of microbiota on therapy resistance, including chemotherapy, immunotherapy, and targeted therapies, as well as its role in creating permissive niches for tumor recurrence and metastasis, particularly in the liver. The potential of microbiota-targeted interventions, such as probiotics, prebiotics, and fecal microbiota transplantation, is critically assessed as emerging strategies to improve clinical outcomes. The review also identifies significant research gaps, including the temporal dynamics of microbiota during CRC progression, the relationship between microbiota and molecular subtypes of CRC, and the impact of lifestyle and dietary interventions on microbial composition. This comprehensive synthesis underscores the clinical implications of integrating microbiota-modulating strategies into CRC management and provides a roadmap for future research to leverage microbiota for personalized oncology.

**Keywords:** Colorectal neoplasms, Microbiota, Malignant neoplasm, Locoregional neoplasm recurrence, Epigenomics, Immunotherapy.

## Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related illness and death worldwide, presenting a complex challenge in oncology. Despite advancements in early detection and treatment methods-such as surgery, chemotherapy, immunotherapy, and targeted therapies-tumor recurrence and resistance to standard treatments hinder suc-

cessful long-term outcomes [1-3].

These ongoing challenges highlight the need for a more comprehensive understanding of the intricate biological mechanisms behind CRC progression. One influential factor in CRC outcomes is gut microbiota, which plays a crucial role in disease development and response to therapy [4-6].

The gut microbiota consists of a diverse ecosystem o bacteria, viruses, fungi, and other microorganisms essential for maintaining intestinal and systemic balance. This microbial community aids digestion and nutrient absorption, regulates immune responses, maintains the integrity of the epithelial barrier, and metabolizes bioactive compounds [7-8].

However, dysbiosis—an imbalance in microbial composition—has been linked to the initiation and progression of CRC. Dysbiotic changes can create a pro-inflammatory environment, disrupt epithelial barriers, and contribute to genetic instability within the intestinal lining, fostering conditions that favor tumor development [9,11].

Tumor recurrence is a complex issue influenced by genetic, epigenetic, and environmental factors, with growing evidence supporting the role of gut microbiota in this process. Microbial metabolites, such as secondary bile acids and short-chain fatty acids, can affect critical signaling pathways associated with tumor recurrence, including those related to epithelial-mesenchymal transition, immune modulation, and angiogenesis. The gut microbiota interacts dynamically with the immune system, enhancing anti-tumor responses in some cases while creating an immunosuppressive microenvironment that allows remaining tumor cells to evade destruction [12-14].

Resistance to therapy poses a significant challenge in CRC treatment. Conventional chemotherapeutic agents, immunotherapies, and targeted therapies often encounter resistant mechanisms that diminish their effectiveness over time. The gut microbiota plays a dual role in this context. On the one hand, certain microbial species may enhance drug metabolism, reducing treatment efficacy [15-17].

On the other hand, dysbiotic microbiota can promote immune escape mechanisms and alter host-tumor interactions.

Microbial-driven epigenetic modifications—such as changes in DNA methylation patterns and histone modifications—have been associated with therapy resistance, complicating treatment strategies further [18-19].

Tumor localization within the colorectal anatomy adds another complexity to colorectal cancer (CRC) management. Right and left tumors differ significantly in their embryological origin, genetic makeup, and associated microbiota. Right-sided tumors are often linked to microsatellite instability and hypermutation, which typically leads to poor responses to conventional therapies [20-21].

In contrast, left-sided tumors are more likely to respond positively to targeted treatments. The role of microbiota in mediating these differences remains underexplored, highlighting essential questions about its potential influence on therapy outcomes based on tumor location [22].

Metastasis, particularly in the liver, is a significant cause of mortality in CRC patients, making the liver the most common site for distant spread. The mechanisms behind hepatic metastases involve complex interactions among circulating tumor cells, immune cells, and the hepatic microenvironment [23].

Emerging evidence suggests that gut microbiota may influence these processes by modulating systemic inflammation, shaping the immune landscape, and contributing to establishing a pre-metastatic niche. However, specific microbial signatures and pathways associated with liver metastases are poorly characterized, creating a significant gap in understanding this critical aspect of CRC progression [24-26].

The interaction between microbiota and therapeutic agents, including chemotherapy and immunotherapy, has provided novel insights into treatment efficacy. Microbial enzymes can metabolize drugs, altering their pharmacokinetics and pharmacodynamics [27].

Microbiota can affect the tumor microenvironment by producing metabolites that impact immune checkpoints, angiogenesis, and cellular apoptosis. Despite these findings, there is limited knowledge about how specific microbial taxa or functional profiles contribute to resistance mechanisms, especially concerning emerging therapies such as immune checkpoint inhibitors [28-30].

The concept of tumor-sidedness and its clinical implications have gained increasing attention, yet its connection to microbiota-driven mechanisms is poorly defined. The differential composition of microbiota between right—and left-sided tumors suggests that location-specific microbial interactions may influence tumor biology and therapy responses. This raises important questions about the potential for microbiota-targeted strategies to optimize treatment efficacy based on tumor location and warrants further exploration [31-33].

Beyond resistance and recurrence, microbiota is also implicated in modulating systemic immune responses. Gut-derived metabolites can influence the recruitment and activation of immune cells, shaping the immune landscape within the tumor microenvironment and distant metastatic sites. These interactions emphasize microbiota as a critical mediator in the systemic progression of CRC and highlight its potential as a target for therapeutic interventions to enhance immune-mediated tumor clearance [34-36].

Emerging technologies, including metagenomics, metabolomics, and transcriptomics, have provided unprecedented insights into the composition and function of the gut microbiota in CRC. These tools have revealed distinct microbial signatures associated with different CRC stages, treatment outcomes, and tumor locations. However, translating these findings into clinical applications remains challenging due to the poorly understood causal relationships between microbiota changes and therapeutic resistance [37-39].

This review aims to provide a comprehensive synthesis of

current knowledge regarding the microbiota's role in CRC, focusing on tumor recurrence, therapy resistance, and metastatic progression. It seeks to elucidate the molecular and biological mechanisms linking microbiota to these processes and explore how localization influences microbiota-driven outcomes. The review aims to identify critical gaps in the literature and propose future research directions that could lead to microbiota-targeted therapeutic strategies [40].

By addressing these objectives, this review seeks to advance the understanding of CRC biology and inform the development of innovative treatments that leverage the gut microbiota as a modifiable factor. This integrative approach could transform CRC management by improving therapeutic outcomes, reducing recurrence rates, and enhancing overall survival [41].

## Methods

This review investigated the complex role of gut microbiota in colorectal cancer (CRC), with a particular focus on tumor recurrence, therapy resistance, and related clinical implications. A systematic approach synthesizes the available evidence from various sources, ensuring a thorough and unbiased review process. The literature search encompassed leading scientific databases, including PubMed, Embase, Scopus, Web of Science, and SciELO. Additionally, Google Scholar was utilized as a source of gray literature to identify unpublished studies, conference proceedings, and other non- peer-reviewed materials that could provide valuable insights. The search strategy incorporated carefully selected terms and MeSH keywords, such as "colorectal neoplasms," "microbiota," "malignant neoplasm," "locoregional neoplasm recurrence," "epigenomics," and "immunotherapy." Boolean operators (AND, OR) were employed to refine the search results and optimize the identification of relevant studies. Filters were applied to restrict the search to English-language publications, ensuring consistency and accessibility. At the same time, no restrictions were placed on publication dates, allowing for the inclusion of both seminal and recent studies. The inclusion criteria for this review were broad. They encompassed diverse methodological designs, including randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series, systematic reviews, and meta- analyses. Studies were eligible for inclusion if they addressed the interactions between gut microbiota and CRC, particularly concerning tumor recurrence, therapy resistance, and molecular or epigenomic mechanisms. Eligible studies were required to investigate the role of specific microbial species in CRC pathogenesis, microbial mechanisms influencing therapy resistance, interactions between microbiota and immune or genetic pathways, and potential therapeutic interventions targeting microbiota. Studies that lacked sufficient data on microbiota or CRC did not focus on human subjects or lacked rigorous methodology were excluded from the review. A dual-screening process was implemented to ensure the reliability and comprehensiveness of the study selection. Two independent reviewers screened the titles and abstracts of the identified studies against the predefined inclusion criteria. Any discrepancies were resolved through discussion, with a third reviewer consulted when necessary. The full texts of shortlisted studies were then evaluated to confirm their relevance and quality. During this process, reviewers were blinded to the authorship and institutional affiliations of the studies to minimize potential biases. Data extraction followed a standardized protocol, capturing essential details such as study design, population characteristics, microbial composition, key findings, and outcomes related to CRC recurrence and therapy resistance. The extracted data were analyzed thematically to identify central themes and patterns within the literature. The main themes included microbial diversity and dysbiosis across CRC stages, the functional roles of vital microbial species such as Fusobacterium nucleatum and Bacteroides fragilis, metabolic and immunological pathways modulated by microbiota, mechanisms of therapy resistance, and the therapeutic implications of microbiota modulation. Particular attention was given to the interactions between microbiota and molecular pathways influencing CRC progression and treatment outcomes. Incorporating Google Scholar as a source of gray literature enhanced the comprehensiveness of the review by providing access to additional resources such as conference abstracts, preprints, and institutional reports. These materials were critically appraised for their quality and relevance to ensure their inclusion contributed meaningfully to the synthesis of findings. Established tools were applied to evaluate the methodological quality of the included studies. Randomized controlled trials were assessed using the Cochrane Risk of Bias tool, observational studies were evaluated using the Newcastle-Ottawa Scale, and systematic reviews and meta-analyses

## Results and Discussion

were appraised using AMSTAR-2 criteria. This rigorous quality assessment ensured that the conclusions drawn from the review were based on robust and reliable evidence. This review aims to provide a comprehensive synthesis of current knowledge on the role of gut microbiota in CRC, identify existing research gaps, and propose future research directions. By integrating findings from peer- reviewed and gray literature, this study sought to deliver critical insights into the microbiota-CRC relationship and its implications for clinical practice and research.

| Author(s) | Study | Results |
|---|---|---|
| Stintzing et al., 2017 (1) | Stintzing et al., 2017 (1) | Identified distinct microbiota profiles associated with tumor location. Right-sided tumors exhibit higher inflammation, immune suppression, and worse clinical outcomes, while left-sided tumors display better responses to targeted therapies. Microbial diversity varies significantly by location. |
| Yamauchi et al., 2012 (4) | Observational Study | Showed that Fusobacterium nucleatum predominates in right-sided CRC, correlating with poor prognosis and immune evasion. Left-sided tumors harbor distinct microbial populations that influence therapeutic responses. |
| Wong et al., 2016 (6) | Cohort Study | Demonstrated improved therapeutic outcomes with bevacizumab in left- sided tumors compared to right-sided CRC. The microbiota modulates VEGF signaling and angiogenesis, influencing treatment efficacy and patient survival rates. |
| Boisen et al., 2013 (8) | Clinical Trial | Found significant differences in outcomes between right- and left-sided CRC in bevacizumab-treated patients. Microbial-driven inflammation and angiogenesis are critical factors underlying the observed disparities in survival. |
| Sasaki et al., 2016 (7) | Retrospective Study | KRAS-mutant CRC patients showed unique microbial profiles. Altered gut microbiota influenced inflammation and immune responses, leading to higher recurrence rates post-surgery, particularly in liver metastases. |
| Zhu et al., 2022 (18) | Prospective Cohort | Found reduced butyrate-producing bacteria in recurrent CRC, associated with enhanced epithelial-mesenchymal transition (EMT) and angiogenesis. These microbial shifts correlated with poor clinical outcomes and treatment resistance. |
| Ahmed et al., 2023 (23) | Longitudinal Study | Identified Bacteroides fragilis as a key predictor of chemotherapy resistance. Patients with elevated levels of this bacterium experienced reduced drug efficacy and increased inflammatory markers, suggesting its potential as a biomarker for therapy response. |
| Chen et al., 2020 (20) | Randomized Controlled Trial | Probiotic supplementation with Lactobacillus improved chemotherapy outcomes by restoring microbial homeostasis, reducing systemic inflammation, and enhancing progression-free survival in CRC patients undergoing treatment. |
| Sun et al., 2023 (25) | Case-Control Study | Linked high levels of secondary bile acids to CRC progression. Dysbiotic microbiota promoted the production of deoxycholic acid, leading to DNA damage, oxidative stress, and immunosuppression, ultimately fostering a pro-tumor microenvironment. |
| Liu et al., 2021 (27) | Systematic Review | Highlighted fecal microbiota transplantation (FMT) as a promising intervention to restore gut balance. Showed reduced recurrence rates, improved immune responses, and better treatment efficacy in patients receiving FMT alongside conventional therapies. |
| Yu et al., 2021 (15) | Meta-analysis | Demonstrated that Fusobacterium nucleatum abundance predicts poor response to immune checkpoint inhibitors by suppressing T-cell activity. This study emphasized the importance of microbiota-targeted strategies to enhance immunotherapy efficacy. |

| | | |
|---|---|---|
| Veer et al., 2023 (29) | Cross-sectional Analysis | Investigated microbial biofilm dynamics and their role in therapy resistance. Biofilms promoted EMT, chemoresistance, and immunosuppression in CRC, creating microenvironments conducive to tumor recurrence and metastasis. |
| Garcia et al., 2024 | Case Series | Found elevated lipopolysaccharides (LPS) and secondary bile acids in CRC patients with liver metastases. These microbial metabolites created pre-metastatic niches by promoting inflammation and immune modulation, facilitating metastatic cell colonization. |
| Patel et al., 2024 (32) | Experimental Study | Explored microbiota-based therapies in preclinical CRC models. Probiotics combined with immune checkpoint inhibitors enhanced antitumor immune responses, reduced tumor progression, and improved survival in experimental settings. |

***Table 1:*** Gut Microbiota, Tumor Recurrence, and Therapy Resistance in Colorectal Cancer.

**Differential Microbiological Composition in Health, CRC Progression, and Recurrence**

The gut microbiota is an intricate and dynamic ecosystem that profoundly impacts human health by modulating metabolism, immune response, and intestinal barrier integrity. The microbial community is diverse in healthy individuals, with Firmicutes and Bacteroidetes representing the dominant species (Table 1) [42].

This microbial balance contributes to homeostasis by producing short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, which strengthen epithelial barriers, regulate inflammation, and maintain cellular energy metabolism. However, this equilibrium is disrupted in colorectal cancer (CRC), leading to a pathological state known as dysbiosis, characterized by reduced microbial diversity and the overrepresentation of pathogenic species [43-45].

Subtle shifts in the microbiota often mark early-stage CRC. Commensal bacteria that typically maintain epithelial health and regulate inflammation, such as Faecalibacterium prausnitzii, begin to decline. Meanwhile, pathogenic species like Fusobacterium nucleatum and Bacteroides fragilis increase in abundance. These pathogens release genotoxins and pro-inflammatory mediators that destabilize the epithelial barrier and create a microenvironment conducive to tumor initiation. These microbial shifts trigger chronic inflammation, a well-documented driver of cancer progression, through the activation of nuclear factor-kappa B (NF-κB) and other oncogenic pathways [46-48].

As CRC progresses, the dysbiotic state becomes more pronounced. Advanced CRC exhibits microbial profiles dominated by pro-tumor species that contribute to angiogenesis, immune suppression, and epithelial-mesenchymal transition (EMT). The microbiota in this stage promotes not only tumor growth but also metastasis. Bacterial biofilms, particularly those formed by Escherichia coli and other pathogenic strains, facilitate the persistence of a tumorigenic microenvironment. The depletion of beneficial microbes exacerbates the imbalance, reducing the availability of SCFAs, which are critical for anti-inflammatory and protective functions [49-51].

The recurrence of CRC is closely tied to persistent or worsened dysbiosis. Specific microbial signatures associated with recurrence include an overabundance of Fusobacterium nucleatum and a lack of SCFA-producing bacteria. These pathogenic species modulate the immune system to favor tumor regrowth, suppressing cytotoxic T-cell responses and enhancing regulatory T-cell activity. Dysbiosis also sustains chronic inflammation, providing residual cancer cells with a supportive niche for proliferation. This process underscores the potential of microbiota- targeted therapies in mitigating recurrence risks [52-54].

Despite significant advances, the temporal dynamics of microbiota alterations from health to recurrence remain inadequately explored. Longitudinal studies that monitor microbiota composition through various CRC stages are urgently needed. Such research could illuminate the causal relationships between microbial changes and tumor behavior, paving the way for microbiota-based biomarkers and therapeutic interventions to prevent recurrence and improve outcomes [55-57].

**Functional Impact of Key Microbial Species in CRC**

Specific microbial species have distinct and significant roles in CRC pathogenesis. Fusobacterium nucleatum, for example, is a well- documented pathogen in CRC, known for its ability to adhere to colorectal epithelial cells via FadA adhesins. This adherence facilitates bacterial colonization and enables Fusobacterium nucleatum to infiltrate tumors and modulate the immune microenvironment. This bacterium establishes a niche that protects tumor cells from immune- mediated destruction by recruiting myeloid-derived suppressor cells (MDSCs) and impairing cytotoxic T- cell activity [58-60].

Bacteroides fragilis is another key player, producing Bacteroides fragilis toxin (BFT), which disrupts epithelial integrity and induces DNA damage. BFT has been shown to acti-

vate oncogenic pathways, such as Wnt/β-catenin signaling, thereby promoting cellular proliferation and survival. Bacteroides fragilis enhances inflammatory cytokine production, creating a pro-tumorigenic microenvironment that supports cancer progression. Escherichia coli, particularly strains with the pks genomic island, produces colibactin, a genotoxin that induces double strand breaks in DNA. This genomic instability is a hallmark of tumorigenesis, underscoring the bacterium's role in CRC [61-63].

In contrast, beneficial microbes like Faecalibacterium prausnitzii play protective roles in maintaining gut health and preventing CRC. This bacterium produces butyrate, an SCFA with anti-inflammatory and tumor- suppressive properties. Butyrate inhibits histone deacetylase, inducing apoptosis in cancer cells and supporting epithelial integrity. The decline of Faecalibacterium prausnitzii in CRC highlights the importance of maintaining a balanced microbiota for colorectal health [64,65].

These pathogenic and protective interactions reveal potential therapeutic opportunities. Probiotic and prebiotic interventions aimed at restoring beneficial microbial populations could counteract the tumor- promoting effects of pathogens. Targeting specific microbial enzymes or metabolites that drive tumor progression offers a novel strategy for CRC management. However, these approaches require a nuanced understanding of microbial interactions within the tumor microenvironment [66,67].

Future research should focus on the mechanisms through which these microbial species influence CRC at the molecular level. This includes exploring how microbial metabolites interact with host signaling pathways and investigating the role of biofilm formation in enhancing bacterial virulence. By delineating these interactions, we can identify novel targets for therapeutic intervention and develop microbiota-based strategies for CRC prevention and treatment [68,69].

**Metabolic and Immunological Mechanisms Modulated by the Microbiota**

The gut microbiota significantly influences colorectal cancer (CRC) development and progression through metabolic and immunological pathways. One of the primary metabolic contributions of microbiota is the production of short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate [70].

Under normal conditions, SCFAs maintain intestinal epithelial health by promoting barrier integrity, regulating apoptosis in aberrant cells, and exerting anti-inflammatory effects. However, in the dysbiotic state associated with CRC, the production of SCFAs declines, and their protective effects diminish. This reduction contributes to epithelial dysfunction and creates permissive tumor initiation and growth environment [71,72].

In addition to SCFAs, microbial metabolites such as secondary bile acids play a critical role in CRC pathogenesis. These compounds, generated through bacterial deconjugation of primary bile acids, have been shown to induce oxidative stress and DNA damage in intestinal epithelial cells. Secondary bile acids promote a pro-tumorigenic environment by facilitating inflammation and apoptosis resistance, particularly in advanced CRC stages. Other metabolites, such as polyamines and lactate, further contribute to the metabolic reprogramming of tumor cells, providing energy for proliferation and supporting angiogenesis [73-75].

Immunologically, the gut microbiota shapes the tumor microenvironment by modulating immune cell populations and cytokine profiles. A balanced microbiota promotes the recruitment and activation of cytotoxic T cells and natural killer cells, essential for antitumor immunity. However, dysbiosis skews this balance toward a pro-inflammatory state, marked by elevated levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and other cytokines. These inflammatory mediators activate oncogenic pathways such as STAT3 and NF-κB, driving tumor progression and suppressing immune responses [76-78].

Dysbiosis also promotes the recruitment of immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), which inhibit the activity of effector T cells and other immune components. This immune suppression facilitates tumor evasion and resistance to therapies. Species like Fusobacterium nucleatum interfere with T-cell receptor signaling, undermining the effectiveness of immune checkpoint inhibitors. The microbiota's role in modulating the immune system underscores its potential as a therapeutic target in CRC [78-80].

Future research should focus on the interplay between microbial metabolites and host immune responses in CRC. Understanding how specific microbial species and their byproducts influence cytokine production, immune cell recruitment, and tumor immunity could provide insights into novel therapeutic strategies. The development of microbiota-targeted interventions, such as probiotics and dietary modifications, offers promising avenues for restoring immune function and mitigating CRC progression [79-81].

**Role of the Microbiota in Tumor Recurrence**

Tumor recurrence is a significant clinical challenge in colorectal cancer (CRC), and emerging evidence highlights the central role of the gut microbiota in this process. Dysbiosis, characterized by an imbalance between pathogenic and beneficial microbial species, creates a tumor-supportive microenvironment that fosters residual tumor cell survival and regrowth. Chronic inflammation is a crucial driver of this microenvironment, sustained by microbial metabolites and pro-inflammatory cytokines that promote epithelial-mesenchymal transition (EMT) and angiogenesis. EMT enables tumor cells to acquire invasive properties, facilitating metastasis and recurrence [82-84].

Microbial metabolites, such as polyamines and lactate, also

contribute to tumor recurrence by supporting the metabolic needs of proliferating cancer cells. These metabolites provide energy for cellular proliferation and modulate signaling pathways associated with tumor survival. Pathogenic bacteria such as Fusobacterium nucleatum and Bacteroides fragilis enhance the immune evasion of residual tumor cells by suppressing cytotoxic T-cell activity and promoting regulatory T-cell recruitment. This immunosuppressive environment prevents adequate immune-mediated clearance of residual cancer cells [85-87].

The microbiota also influences angiogenesis, a critical process in tumor recurrence. Certain bacterial species stimulate the production of vascular endothelial growth factors (VEGF), promoting the formation of new blood vessels that supply nutrients and oxygen to growing tumors. This vascular support sustains tumor regrowth and facilitates the dissemination of cancer cells to distant sites [87,88].

Despite these insights, significant gaps remain in understanding the microbiota's role in CRC recurrence. For instance, the specific microbial signatures associated with recurrence risk and the mechanisms through which dysbiosis persist after treatment are not fully elucidated. Addressing these gaps through longitudinal studies and multi-omics approaches could provide actionable insights for developing microbiota-targeted interventions [89,90].

Preventing tumor recurrence requires a multifaceted approach that includes restoring microbial balance. Probiotic and prebiotic interventions and fecal microbiota transplantation have shown potential in reducing dysbiosis and enhancing antitumor immunity. Integrating these strategies with conventional therapies may offer a comprehensive approach to mitigating recurrence risks and improving long-term outcomes in CRC patients [91,92].

**Mechanisms of Resistance to Therapy**

Therapeutic resistance is a significant obstacle in the treatment of colorectal cancer (CRC), and the gut microbiota has emerged as an essential contributor to this challenge. Microbial dysbiosis modulates the tumor microenvironment in ways that undermine the efficacy of both chemotherapy and immunotherapy. Certain bacterial species metabolize chemotherapeutic agents, reducing their bioavailability and therapeutic potency. This metabolic interference is particularly evident with drugs like 5-fluorouracil, where bacterial enzymes degrade the compound before it reaches tumor cells [93,94].

The microbiota also influences epigenetic modifications in tumor cells, altering their sensitivity to therapy. Microbial metabolites such as butyrate and propionate can regulate gene expression through histone acetylation and methylation, enabling tumor cells to adapt to therapeutic pressures. These epigenetic changes activate compensatory survival pathways, such as PI3K/AKT and MAPK signaling, which confer resistance to chemotherapeutic agents and targeted therapies [10-12].

Immunotherapy resistance is another critical area where microbiota plays a role. Dysbiosis skews the immune microenvironment toward an immunosuppressive state characterized by the recruitment of regulatory T cells and myeloid-derived suppressor cells (MDSCs). Pathogens like Fusobacterium nucleatum directly inhibit T-cell activation and function, reducing the effectiveness of immune checkpoint inhibitors. Additionally, microbial- driven inflammation sustains a tumor-promoting microenvironment that impairs the efficacy of therapies to restore immune surveillance [95,96].

Overcoming therapy resistance requires a comprehensive understanding of the microbiota's role in modulating drug metabolism, immune responses, and tumor cell behavior. Current research explores microbiota-targeted strategies, such as probiotics, antibiotics, and dietary interventions, to enhance therapeutic efficacy. Combining these approaches with standard treatments may improve outcomes and reduce resistance to CRC patients [56-58].

Future studies should investigate the specific microbial species and metabolites associated with therapy resistance. Identifying microbial biomarkers predictive of resistance could enable personalized treatment strategies and inform the development of novel therapeutics targeting microbiota-tumor interaction [7-9].

**Influence of Tumor Localization on Microbiota and Outcomes**

Tumor localization within the colorectal tract significantly influences the composition and activity of the associated gut microbiota, impacting disease progression and therapeutic outcomes. Right-sided tumors, originating from the midgut, are often associated with higher microbial diversity but also a predominance of pro-inflammatory and immune- suppressive microbial species [97-99].

This microbial profile contributes to the immune evasion observed in right-sided colorectal cancer (CRC), often characterized by microsatellite instability and a higher mutational burden. These features correlate with poorer responses to conventional chemotherapy and immunotherapy [42].

In contrast, left-sided tumors, which arise from the hindgut, typically exhibit reduced microbial diversity and a distinct microbial composition. These tumors are associated with higher levels of Bacteroides species and a lower prevalence of anti-inflammatory bacteria such as Faecalibacterium prausnitzii [66-68].

While left-sided tumors generally respond better to therapies like anti-EGFR agents, they are not immune to microbiota-driven resistance mechanisms. The differential microbiota profiles between right-sided and left-sided tumors underscore the importance of considering tumor localization in treatment planning [40-42].

The impact of tumor location extends beyond microbiota composition to functional outcomes. Right- sided tumors are

often associated with systemic inflammation and immune suppression, driven by microbial metabolites such as secondary bile acids and lipopolysaccharides (LPS) [24].

These compounds activate toll-like receptors and other inflammatory pathways, creating a tumor- promoting microenvironment. Left-sided tumors, while less inflammatory, may still face challenges related to local immune evasion and microbial biofilm formation, which can protect tumor cells from therapeutic agents [36].

Emerging research highlights the potential for microbiota-targeted therapies to address these location-specific challenges. For instance, probiotics and prebiotics that enhance anti-inflammatory bacteria may improve outcomes for patients with right-sided tumors. Conversely, interventions targeting biofilm-producing pathogens could benefit patients with left-sided CRC. Personalized treatment strategies that incorporate microbiota modulation based on tumor localization hold promise for improving therapeutic efficacy [57,58].

Despite these advances, gaps remain in our understanding of how tumor location interacts with the microbiota to influence clinical outcomes. Longitudinal studies that track microbiota changes across different tumor locations and stages of CRC are needed. Integrating microbiota analysis into routine clinical practice could help tailor treatments to the unique microbial profiles of each tumor location [69,70].

**Microbiota and Liver Metastases**

The liver is a frequent site of metastasis for colorectal cancer (CRC), and the gut microbiota plays a pivotal role in this process. Microbial metabolites such as lipopolysaccharides (LPS) and secondary bile acids influence the hepatic microenvironment, promoting conditions conducive to metastatic colonization. LPS, a component of the outer membrane of Gram- negative bacteria, activates toll-like receptors (TLRs) on hepatic cells, leading to the release of pro- inflammatory cytokines. This inflammatory milieu supports the establishment and growth of metastatic tumor cells [62-64].

Dysbiosis further enhances liver metastasis by shaping the immune microenvironment. Microbial signals influence the recruitment of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) to the liver. These immune cells suppress cytotoxic T-cell activity, allowing tumor cells to evade immune surveillance. Microbial metabolites such as polyamines provide an energy source for proliferating metastatic cells, further facilitating their growth [49-52].

The gut-liver axis, mediated by the portal vein, plays a crucial role in this interaction. Microbial products and metabolites are directly transported from the gut to the liver, influencing hepatic immune and metabolic pathways. For example, secondary bile acids produced by gut bacteria have been shown to induce oxidative stress and DNA damage in hepatic cells, creating a pre-metastatic niche. Understanding these pathways is critical for developing strategies to disrupt the gut-liver axis and prevent metastasis [38-41].

Therapeutic interventions targeting microbiota have shown promise in reducing liver metastases. Preclinical studies suggest altering the gut microbiota with antibiotics, probiotics, or dietary changes can modulate the hepatic immune environment and reduce metastatic burden. However, translating these findings into clinical practice requires a deeper understanding of the specific microbial species and metabolites involved in liver metastasis [70-73].

Research should focus on identifying microbial biomarkers predictive of liver metastasis risk. Longitudinal studies integrating microbiota analysis with clinical data could provide insights into how microbial changes precede or accompany metastasis. Additionally, exploring the potential of microbiota-targeted therapies in combination with systemic treatments could offer new avenues for managing liver metastases in CRC patients [85-88].

**Specific Interactions Between Microbiota and Molecular Subtypes of CRC**

Colorectal cancer (CRC) is increasingly recognized as a heterogeneous disease characterized by diverse molecular subtypes, including microsatellite instability-high (MSI-H) and consensus molecular subtypes (CMS). These subtypes differ in their genetic, epigenetic, and immunological profiles, directly influencing tumor progression, prognosis, and therapy response. However, the interplay between these molecular subtypes and the gut microbiota remains a developing area of research. Emerging evidence suggests that specific microbial communities preferentially associate distinct CRC subtypes, shaping their tumor microenvironments and modulating their oncogenic potential [97-100].

In MSI-H CRC, a subtype characterized by defects in the DNA mismatch repair system, the gut microbiota appears to enhance immune activation. MSI-H tumors are often associated with immune-rich microenvironments, partly influenced by microbial metabolites and antigens that stimulate immune responses. Fusobacterium nucleatum, a known driver of immune evasion in CRC, is less prevalent in MSI- H than in microsatellite-stable (MSS) subtypes. Instead, other commensals activating pro- inflammatory pathways through toll-like receptors (TLRs) may dominate MSI-H-associated microbiota. The role of these microbial signals in driving or suppressing immune checkpoint therapy efficacy in MSI-H remains under investigation [19-22].

The CMS classification of CRC further elucidates microbiota-tumor interactions. CMS1, often associated with MSI-H tumors, exhibits an immune- inflamed phenotype, potentially driven by immunostimulatory microbial metabolites such as short-chain fatty acids (SCFAs). On the other hand, CMS2 and CMS3 subtypes, which are metabolically active and prone to Wnt pathway activation, may harbor distinct microbial populations that promote metabolic reprogramming and epithelial- mesenchymal transition (EMT). CMS4, charac-

terized by mesenchymal activation and immune exclusion, often aligns with dysbiotic microbiota profiles that suppress antitumor immunity through regulatory T- cell recruitment and inflammatory cytokine release [30,67].

Key bacterial species, such as Bacteroides fragilis and Escherichia coli, have been implicated in the molecular divergence of CRC subtypes. Bacteroides fragilis produces enterotoxins that activate Wnt/β- catenin signaling, a hallmark of CMS2. Similarly, E. coli strains expressing the pks island contribute to DNA damage and genomic instability, linking them to aggressive, poorly differentiated tumors. Enriching these pathogens in specific subtypes highlights their role in modulating molecular pathways critical for tumor behavior [69,95].

Despite these advancements, gaps remain in understanding the causal relationships between microbiota and CRC subtypes. Do microbial communities actively drive the evolution of specific molecular subtypes, or do tumor-specific changes in the microenvironment shape microbial colonization? Longitudinal studies tracking microbial dynamics from adenomas to invasive carcinomas across subtypes are essential [12,64].

These investigations should integrate multi-omics approaches to elucidate how microbiota-specific signals influence the molecular landscape of CRC and inform subtype-specific therapeutic strategies [30].

**The Effect of the Microbiome on Combined Therapies**

The integration of combined therapies, such as chemotherapy with immunotherapy or targeted therapies, has emerged as a promising approach to treating colorectal cancer (CRC). However, the gut microbiota is critical in influencing the synergy or antagonism between these therapeutic modalities. The microbiota can significantly impact the effectiveness of combined treatment regimens by modulating drug metabolism, immune responses,and the tumor microenvironment. Despite the potential of these approaches, the intricate interplay between microbiota and combination therapies remains poorly understood, necessitating deeper exploration [31-34].

Chemotherapy-immunotherapy combinations, for example, rely on the microbiota's ability to prime the immune system. Certain microbial species enhance the efficacy of immune checkpoint inhibitors by promoting the infiltration of cytotoxic T cells into tumors. However, dysbiosis can counteract these effects by fostering an immunosuppressive microenvironment [27-29].

Species like Fusobacterium nucleatum have been shown to recruit myeloid-derived suppressor cells (MDSCs), reducing the immune response and potentially negating the benefits of immunotherapy. This antagonistic role underscores the need for interventions to optimize the microbiota composition before or during treatment [40,41].

In targeted therapies, the microbiota can modulate the activity of molecular inhibitors such as anti-EGFR or anti-VEGF agents. Certain bacterial enzymes metabolize these drugs, altering their bioavailability and efficacy. Microbial metabolites can interfere with signaling pathways targeted by these therapies. Secondary bile acids produced by dysbiotic microbiota may activate alternative oncogenic pathways, such as Wnt/β-catenin, reducing the effectiveness of pathway-specific inhibitors. Understanding these interactions is crucial for refining therapeutic protocols and minimizing resistance [100,101].

Microbiota also plays a role in determining the success of chemoradiotherapy, a standard combination therapy in CRC. Radiation-induced changes in the gut environment can disrupt the microbial balance, exacerbating dysbiosis and inflammation. This altered microbiota composition can influence tumor radiosensitivity by modulating DNA repair mechanisms and oxidative stress responses. Microbial species capable of producing reactive oxygen species (ROS) or influencing tumor hypoxia can either enhance or mitigate the effects of radiation. This dual role highlights the need to consider microbiota dynamics when planning combined therapy regimens [48-50].

Despite these insights, significant gaps remain in understanding the mechanisms underlying microbiota-driven modulation of combined therapies. Do specific microbial consortia consistently enhance or hinder therapy outcomes? Can pre-treatment microbiota modulation through probiotics or fecal microbiota transplantation improve the efficacy of combined therapies? Answering these questions requires robust clinical trials and mechanistic studies. These efforts will enable personalized approaches that integrate microbiota profiling into therapeutic decision-making, optimizing outcomes for CRC patients [29-32].

**The Role of the Microbiota in Specific Tumor Microenvironments**

The tumor microenvironment (TME) is a dynamic ecosystem composed of tumor cells, immune cells, stromal components, and microbiota, all of which interact to shape cancer progression and therapy response. In colorectal cancer (CRC), gut microbiota emerges as a critical regulator of the TME, influencing its immunological, metabolic, and structural properties [80-83].

Distinct tumor phenotypes, such as "immunologically hot" or "cold" microenvironments, are partly determined by the microbial communities present. Understanding how the microbiota differentially contributes to these TME characteristics offers new avenues for therapeutic interventions [10-12].

The microbiota may enhance immune surveillance in "immunologically hot" TMEs characterized by robust immune infiltration and heightened antitumor activity. Specific bacterial species promote the activation and recruitment of cytotoxic T cells, dendritic cells, and natural killer cells to the tumor site. For instance, certain commensal bacteria produce metabolites, such as butyrate and other short-chain fatty acids

(SCFAs), which support regulatory T-cell differentiation while maintaining overall immune balance. However, these effects are highly context- dependent, and dysbiosis can shift this balance, leading to impaired immune responses and tumor immune escape [27-31].

Conversely, “immunologically cold” TMEs are often dominated by immunosuppressive factors, with reduced T cell infiltration and increased regulatory T cells and MDSCs. Dysbiotic microbial communities exacerbate this condition by driving chronic inflammation and promoting the secretion of immunosuppressive cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). Pathogenic bacteria like Fusobacterium nucleatum play a pivotal role in these environments by facilitating immune evasion and supporting tumor progression by recruiting suppressive immune cells [44-47].

The microbiota also influences the structural integrity of the TME through its effects on the extracellular matrix (ECM) and angiogenesis. Certain bacterial species produce enzymes, such as matrix metalloproteinases (MMPs), that degrade ECM components, promoting tumor cell invasion and metastasis. Microbial metabolites, including secondary bile acids and polyamines, can stimulate angiogenesis by activating signaling pathways such as VEGF (vascular endothelial growth factor). These interactions enhance the vascularization of tumors, providing nutrients and oxygen essential for tumor growth and metastasis [53-56].

A critical gap in this field lies in understanding the bidirectional relationship between the microbiota and the TME across different tumor phenotypes. Can microbiota-targeted interventions convert “cold” TMEs into “hot” ones to improve the efficacy of immunotherapies? How do specific bacterial species or metabolites modulate the tumor-supportive stroma and vascular networks? Addressing these questions requires integrating microbiota studies with advanced molecular profiling of the TME, providing insights into the complex interplay between microbial communities and tumor biology [64-67].

**Impact of Lifestyle and Diet on Microbial Alterations in CRC**

Lifestyle factors, particularly diet, are recognized as pivotal modifiers of the gut microbiota, directly influencing colorectal cancer (CRC) development, progression, and response to therapy. The gut microbiota is highly dynamic and responsive to dietary components, with shifts in microbial composition linked to varying CRC risks across populations. High-fiber diets, rich in whole grains, fruits, and vegetables, foster microbial diversity and promote the production of beneficial metabolites like short-chain fatty acids (SCFAs). Diets high in red and processed meats, refined sugars, and saturated fats contribute to dysbiosis, fostering a pro-inflammatory and carcinogenic environment in the gut [74-77].

One of the fundamental mechanisms through which diet impacts microbiota and CRC is the modulation of microbial metabolites. Fiber-rich diets promote the growth of commensal bacteria, such as Faecalibacterium prausnitzii and Roseburia spp., which produce SCFAs like butyrate. These metabolites play critical roles in maintaining the epithelial barrier, suppressing inflammation, and inducing apoptosis in tumor cells. In contrast, diets rich in animal fats and proteins favor the proliferation of bile-tolerant bacteria like Bacteroides and Bilophila, which produce secondary bile acids. These genotoxic metabolites have been implicated in DNA damage, oxidative stress, and CRC progression [36,90-92].

Dieting also influences immune modulation via the microbiota. High-fat and low-fiber diets lead to reduced microbial diversity and the overgrowth of pathogenic species, triggering chronic inflammation. Dysbiotic microbiota release lipopolysaccharides (LPS) and other pro-inflammatory molecules, which activate toll-like receptors (TLRs) and nuclear factor kappa B (NF-κB) signaling pathways in the gut epithelium. This chronic activation of inflammatory cascades fosters a tumor-promoting microenvironment. Dietary interventions that restore microbial balance can mitigate these effects, highlighting the therapeutic potential of personalized nutrition in CRC management [83, 94-96].

Lifestyle factors, including alcohol consumption and sedentary behavior, further compound microbial dysbiosis and CRC risk. Alcohol disrupts the gut barrier, increasing intestinal permeability and translocation of bacterial endotoxins. This disruption exacerbates systemic inflammation and promotes hepatic carcinogenesis in cases of metastatic CRC involving the liver. On the other hand, physical activity has been shown to positively influence microbial diversity and reduce inflammation, suggesting that integrative lifestyle modifications may complement dietary strategies in CRC prevention and management [3-5,102].

Several gaps remain in understanding the precise relationship between lifestyle, diet, and microbiota- mediated CRC. How do specific dietary patterns interact with genetic predispositions to modify CRC risk? Can real-time microbiota monitoring guide nutritional adjustments to optimize treatment outcomes? Longitudinal studies integrating dietary data with microbiota profiling and metabolomics are essential to answer these questions. Personalized dietary interventions, informed by microbiota composition, hold the potential to revolutionize CRC prevention and treatment, offering a low-cost, non- invasive strategy to mitigate disease burden [16-18,60].

**Biofilm Mechanisms in Recurrence and Metastasis**

Bacterial biofilms are increasingly recognized as critical players in colorectal cancer (CRC) progression, recurrence, and metastasis. Biofilms, structured communities of bacteria encased in an extracellular polymeric substance, provide a protective niche that enhances microbial survival and persistence. These structures contribute to CRC by promoting

chronic inflammation, disrupting epithelial barriers, and enabling bacterial-host interactions that facilitate tumorigenesis. Biofilms have been observed in up to 89% of CRC cases, with a preference for right-sided tumors, suggesting a spatial association with CRC development [47-51,99].

One of the primary ways biofilms influence CRC is by creating a pro-inflammatory microenvironment. Bacteria within biofilms release lipopolysaccharides (LPS) and other inflammatory mediators, activating pathways such as nuclear factor kappa B (NF-κB) and toll-like receptor (TLR) signaling. This chronic inflammation induces the production of cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which promote epithelial-mesenchymal transition (EMT), angiogenesis, and tumor cell proliferation. Biofilm-associated bacteria such as Fusobacterium nucleatum enhance immune evasion by recruiting myeloid-derived suppressor cells (MDSCs) and suppressing cytotoxic T-cell activity [38-42,85].

Biofilms also significantly disrupt the epithelial barrier, a hallmark of CRC initiation and progression. The extracellular matrix of biofilms facilitates bacterial adherence to epithelial cells, leading to increased permeability and translocation of bacterial metabolites and toxins. For instance, colibactin, a genotoxin produced by certain Escherichia coli strains within biofilms, induces DNA double-strand breaks, fostering genomic instability. These disruptions accelerate the transformation of normal epithelial cells into malignant ones, underpinning the role of biofilms in CRC initiation and progression [14- 17,55].

In recurrence and metastasis, biofilms create niches that protect dormant tumor cells, facilitating their survival during and after therapy. Biofilm-associated bacteria can produce metabolites such as polyamines and lactate, which fuel tumor cell metabolism and promote survival under hypoxic conditions. Furthermore, the extracellular matrix of biofilms serves as a physical barrier against chemotherapeutic agents, contributing to therapy resistance. These protective mechanisms allow residual tumor cells to evade treatment and reestablish tumors at primary or distant sites [46-48,70].

Despite advances in understanding the role of biofilms in CRC, significant gaps remain. The molecular interactions between biofilms and host epithelial cells and the mechanisms underlying biofilm-driven immune modulation require further investigation. Also, biofilms' role in metastatic seeding and pre-metastatic niche formation is poorly understood [20,32].

Targeting biofilm formation and maintenance could provide a novel therapeutic strategy to prevent CRC progression and recurrence. Future studies should explore biofilm-specific interventions, such as quorum-sensing inhibitors, probiotics, and microbiota-modulating agents, to disrupt these microbial communities and enhance CRC treatment outcomes [80,91].

**Temporal Dynamics of Microbiota Changes During Treatment**

The gut microbiota undergoes significant alterations during colorectal cancer (CRC) treatment, driven by the direct and indirect effects of therapeutic interventions such as chemotherapy, radiotherapy, and immunotherapy. These temporal changes influence treatment efficacy, patient outcomes, and long-term recovery yet remain inadequately characterized. Understanding the microbiota's dynamic evolution during treatment is essential for optimizing therapeutic strategies and minimizing adverse effects [17,48,76].

During the initiation of chemotherapy or radiotherapy, microbiota often experiences a rapid decline in diversity. This dysbiosis is associated with the overgrowth of opportunistic pathogens and the loss of beneficial commensal bacteria, disrupting intestinal homeostasis. Chemotherapeutic agents such as 5- fluorouracil target rapidly dividing cancer cells and affect proliferative gut epithelial cells and resident microbes. This collateral damage compromises the intestinal barrier, increasing susceptibility to infections and inflammation, exacerbating treatment side effects, and impairing patient recovery [31,54,83].

As treatment progresses, microbial metabolites such as short-chain fatty acids (SCFAs) and secondary bile acids are significantly altered, further influencing treatment outcomes. Reduced butyrate levels, a key SCFA with anti-inflammatory and antitumor properties, have been linked to increased treatment resistance and enhanced tumor cell survival. Concurrently, the accumulation of secondary bile acids promotes oxidative stress and DNA damage in colonic epithelial cells, potentially counteracting the therapeutic benefits of antineoplastic agents. These dynamic changes underscore the interplay between microbiota composition and metabolic function during treatment [44,57,69].

Temporal shifts in the immune microenvironment, mediated by microbiota, also play a pivotal role in therapy responses. Dysbiosis-driven inflammation activates pro-tumor pathways such as NF-κB and STAT3, diminishing the efficacy of immune-based therapies like immune checkpoint inhibitors (ICIs). Moreover, specific microbial taxa, such as Fusobacterium nucleatum, can exacerbate immune suppression by recruiting regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). This immunosuppressive state, shaped by dynamic microbial interactions, hinders adequate tumor clearance and promotes residual tumor cell survival [94,96,100].

Post-treatment recovery is another critical period during which microbiota composition can significantly influence outcomes. Studies suggest that the microbiota's ability to restore homeostasis after therapy is linked to long-term remission and reduced recurrence risk. Probiotic and prebiotic interventions during recovery have shown promise in accelerating microbiota restoration, enhancing epithelial barrier integrity, and mitigating chronic inflammation. However, such

interventions' optimal timing and composition remain active research areas [1-3,24].

Studies should focus on real-time monitoring of microbiota changes using advanced metagenomic and metabolomic techniques to capture the temporal dynamics of microbiota during treatment. Longitudinal analyses are crucial to identify critical windows for therapeutic intervention and to design strategies that harness the microbiota's potential to enhance treatment efficacy while minimizing adverse effects. Addressing these temporal dynamics holds significant promise for integrating microbiota-targeted therapies into standard CRC treatment protocols, ultimately improving patient outcomes [57,72,94].

**Microbiota-Gender Axis in Colorectal Cancer**

Gender differences in colorectal cancer (CRC) incidence, progression, and treatment outcomes are well-documented, with men generally exhibiting higher rates of CRC than women. However, the underlying mechanisms driving these disparities remain poorly understood. Emerging evidence suggests that the gut microbiota plays a critical role in these differences by modulating metabolic, hormonal, and immune pathways. Exploring the gender-specific interactions between microbiota and CRC could uncover novel strategies for personalized prevention and treatment [98-100,102].

Hormonal influences, particularly estrogen, have been implicated in shaping microbiota composition and diversity. Estrogen metabolites influence the gut microbiota, favoring the proliferation of bacteria associated with anti-inflammatory and tumor- suppressive effects [90].

Women tend to have higher levels of bacteria that produce short-chain fatty acids (SCFAs), such as butyrate, which maintain epithelial barrier integrity and modulate immune responses. In men, the gut microbiota may harbor a higher abundance of pro-inflammatory species, predisposing them to chronic inflammation and increased CRC risk [19,20].

Gender differences in the microbiota also extend to immune regulation. The female microbiota promotes a more robust antitumor immune response, characterized by greater recruitment and activation of cytotoxic T cells and reduced myeloid-derived suppressor cells (MDSCs) levels. Conversely, the male microbiota may skew immune responses toward a pro-inflammatory state, activating pathways like NF- κB and STAT3, contributing to tumorigenesis and immune evasion. These gender-specific immune interactions highlight the need for tailored immunotherapeutic strategies considering microbiota-driven differences [31-33,103].

Metabolic pathways influenced by the microbiota also display gender-specific patterns. For example, bile acid metabolism, regulated by the gut microbiota, differs between men and women. In men, elevated levels of secondary bile acids, which are carcinogenic, have been associated with higher CRC risk. In women, estrogen modulates bile acid synthesis and reduces secondary bile acid levels, potentially mitigating their harmful effects. Additionally, microbiota's role in metabolizing dietary components like fiber and polyphenols may vary between genders, impacting SCFA production and overall CRC risk [65-68,92].

Significant gaps remain in understanding the microbiota-gender axis in CRC. Current research has focused mainly on cross-sectional studies, which fail to capture dynamic changes in microbiota composition and function over time. Furthermore, the interaction between microbiota, gender, and other risk factors such as age, diet, and genetics is not well- characterized. To address these gaps, longitudinal studies incorporating multi-omics approaches are needed to disentangle the complex interplay between microbiota and gender in CRC [26,85,101].

Gender-specific microbiota-targeted interventions represent a promising avenue for CRC prevention and treatment. For example, probiotics or dietary interventions tailored to enhance estrogen-modulated bacterial populations could benefit women. Strategies to reduce pro-inflammatory or secondary bile acid- producing bacteria in men may lower CRC risk. Understanding these gender-specific microbiota dynamics could lead to more precise and effective therapeutic approaches, improving outcomes for both men and women with CRC [4-7,19].

**Impact of Antimicrobial Therapies on the Microbiome and CRC**

Antimicrobial therapies, including antibiotics and other microbiota-targeted interventions, profoundly affect gut microbiota composition and function, often leading to dysbiosis. While these therapies are indispensable in treating bacterial infections, their impact on colorectal cancer (CRC) development, progression, and treatment outcomes has emerged as a critical area of research. Understanding the nuanced interplay between antimicrobial interventions and the gut microbiome is essential for optimizing CRC prevention and therapy [48,54,103].

Antibiotics disrupt microbial diversity and selectively deplete beneficial bacterial populations, such as those producing short-chain fatty acids (SCFAs) like butyrate. These compounds are crucial for maintaining epithelial barrier integrity, modulating inflammation, and promoting apoptosis in cancer cells. Reduced SCFA production following antibiotic use compromises these protective effects, creating a pro-inflammatory environment conducive to tumorigenesis. The overgrowth of opportunistic pathogens, such as Clostridium difficile or Fusobacterium nucleatum, in the aftermath of antibiotic treatment may exacerbate CRC risk by promoting inflammation and genotoxicity [39,56,84].

The timing and duration of antibiotic exposure also play pivotal roles in modulating CRC risk. Studies suggest that prolonged or repeated antibiotic use, particularly in early life

or before cancer diagnosis, significantly alters the gut microbiota, potentially predisposing individuals to CRC later in life. In contrast, short-term, targeted antibiotic regimens used alongside cancer treatments may reduce specific pathogenic bacteria, potentially enhancing therapeutic outcomes. These dual effects underscore the complexity of antimicrobial interventions in the context of CRC [11,25,59].

Antibiotic-induced dysbiosis also impacts the efficacy of anticancer therapies, including chemotherapy and immunotherapy. Certain bacteria metabolize chemotherapeutic agents, reducing their bioavailability and effectiveness. Conversely, some antibiotics may sensitize tumor cells to chemotherapy by depleting specific microbial populations that confer resistance. Similarly, dysbiosis caused by broad- spectrum antibiotics can impair immune responses, diminishing the effectiveness of immune checkpoint inhibitors. Understanding these interactions is critical for effectively integrating antibiotic use with oncological treatments [66,78-81].

Beyond antibiotics, other antimicrobial agents, such as antifungals and antivirals, may indirectly influence CRC through their effects on the gut microbiota. For instance, antifungal therapies targeting Candida species can disrupt fungal-bacterial interactions, which are increasingly recognized as influential in shaping the gut ecosystem. These disruptions may alter microbial community structure, influencing CRC progression and therapy responses. The broader implications of such interventions remain underexplored, representing a critical research gap [20-22,104].

Several strategies have been proposed to mitigate the adverse effects of antimicrobial therapies on microbiota and CRC outcomes. Prophylactic use of probiotics or prebiotics during antibiotic treatment may help preserve microbial diversity and prevent dysbiosis. Fecal microbiota transplantation (FMT) has also shown promise in restoring gut microbial balance following antibiotic-induced disruptions. Precision medicine approaches that consider an individual's baseline microbiota composition could guide the selection of antimicrobial regimens, minimizing unintended consequences while maximizing therapeutic benefits [49,68,87].

Significant challenges remain in understanding the long-term effects of antimicrobial therapies on gut microbiota and CRC. Current research is limited by a lack of longitudinal studies examining post-treatment microbiota recovery and its implications for CRC risk and recurrence. The interaction between antimicrobial interventions and other factors, such as diet, genetics, and cancer therapy, requires deeper investigation. Addressing these gaps through comprehensive, multi-disciplinary research will be essential for leveraging antimicrobial therapies to improve CRC outcomes [4-6,43].

Antimicrobial therapies represent a double-edged sword in CRC management. While they hold the potential for targeting pathogenic microbiota and enhancing treatment efficacy, their capacity to disrupt microbial homeostasis poses risks that must be carefully managed. Developing strategies to mitigate these risks while maximizing therapeutic benefits will be a crucial step forward in integrating antimicrobial interventions into CRC care [77,100,105].

**Connection Between Microbiota and Primary Prevention in High-Risk Populations**

The role of gut microbiota in the primary prevention of colorectal cancer (CRC) is increasingly recognized, particularly in high-risk populations such as individuals with a family history of CRC, hereditary syndromes like Lynch syndrome, or chronic inflammatory conditions like inflammatory bowel disease (IBD). Understanding how specific microbial compositions contribute to CRC risk offers opportunities to develop targeted interventions that modify the gut microbiota to reduce susceptibility [27,58,88].

High-risk populations often exhibit early signs of dysbiosis, even before the onset of CRC. These changes include a reduction in beneficial microbial species such as Faecalibacterium prausnitzii and an increase in pathogenic bacteria like Fusobacterium nucleatum. The latter is known for its pro- inflammatory properties and ability to promote genomic instability, creating a fertile environment for tumorigenesis. Early identification of such microbial imbalances could enable preemptive interventions to restore microbial homeostasis and mitigate CRC risk [42,56,94].

Dietary interventions are among the most accessible and impactful strategies for microbiota modulation in high-risk populations. Diets rich in fiber, for instance, promote the growth of SCFA-producing bacteria, which enhance epithelial barrier integrity and suppress inflammation. Conversely, high-fat and low- fiber diets are associated with increased production of secondary bile acids, which are carcinogenic. Personalized dietary recommendations based on an individual's microbiota profile could offer a practical approach to primary prevention, tailoring interventions to the specific needs of high-risk individuals [26,72,100].

Probiotic and prebiotic supplementation represent another promising avenue for CRC prevention. Probiotics containing beneficial bacteria, such as Lactobacillus and Bifidobacterium species, have demonstrated anti-inflammatory and tumor- suppressive effects in preclinical models. Prebiotics, such as inulin and fructose oligosaccharides, serve as substrates for beneficial bacteria, promoting their proliferation and activity. In high-risk populations, combining these approaches could help maintain microbial diversity and prevent dysbiosis-related carcinogenesis. However, these interventions' long- term efficacy and safety require rigorous clinical evaluation [19,48].

Fecal microbiota transplantation (FMT) is an emerging strategy for microbiota modulation in CRC prevention. While primarily used to treat Clostridioides difficile infections, FMT has shown potential in restoring microbial diversity and re-

ducing inflammation in patients with IBD, a known risk factor for CRC [30,76].

Preliminary studies suggest that FMT could be adapted for high-risk individuals, particularly those with hereditary predispositions or existing dysbiosis. However, ethical and logistical challenges, including donor selection and standardization of protocols,must be addressed before widespread implementation [25,94].

Beyond direct interventions, microbiota-based biomarkers offer the potential for early identification of high-risk individuals. Specific microbial signatures, such as the abundance of Fusobacterium nucleatum or depletion of SCFA producers, could serve as non- invasive indicators of CRC risk. Integrating microbiota analysis into routine screening programs for high-risk populations could improve early detection and enable timely interventions [18,60].

Despite these promising strategies, significant gaps remain in our understanding of effectively leveraging microbiota for primary prevention in high-risk populations. Longitudinal studies are needed to elucidate the long-term effects of microbiota modulation on CRC risk. Additionally, research must address the variability in individual microbiota profiles and how genetics, age, and environmental exposures interact with microbial communities to influence CRC susceptibility [69,101].

The integration of microbiota-targeted strategies into CRC prevention programs also faces practical challenges. Public health initiatives must consider the accessibility and affordability of dietary modifications, probiotics, and FMT interventions. Moreover, ensuring adherence to these strategies in high-risk populations will require effective education and engagement efforts to emphasize their benefits [12- 14,33].

In conclusion, microbiota represents a promising target for primary prevention of CRC, particularly in high-risk populations. While the field is still in its early stages, microbiota research and technology advancements can potentially transform prevention strategies, reducing CRC incidence and improving outcomes for at-risk individuals. Continued investment in multidisciplinary research and collaboration between clinicians, microbiologists, and public health experts will be essential to realize this vision [43,67-70].

**Development of Microbiological Biomarkers for Prediction**

Identifying microbiological biomarkers represents a transformative approach to improving the prediction of treatment response, recurrence risk, and prognosis in colorectal cancer (CRC). Biomarkers derived from the gut microbiota can guide personalized treatment strategies and enable earlier interventions, particularly in populations at heightened risk for CRC or those undergoing therapy. Despite significant advancements in understanding the microbiota's role in CRC, the development and clinical application of microbiological biomarkers remain nascent, necessitating further exploration [31,65].

Microbial biomarkers for CRC prediction are primarily based on shifts in the abundance of specific bacterial species or microbial-derived metabolites. For instance, an elevated presence of Fusobacterium nucleatum has been consistently associated with poor prognosis, treatment resistance, and increased risk of recurrence. Conversely, the depletion of SCFA-producing bacteria, such as Faecalibacterium prausnitzii, correlates with impaired anti-inflammatory mechanisms and worse clinical outcomes. These microbial profiles can be detected through non- invasive methods, such as stool sample analysis, making them practical for routine clinical use [58,76,99].

Integrating multi-omics technologies, including metagenomics, transcriptomics, and metabolomics, has significantly advanced the identification of microbiological biomarkers. Metagenomics provides insights into the composition and functional potential of the microbiota, while transcriptomics elucidates microbial gene expression patterns under different physiological and pathological conditions. Metabolomics, on the other hand, focuses on quantifying microbial-derived metabolites, such as SCFAs and secondary bile acids, which play critical roles in CRC pathophysiology. Combining these approaches enables a comprehensive understanding of how microbiota changes impact CRC outcomes, facilitating the discovery of robust biomarkers [100- 102].

Several challenges hinder the clinical translation of microbiological biomarkers. One major limitation is the variability in microbiota composition across individuals, influenced by genetics, diet, lifestyle, and environmental exposures. This variability complicates the establishment of universal biomarker thresholds and necessitates the development of context-specific biomarkers tailored to individual or population-level differences. Many studies identifying potential biomarkers are cross-sectional, providing only snapshots of microbiota changes without capturing their dynamic evolution during CRC progression or treatment [78-80,104].

To address these challenges, longitudinal studies are essential to track microbiota changes over time and establish causal relationships between microbial alterations and CRC outcomes. Such studies should incorporate diverse populations for geographic, dietary, and genetic variability in microbiota composition. Integrating microbiota data with clinical parameters, such as tumor stage, genetic mutations, and treatment regimens, will enhance the predictive power of biomarkers and their relevance in personalized medicine [30-34,86].

The application of microbiological biomarkers in predicting treatment response is an up-and-coming area of research. For example, certain microbial species are known to modulate the efficacy of immune checkpoint inhibitors and chemotherapeutic agents. Identifying microbial signatures associated with favorable or unfavorable responses could enable clinicians to tailor therapies, accordingly, optimizing treatment efficacy and minimizing adverse effects. Biomarkers

predictive of recurrence risk could guide the intensity and duration of post-treatment surveillance, improving long-term outcomes [8-12- 54].

In the context of CRC prevention, microbiological biomarkers could identify individuals at elevated risk before clinical symptoms emerge. For instance, microbial signatures indicative of early dysbiosis or inflammation could serve as early warning signs, prompting interventions such as dietary modifications, probiotics, or microbiota-targeted therapies. This proactive approach has the potential to significantly reduce CRC incidence and improve survival rates in high-risk populations [98-103].

Integrating microbiological biomarkers into clinical practice will require robust validation through large- scale, multi-center clinical trials. Standardization of sample collection, processing, and analysis protocols is critical to ensure reproducibility and reliability across studies. Additionally, the development of user- friendly diagnostic tools, such as microbiota-based assays or point-of-care testing devices, will facilitate the adoption of biomarkers in routine clinical workflows [102-105].

Developing microbiological biomarkers for CRC prediction holds immense promise but requires concerted efforts to overcome existing challenges. By leveraging advances in microbiota research and technology, clinicians and researchers can transform the management of CRC, shifting from reactive treatments to proactive, personalized interventions. Future research should prioritize validating and standardizing biomarkers, ensuring their utility across diverse clinical settings and populations [105-107].

**Microbiota-Epigenetics Interplay in CRC**

The interaction between the gut microbiota and the epigenetic landscape in colorectal cancer (CRC) is an emerging field of study, offering new insights into tumorigenesis and therapy resistance. Epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNA expression, regulate gene expression without altering the underlying DNA sequence. These modifications are dynamic and can be influenced by external factors, including the gut microbiota. Understanding microbiota's role in shaping the epigenetic environment is essential for unraveling the molecular mechanisms underpinning CRC progression and resistance to treatment [94-97,102].

One of the primary mechanisms by which microbiota influences the epigenome is the production of microbial metabolites, such as short-chain fatty acids (SCFAs). Butyrate, a key SCFA produced by commensal bacteria, is a histone deacetylase (HDAC) inhibitor. This activity promotes the acetylation of histones, leading to an open chromatin structure and the activation of tumor-suppressor genes. However, dysbiosis in CRC reduces butyrate- producing bacteria, diminishing its protective epigenetic effects and allowing oncogenic pathways to dominate [16,41,64].

Conversely, microbial-derived secondary bile acids and genotoxins contribute to harmful epigenetic changes. Secondary bile acids, such as deoxycholic acid, induce oxidative stress and DNA damage, promoting hypermethylation of tumor-suppressor genes. Similarly, colibactin, a genotoxin produced by Escherichia coli, can cause DNA double-strand breaks, triggering error-prone repair mechanisms and epigenetic dysregulation. These modifications enhance genomic instability, a hallmark of cancer, and create a permissive environment for tumor initiation and progression [7-9,58].

The microbiota also impacts non-coding RNA expression, particularly microRNAs (miRNAs), which play crucial roles in post-transcriptional regulation of gene expression. Dysbiosis alters miRNA profiles in intestinal epithelial cells, influencing inflammation, cell cycle regulation, and apoptosis pathways. For example, certain microbial species can upregulate oncogenic miRNAs while downregulating tumor- suppressive miRNAs, exacerbating tumor growth and resistance to therapy. Investigating these miRNA- microbiota interactions could reveal novel targets for CRC treatment [49-51,103].

Another significant aspect of microbiota-epigenetics interplay is the influence on immune cell function. Epigenetic modifications induced by microbial metabolites regulate the differentiation and activity of immune cells, such as T cells and macrophages. Dysbiosis-driven epigenetic changes can skew immune responses toward a pro-inflammatory state, supporting tumor-promoting inflammation and impairing anti-tumor immunity. HDAC inhibition by butyrate enhances regulatory T cell function, which is beneficial in maintaining gut homeostasis but may suppress effective anti-tumor responses in a dysbiotic context [85-88,102].

The temporal dynamics of microbiota-induced epigenetic changes throughout CRC progression and treatment are poorly understood. Longitudinal studies are needed to map these changes and identify critical windows for therapeutic intervention. The reversibility of microbiota-induced epigenetic modifications offers a promising avenue for treatment. Still, further exploration is required to determine the efficacy of probiotics, prebiotics, and fecal microbiota transplantation in restoring epigenetic balance [19,47-52].

From a therapeutic perspective, targeting the microbiota-epigenetic axis holds the potential for improving CRC management. For example, combining HDAC inhibitors with microbiota- modulating strategies could amplify the activation of tumor-suppressor genes while mitigating the oncogenic effects of dysbiosis. Similarly, leveraging miRNA therapeutics to counteract the epigenetic impact of pathogenic bacteria may enhance treatment outcomes and reduce resistance [54,78- 81].

The interplay between the gut microbiota and the epigenetic landscape in CRC represents a complex but promising frontier in cancer research. By elucidating these interactions, researchers can identify novel biomarkers and therapeutic targets, paving the way for personalized medicine. Future

efforts should focus on integrating microbiota and epigenetic data into multi-omics frameworks to provide a comprehensive understanding of CRC biology and identify synergistic strategies for intervention [96-98,106].

**Clinical Implications of Microbiota Modulation**

Modulating the gut microbiota offers a promising avenue for improving colorectal cancer (CRC) prevention, treatment, and recurrence management. Clinical strategies such as probiotics, prebiotics, dietary interventions, and fecal microbiota transplantation (FMT) are being explored to restore microbial balance, enhance immune responses, and mitigate therapy resistance. However, the clinical integration of these approaches requires a deeper understanding of their mechanisms, efficacy, and safety [88,97,104].

Probiotics, defined as live microorganisms that confer health benefits when administered adequately, have shown potential in CRC management. Specific strains, such as Lactobacillus and Bifidobacterium species, can produce short-chain fatty acids (SCFAs), modulate inflammatory responses, and enhance epithelial barrier function [50-57].

These effects may reduce the risk of CRC development and improve therapeutic outcomes. Clinical trials investigating the co-administration of probiotics with chemotherapy or immunotherapy have reported enhanced treatment efficacy and reduced gastrointestinal toxicity. However, identifying individual patients' optimal strains, doses, and combinations remains challenging [78-80,108].

Prebiotics, which are dietary fibers that promote the growth of beneficial gut bacteria, represent another avenue for microbiota modulation. Compounds like inulin and fructooligosaccharides have been shown to increase SCFA production and support the development of butyrate-producing bacteria. Prebiotic interventions may also mitigate dysbiosis- induced inflammation, reducing CRC risk and recurrence. Despite their promise, prebiotics require further evaluation in clinical settings to determine their efficacy in diverse patient populations and CRC subtypes [97-100].

FMT, the transfer of stool from a healthy donor to a recipient, has garnered attention for its ability to restore microbial diversity. While primarily used to treat recurrent Clostridioides difficile infections, FMT has shown potential in CRC management by reversing dysbiosis and enhancing immune responses. Preclinical studies have demonstrated that FMT can reduce tumor growth and improve the efficacy of immune checkpoint inhibitors. Early-phase clinical trials are now exploring its role in CRC treatment, although concerns about long-term safety, donor selection, and regulatory challenges must be addressed [14,68-72].

Dietary interventions targeting gut microbiota offer a non-invasive strategy to influence CRC outcomes. Diets rich in fiber, polyphenols, and omega-3 fatty acids have been associated with favorable microbiota profiles and reduced inflammation. Conversely, high- fat and high-fat meat diets are linked to dysbiosis and increased CRC risk. Personalized dietary plans based on microbiota composition could complement existing therapies, but more robust clinical evidence is needed to substantiate these recommendations [40,106-108].

While these strategies hold promise, microbiota modulation's potential risks and limitations must also be considered. Altering the microbiota may disrupt other microbial-host interactions, leading to unintended consequences. For example, excessive use of probiotics or prebiotics could promote the overgrowth of certain species, resulting in dysbiosis or even infections. Similarly, the long-term effects of FMT remain poorly understood, with concerns about the transfer of pathogenic or resistant bacteria from donors to recipients [30-33].

The heterogeneity of the gut microbiota across individuals adds another layer of complexity to clinical implementation. Age, diet, genetics, and tumor location influence microbiota composition and response to modulation. Personalized approaches, guided by comprehensive microbiota profiling, are essential to maximize the benefits of these interventions while minimizing risks. Integrating microbiota-targeted strategies into precision medicine frameworks could revolutionize CRC management by tailoring treatments to the unique microbiota signatures of individual patients [54-56].

Emerging technologies, such as metagenomics, metabolomics, and machine learning, are expected to advance microbiota-based therapies. These tools can identify microbial biomarkers for CRC risk stratification, predict patient responses to microbiota interventions, and optimize treatment protocols. Identifying specific microbial signatures associated with therapy resistance could guide the selection of probiotics or dietary modifications to enhance treatment efficacy [66-69].

The clinical modulation of the gut microbiota represents a transformative approach to CRC management. While current evidence highlights its potential, further research is needed to address gaps and establish robust clinical guidelines. As the field evolves, interdisciplinary collaboration between microbiologists, oncologists, and bioinformaticians will be crucial to harnessing the full therapeutic potential of microbiota in CRC prevention and treatment [35-38].

**Regional Differences in Microbiota and CRC Incidence**

Geographical and environmental factors significantly influence the composition and function of the gut microbiota, contributing to regional variations in colorectal cancer (CRC) incidence and outcomes. Diverse factors, including diet, lifestyle, genetic predispositions, and healthcare accessibility drive these differences. Understanding how regional disparities in microbiota composition correlate with CRC prevalence is critical for developing context- specific prevention and treatment strategies [5-8,94].

In regions with high CRC incidence, such as Western coun-

tries, the gut microbiota is often characterized by reduced diversity and increased abundance of pro- inflammatory species. Diets rich in red and processed meats, saturated fats, and low fiber contribute to this dysbiosis [102].

Such diets promote the growth of bacteria that produce secondary bile acids and other carcinogenic metabolites, creating a pro-tumorigenic microenvironment. Populations in regions with lower CRC incidence, such as parts of Asia and Africa, tend to consume diets high in fiber and plant-based foods, which support beneficial microbes like butyrate- producing species. This protective microbiota profile is associated with lower levels of chronic inflammation and enhanced intestinal barrier function [78-80].

Emerging evidence suggests that shifts in microbiota composition occur rapidly with dietary changes, even among genetically similar populations. Migrant studies reveal that individuals moving from low- incidence to high-incidence regions acquire microbiota profiles resembling those of the host population within a few years. These findings highlight the plasticity of the gut microbiota and its responsiveness to environmental factors, underscoring the potential of dietary interventions to mitigate CRC risk in high-incidence regions [85-88].

In addition to diet, environmental factors such as sanitation, antibiotic usage, and exposure to pathogens influence microbiota composition. For instance, populations in urbanized areas with widespread antibiotic use often exhibit lower microbial diversity, predisposing to dysbiosis. Greater exposure to diverse microbes through traditional diets and less sanitized environments in rural settings contributes to a more robust and protective microbiota. However, urbanization and the adoption of Westernized diets in low-incidence regions are associated with rising CRC rates, emphasizing the interplay between environment, microbiota, and cancer risk [79-82].

Genetic predispositions also interact with regional microbiota profiles to influence CRC risk. Specific genetic variants linked to CRC susceptibility, such as those affecting immune regulation or epithelial barrier function, may shape microbiota composition. These interactions can modulate microbiota's ability to influence inflammation and tumorigenesis. Regional differences in the prevalence of these genetic variants may partially explain disparities in CRC incidence, although this area remains underexplored [98-100].

Gaps persist in our understanding of regional microbiota differences and their implications for CRC. Few studies have systematically compared microbiota profiles across diverse populations or linked these differences to clinical outcomes. Furthermore, the influence of regional microbiota variations on treatment efficacy and resistance has received little attention. For instance, immunotherapy responses may differ based on microbiota composition, influenced by dietary and environmental factors [106-108].

Large-scale, multicenter studies are needed to map microbiota profiles across populations and correlate these with CRC risk and treatment outcomes to address these gaps. Advanced metagenomic and metabolomic analyses can provide detailed insights into the functional capabilities of region-specific microbiota. Such studies should also account for confounding factors, such as diet, lifestyle, and socioeconomic status, to disentangle the complex interactions driving regional disparities in CRC [49- 52].

Regional microbiota differences also have implications for the development of targeted interventions. Probiotic and prebiotic formulations could be tailored to the microbial signatures of specific populations, optimizing their efficacy. Similarly, dietary guidelines could be customized based on regional dietary habits and microbiota profiles to prevent CRC or support treatment. These approaches require collaborative efforts between microbiologists, nutritionists, and public health professionals to ensure cultural appropriateness and feasibility [33-36].

Regional differences in the gut microbiota provide valuable insights into CRC risk and prevention. Addressing these disparities through tailored microbiota-based interventions can potentially reduce the global burden of CRC. However, achieving this goal will require concerted efforts to fill existing knowledge gaps and integrate microbiota research into public health strategies [19-23].

**Connection Between Microbiota and Next- Generation Immunotherapy**

The interplay between the gut microbiota and next- generation immunotherapies, such as CAR-T cells and personalized cancer vaccines, is a rapidly evolving field with immense potential to revolutionize colorectal cancer (CRC) treatment. Although significant advances have been made in understanding microbiota's role in shaping immune responses, the precise mechanisms through which it modulates these novel therapies remain underexplored. Addressing these questions could unlock new strategies for enhancing therapeutic efficacy and overcoming resistance [5, 84-86].

The gut microbiota has been shown to influence the efficacy of immune checkpoint inhibitors (ICIs) by modulating systemic immune responses. Extending these findings to CAR-T cell therapy, a similar mechanism may apply, wherein specific microbial metabolites or bacterial species prime the immune system for enhanced CAR-T cell functionality. Certain microbiota-derived short-chain fatty acids (SCFAs), such as butyrate, have been implicated in promoting T-cell activation and proliferation, which are critical for the success of CAR-T therapies. Conversely, dysbiosis may suppress these immune pathways, reducing CAR-T cell efficacy [30, 97-99].

CAR-T cells engineered to target CRC-specific antigens face challenges such as an immunosuppressive tumor microenvironment and limited infiltration into tumor sites. The gut

microbiota may play a role in overcoming these barriers by modulating the tumor microenvironment. Microbiota- driven activation of pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) on immune cells, could enhance cytokine production and T-cell recruitment to the tumor. Additionally, microbiota- mediated modulation of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) may alleviate immunosuppression, creating a more permissive environment for CAR-T cell activity [102- 105].

Personalized cancer vaccines, which aim to elicit robust tumor-specific immune responses, are another promising area influenced by the microbiota. The gut microbiota can shape vaccine responses by influencing antigen presentation and T-cell priming. Studies suggest that certain bacterial species, such as Akkermansia muciniphila, are associated with improved vaccine efficacy, potentially by enhancing dendritic cell activation and cross-presentation of tumor antigens. However, pro-inflammatory or pathogenic bacteria may hinder vaccine responses by inducing chronic inflammation or immune exhaustion [16,29-32].

While preclinical studies have demonstrated the microbiota's role in enhancing immunotherapy responses, translating these findings into clinical practice has proven challenging. Variability in microbiota composition across individuals, influenced by diet, genetics, and environmental factors, complicates the identification of universal microbial signatures predictive of therapy success [40,57-60].

Another area requiring further exploration is the potential for microbiota-based interventions to mitigate the toxicities associated with immunotherapies. Cytokine release syndrome (CRS)and neurotoxicity are common adverse effects of CAR-T cell therapy, and emerging evidence suggests that microbiota may influence the severity of these side effects. By modulating systemic inflammation, microbiota-targeted therapies could provide a means of reducing immunotherapy-related toxicities while preserving efficacy [2-5,70].

Integrative approaches combining microbiota profiling, metagenomics, and immunomics are essential to advance this field. These methodologies can identify key microbial species and metabolites associated with favorable immunotherapy outcomes, providing a basis for therapeutic intervention. Clinical trials evaluating the impact of probiotics, prebiotics, and fecal microbiota transplantation (FMT) on immunotherapy efficacy and safety are needed to validate preclinical findings [50, 87-90].

Another exciting avenue is the development of synthetic biology approaches to engineering microbiota for therapeutic purposes. Engineered bacteria capable of producing immunomodulatory molecules could be used to enhance CAR-T cell functionality or vaccine responses. Such strategies could provide a targeted and controllable means of modulating the microbiota to support immunotherapy [33-36].

The gut microbiota holds significant potential to improve the efficacy and safety of next-generation immunotherapies for CRC. While challenges remain, ongoing research into the microbiota-immunotherapy interface will likely yield transformative insights, paving the way for more personalized and effective cancer treatments [41-44].

**Adverse Effects of Microbial Modulation**

While microbiota-targeted therapies such as probiotics, prebiotics, and fecal microbiota transplantation (FMT) hold significant promises for enhancing colorectal cancer (CRC) treatment, these interventions are not without risks. Understanding the potential adverse effects of microbial modulation is critical to developing safe and effective therapies. Adverse outcomes may stem from unintended gut microbiome disruptions, host immunity interactions, and unforeseen impacts on systemic health [96-98].

One of the primary concerns with microbiota modulation is the potential for inducing dysbiosis. While these interventions aim to restore microbial balance, introducing exogenous microbial species or metabolites can disrupt microbial communities, particularly in individuals with preexisting conditions or weakened microbiomes. For example, specific probiotic strains may outcompete native beneficial bacteria, reducing microbial diversity and inadvertently creating an imbalance. This dysbiosis could exacerbate inflammation or compromise gut barrier function, increasing susceptibility to infections or other complications [105-108].

Another risk is the transfer of antibiotic resistance genes via horizontal gene transfer among microbial species introduced through FMT or probiotics. This phenomenon has been observed in preclinical studies, where the introduction of resistant bacteria led to the propagation of resistance genes within the gut microbiome. In the context of CRC patients, who may already be immunocompromised or undergoing aggressive therapies, this poses a significant threat, potentially limiting treatment options for microbial infections [99-102].

While effective in treating conditions such as recurrent Clostridioides difficile infection, FMT carries specific risks in the oncology setting. The variability in donor microbiota composition can lead to inconsistent outcomes, and the introduction of pathogenic or opportunistic bacteria can result in severe infections. Moreover, the long-term effects of FMT on the gut microbiome and systemic health are not well understood. There is also a concern that FMT might inadvertently introduce microbial species associated with pro-tumorigenic activities, counteracting its intended benefits [1-3,27].

Another consideration is the potential for microbiota- targeted therapies to interact with systemic immunity in ways that exacerbate immune-related adverse events. For instance, probiotics that enhance immune responses could inadvertently trigger excessive inflammation, particularly in patients undergoing immunotherapy. This could increase the risk of cytokine release syndrome (CRS) or immune-related toxicities. Similarly, prebiotics that promote the growth of certain bacterial species might unintentionally enhance the activity

of pro- inflammatory microbes [14-17,35].

The use of engineered microbial species presents additional risks. While synthetic biology approaches hold promises for developing highly targeted therapies, introducing genetically modified bacteria into the gut environment raises concerns about off- target effects and ecological disruption. These organisms may interact with the native microbiome in unpredictable ways, potentially leading to adverse outcomes [41-43,58].

To mitigate these risks, rigorous preclinical and clinical evaluation of microbiota-targeted therapies is essential. This includes characterizing the safety profiles of individual strains or microbial consortia,assessing their long-term effects on the microbiome, and understanding their interactions with host immunity. Standardized protocols for donor screening and microbial preparation in FMT are also necessary to minimize the risk of adverse events [58-61,74].

Personalized approaches to microbiota modulation may reduce the likelihood of adverse outcomes. By tailoring interventions to individual patients' unique microbial and genetic profiles, clinicians can minimize the risk of dysbiosis or other complications. For example, metagenomic sequencing can identify specific microbial imbalances, guiding the selection of probiotics or prebiotics that target those imbalances without disrupting the broader microbiome [78-80,93].

In conclusion, while microbiota-targeted therapies represent a promising frontier in CRC treatment, their potential adverse effects must be carefully managed to maximize benefits while minimizing harm. Ongoing research and robust clinical trials will be critical in addressing these challenges and ensuring the safe integration of microbial modulation into oncology care [94-96,105].

**Genetic Alterations and Microbiota in CRC Development and Recurrence**

The interplay between genetic alterations in colorectal cancer (CRC) and the gut microbiota is a burgeoning field of study, offering insights into how microbial dynamics influence tumorigenesis, disease progression, recurrence, and therapeutic resistance. Genetic mutations, epigenetic modifications, and chromosomal instabilities are hallmarks of CRC, and the microbiota has been implicated in modulating these processes, either by making mutagenic events or by shaping the tumor microenvironment [102-106].

Mutational landscapes in CRC often involve vital pathways such as Wnt/β-catenin, TP53, APC, KRAS, and mismatch repair genes (MMR), particularly in microsatellite instability-high (MSI-H) subtypes. Studies indicate that certain microbial species may contribute to these alterations. Bacteria such as Fusobacterium nucleatum have been shown to interact directly with epithelial cells to promote genomic instability through inflammatory signaling. Chronic inflammation induced by dysbiotic microbiota creates oxidative stress and DNA damage, providing fertile ground for the accumulation of mutations in these pathways [105-108].

Moreover, microbial metabolites such as colibactin, produced by pks-positive Escherichia coli, can induce DNA double-strand breaks directly, contributing to mutagenesis and tumor progression. Secondary bile acids, another byproduct of microbial metabolism, exacerbate genomic instability by generating reactive oxygen species (ROS) and promoting epigenetic changes. These include DNA hypermethylation and histone modifications that silence tumor suppressor genes or activate oncogenes. Dysbiosis amplifies these effects, tipping the balance towards a pro- tumorigenic environment [17-20].

Another critical area of focus is the relationship between microbiota and epigenetic alterations in CRC. Aberrant DNA methylation patterns, commonly observed in CRC, are influenced by microbial metabolites such as butyrate. While butyrate is generally protective, promoting apoptosis and maintaining epithelial integrity, its function becomes compromised in dysbiotic states. Low butyrate levels reduce its ability to regulate histone acetylation and gene expression, resulting in epigenetic landscapes conducive to tumor growth [26-28].

Additionally, gut microbiota influences chromosomal instability (CIN) in CRC. Dysbiotic bacterial communities can disrupt the mitotic process, increasing chromosomal segregation and aneuploidy rates. This genetic instability drives cloning, enabling tumor cells to acquire traits necessary for survival, proliferation, and metastasis. Microbial-induced CIN is particularly significant in CRC recurrence, allowing residual tumor cells to adapt and resist therapeutic pressures [33-37].

Therapeutic resistance in CRC is intricately linked to genetic alterations influenced by microbiota. For instance, microbial modulation of the PI3K/AKT/mTOR pathway through inflammatory mediators and metabolites affects cellular responses to chemotherapeutic agents. Similarly, mutations in DNA repair pathways exacerbated by microbial interactions can reduce the efficacy of targeted therapies, such as PARP inhibitors, which rely on functional homologous recombination repair mechanisms [41-44,55].

Despite these advances, significant gaps remain in understanding the bidirectional relationship between genetic alterations and microbiota in CRC. Current studies are limited by their cross-sectional design, which fails to capture the dynamic interactions between microbial changes and evolving tumor genetics over time. Longitudinal studies are crucial for elucidating how specific microbial communities drive or respond to genetic shifts in CRC progression and recurrence [51-53,59].

Addressing these gaps requires integrating microbiome research with genomic and epigenomic profiling. Multi-omics approaches, combining metagenomics, transcriptomics, and epigenomics, can provide a comprehensive view of how microbial and host factors converge to drive CRC. This knowledge could pave the way for novel therapeutic strategies targeting microbiota and tumor genetics [60-63].

The gut microbiota plays a multifaceted role in shaping CRC's genetic and epigenetic landscape. By understanding these interactions, researchers and clinicians can develop microbiota-informed interventions that mitigate genetic alterations, prevent recurrence, and overcome therapeutic resistance. As this field evolves, it can potentially revolutionize personalized medicine approaches in CRC care [68- 71].

**Gaps and Research Needs in Microbiota and CRC Studies**

While significant progress has been made in understanding the role of gut microbiota in colorectal cancer (CRC), critical gaps remain. One of the most pressing challenges is the lack of longitudinal studies that track microbiota changes throughout the disease trajectory. Most existing studies are cross-sectional, providing only snapshots of the microbiota at specific time points. This limitation makes it difficult to establish causal relationships between microbiota changes and CRC progression or treatment outcomes [73-75,78.

Another significant gap is the variability in microbiota analysis techniques. Differences in sample collection, DNA extraction, sequencing methods, and bioinformatics pipelines can lead to inconsistent results. Standardizing these methodologies is essential for ensuring reproducibility and comparability across studies. Moreover, the heterogeneity of the human microbiota, influenced by factors such as diet, lifestyle, and geography, complicates the generalization of findings [89-92].

Integrating multi-omics approaches, including metagenomics, transcriptomics, and metabolomics, represents a promising avenue for addressing these gaps. By providing a comprehensive view of microbial activity and its impact on host physiology, multi-omics studies can uncover the complex interactions between the microbiota, tumor biology, and therapy responses. However, these approaches' high cost and technical complexity remain barriers to widespread adoption [95-98].

Another critical gap is the lack of mechanistic studies. While associations between specific microbial species and CRC outcomes have been identified, the underlying molecular mechanisms remain poorly understood. The pathways through which microbial metabolites influence immune evasion or therapy resistance need further exploration. Experimental models, such as germ-free mice and organoids, can provide valuable insights into these mechanisms [100-103].

Finally, translating microbiota research into clinical applications is still in its infancy. Few studies have evaluated the efficacy of microbiota-targeted interventions, such as probiotics, prebiotics, and fecal microbiota transplantation, in CRC patients [106]. Large-scale clinical trials are needed to validate the safety and effectiveness of these approaches. Developing microbial biomarkers for early detection, prognosis, and treatment response could also revolutionize CRC management [108].

## Conclusion

The review's conclusion highlights gut microbiota's complex and dynamic role in the development, recurrence, and therapeutic resistance of colorectal cancer (CRC). It emphasizes that dysbiosis significantly contributes to tumor development through chronic inflammation, genetic and epigenetic changes, and immune system modulation. The evidence indicates that microbial metabolites, including short-chain fatty acids (SCFAs) and secondary bile acids, influence tumor progression and treatment responses, creating opportunities for novel interventions.

Insights from the review advocate for integrating microbiota-modulating strategies—such as probiotics, prebiotics, dietary interventions, and fecal microbiota transplantation—into comprehensive management plans for CRC. These strategies aim to restore microbial balance, enhance treatment effectiveness, and minimize adverse outcomes. However, the complexity of microbial-host interactions and the variability in microbiota composition among individuals necessitate personalized treatment strategies supported by advanced technologies like metagenomics, metabolomics, and multi-omics frameworks.

Despite advancements, significant gaps remain in understanding the temporal dynamics of microbiota changes during CRC progression and treatment, as well as the impact of tumor location and molecular subtypes on microbial interactions. Addressing these gaps will require rigorous longitudinal studies and large-scale clinical trials to validate and translate findings into practical clinical applications.

The review concludes that targeting gut microbiota represents a promising frontier in preventing, treating, and managing CRC recurrence. Future research should focus on identifying predictive microbial biomarkers, exploring the role of specific microbial species in therapy resistance, and refining microbiota-based interventions to improve patient outcomes. These initiatives will pave the way for precision oncology approaches that utilize gut microbiota to enhance CRC patients' survival and quality of life.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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