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Microbiome and Treatment Resistance in Colorectal Cancer: Mechanisms and Solutions

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ABSTRACT

This review investigates the complex role of the gut microbiome in modulating treatment resistance in colorectal cancer (CRC), examining mechanisms that influence therapeutic outcomes across chemotherapy, immunotherapy, and targeted therapies. Through a systematic search of databases, including PubMed, Scopus, Embase, Web of Science, SciELO, and gray literature from Google Scholar, we identified relevant studies addressing microbial interactions with cancer treatments. Key insights reveal how specific microbial species, such as *Fusobacterium nucleatum*, impact chemotherapy efficacy by altering drug metabolism and promoting immune evasion. Genetic mutations in patients, notably in immune-regulatory genes like MSH2 and MLH1, further shape microbiome composition, contributing to an immunosuppressive environment that fosters CRC progression and resistance. The review also addresses immunotherapeutic outcomes, highlighting the role of microbial species in modulating immune checkpoints, such as PD-1 and PD-L1, and influencing CAR-T cell therapy. Microbial metabolites, including short-chain fatty acids, impact tumor microenvironment signaling pathways associated with resistance. Therapeutic strategies, such as dietary interventions, probiotics, prebiotics, and fecal microbiota transplantation, are discussed as potential approaches to modify the microbiome, enhance treatment responses, and reduce recurrence risks. This synthesis underscores the need to explore further microbiome-targeted therapies and their integration into precision oncology for optimized CRC management.

Keywords: Colorectal Neoplasms; Microbiota; Drug Resistance; Neoplasm; Immunotherapy; Short-Chain Fatty Acids; Dysbiosis

Abbreviations: CRC: Colorectal Cancer; SCFAs: Short-Chain Fatty Acids; FMT: Fecal Microbiota Transplantation; EMT: Epithelial-To-Mesenchymal Transition; MMR: Mutations in DNA Mismatch Repair; MSI-H: Microsatellite Instability-High; MSS: Microsatellite Stable; TNF-α: Tumor Necrosis Factor-Alpha; LPS: Like Lipopolysaccharides; ROS: Reactive Oxygen Species

Introduction

Colorectal cancer (CRC) stands as one of the most common and lethal cancers worldwide, contributing significantly to cancer-related morbidity and mortality. Despite advances in screening, diagnosis, and therapeutic strategies, the prognosis for advanced CRC remains poor [1-3]. Treatment resistance poses a considerable challenge, complicating efforts to manage and eradicate the disease effectively. CRC development has been attributed to genetic mutations, lifestyle factors, and environmental influences. However, recent studies have highlighted the gut microbiome as critical in CRC progression and therapeutic responses [4,5]. The gut microbiota, a diverse community of microorganisms within the gastrointestinal tract, plays a significant role in CRC pathogenesis by influencing inflammation, immune modulation, and metabolic reprogramming [6,7]. Research into the microbiome's impact on CRC has revealed that specific bacterial populations may promote or inhibit tumor development. Pathogenic bacteria, such as *Fusobacterium nucleatum*, promote tumorigenesis through pro-inflammatory pathways, immune suppression, and the production of metabolites that support cancer cell survival [8-10].

On the other hand, beneficial bacteria, such as Bifidobacterium and Lactobacillus, exhibit anti-inflammatory properties that may protect against CRC. Despite these insights, significant gaps remain in understanding how specific microbial communities and metabolites contribute to CRC treatment resistance.

Clarifying these interactions is essential for developing strategies that target microbiomes to enhance treatment efficacy [11-13]. Dysbiosis or an imbalance in microbial composition, is frequently observed in CRC patients and is associated with increased inflammation and immune dysregulation. Dysbiosis can disrupt the delicate balance of pro- and anti-inflammatory signals in the gut, creating a microenvironment conducive to tumor growth and treatment resistance [14,15]. However, the precise mechanisms by which dysbiosis contributes to resistance to CRC treatments, such as chemotherapy and immunotherapy, remain poorly understood. Research focusing on the interplay between dysbiosis and treatment resistance could reveal novel therapeutic targets within the microbiome [16,17]. One key area of interest is the microbiome's role in modulating chemotherapy efficacy. Studies have shown that certain bacterial species, particularly *F. nucleatum*, can metabolize chemotherapeutic agents, reducing their effectiveness [18]. This interaction enables cancer cells to evade the cytotoxic effects of chemotherapy, ultimately promoting resistance. Identifying specific microbial enzymes and metabolic pathways involved in these interactions could lead to developing strategies to inhibit microbial interference, potentially enhancing chemotherapy's effectiveness [19,20]. The relationship between microbiome and CRC treatment resistance has garnered considerable attention recently. Resistance to chemotherapy, immunotherapy, and targeted therapies remains a crucial challenge in effective CRC management [21].

Studies have identified specific bacteria that may contribute to treatment resistance by altering immune responses or impacting cancer cell survival. *Fusobacterium nucleatum* is associated with inflammation and has been linked to resistance against standard chemotherapeutic agents. This bacterium can modulate cell-signaling pathways that promote tumor cell survival, leading to poorer patient outcomes [22,23]. In addition to direct microbial impacts on cancer cells, the microbiome influences the immune landscape within the tumor microenvironment. Certain gut bacteria affect immune checkpoint activity, which is critical for the efficacy of immunotherapies. While immune checkpoint inhibitors, like PD-1 and PD-L1 inhibitors, have succeeded in various cancers, their effectiveness in CRC has been limited [24]. This limited response is partly due to the gut microbiome's role in regulating immune checkpoints, as some microbial metabolites can either stimulate or inhibit immune responses, thereby altering the response to immunotherapies [25]. Metabolic reprogramming by the microbiome also plays a crucial role in CRC progression and treatment resistance. Short-chain fatty acids (SCFAs), such as butyrate, produced by gut bacteria, have shown tumor-suppressive properties under certain conditions but may also support tumor growth in others [26]. This dual role of SCFAs highlights the complex metabolic interactions within the CRC microenvironment. Microbial metabolites, including polyamines, are similarly implicated in modifying cellular energy pathways, making cancer cells more resilient to standard treatments [27].

Immunotherapy has emerged as a promising approach for various cancers, including CRC. However, its efficacy in CRC, especially in microsatellite-stable tumors, has been limited. Evidence suggests that the gut microbiome may modulate immune responses, influencing the success of immune checkpoint inhibitors [28]. Specific bacterial profiles or metabolites have been implicated in enhancing or inhibiting immune responses, although the exact mechanisms remain unclear. Understanding these relationships could facilitate the design of microbiome-based interventions that improve immunotherapy outcomes for CRC patients [29]. The gut microbiome also impacts the effectiveness of targeted therapies, which aim to inhibit molecular pathways essential for tumor growth. Some bacterial species can alter the tumor microenvironment, decreasing the efficacy of these drugs [30]. For instance, bacteria involved in bile acid metabolism may activate signaling pathways that enhance cancer cell survival and proliferation. Investigating these microbial interactions with targeted therapies could provide insights into microbiome-targeted strategies that enhance the efficacy of these treatments [31]. Another layer of complexity in CRC treatment resistance is the interaction between microbial metabolites and cancer cell metabolism. Short-chain fatty acids (SCFAs), such as butyrate and propionate, produced by gut bacteria, exhibit pro- and anti-tumor properties depending on the context [32].

SCFAs can support immune function and reduce inflammation but may also fuel cancer cell metabolism under certain conditions. Understanding the precise conditions under which SCFAs promote or inhibit tumor growth is crucial for developing microbiome-based interventions to counteract CRC resistance [33]. The role of the microbiome in CRC extends to epigenetic regulation. Certain bacteria can induce DNA methylation and histone modifications, altering gene expression to support cancer cell survival. These epigenetic changes may contribute to treatment resistance, allowing cancer cells to evade therapeutic effects [34,35]. Despite some advances in understanding these microbial-induced modifications, more research is needed to elucidate the specific bacteria and epigenetic pathways involved. Targeting these pathways could support the development of therapies that overcome resistance by addressing microbial influences on the epigenetic landscape of CRC cells [36]. The microbiome holds promise as a predictive biomarker for CRC treatment response. Identifying microbial signatures associated with favorable or unfavorable reactions to therapy could guide personalized approaches, enabling clinicians to tailor treatments based on the patient's unique microbial profile [37]. This could reduce the likelihood of resistance and improve therapeutic efficacy. Research to establish reliable microbial biomarkers for clinical applications is crucial for advancing personalized medicine in CRC [38]. Diet is another factor influencing the microbiome, impacting CRC progression and therapeutic responses.

Diets rich in fiber, for instance, support SCFA-producing bacteria, potentially reducing inflammation and enhancing treatment efficacy [10]. Diets high in processed foods may disrupt the microbial balance, exacerbating treatment resistance. Further exploration of diet-microbiome interactions could yield valuable insights into dietary interventions that optimize CRC outcomes by supporting a healthy microbiome [39,40]. Adjunctive therapies, such as probiotics, prebiotics, and fecal microbiota transplantation (FMT), emerge as potential strategies for restoring microbial balance in CRC patients. Preliminary studies suggest these interventions may enhance treatment outcomes by reducing inflammation and modulating immune responses. However, rigorous clinical trials are needed to evaluate their safety, efficacy, and best practices for integrating conventional CRC therapies [41,42]. Another critical area of research concerns the microbiome's role in CRC metastasis. Certain bacteria have been implicated in promoting epithelial-to-mesenchymal transition (EMT), which enables cancer cells to invade other tissues and spread. Understanding the microbial mechanisms behind EMT could lead to new targets for therapies aimed at limiting CRC metastasis, ultimately improving patient outcomes [43]. Despite growing insights, consistent microbial biomarkers for predicting treatment responses remain elusive. Standardizing these microbial markers could enable personalized treatment approaches, guiding therapeutic decisions based on individual microbial compositions.

Future research should prioritize the identification of reliable microbial markers that inform CRC treatment strategies [23,44]. Interactions between the microbiome and host signaling pathways, such as NF-κB and Wnt, add another layer of complexity to CRC resistance. Certain bacteria can activate these pathways, supporting tumor cell survival and resistance to apoptosis. Targeting these microbial-induced pathways could represent a novel approach to overcoming CRC resistance, although further investigation is needed to bring this knowledge into clinical practice [36,45]. The microbiome also appears to influence CRC recurrence. Specific bacterial populations may increase the likelihood of cancer returning after treatment, suggesting that targeting these populations could improve long-term outcomes. Investigating microbiome-based prevention strategies may offer valuable insights into reducing CRC recurrence and enhancing patient survival [18,46]. Gut microbiome plays a complex and pivotal role in CRC progression and treatment resistance. While specific microbial tax and metabolites promote cancer growth and resistance, others may support therapeutic efficacy. A deeper understanding of these interactions will facilitate the development of microbiome-based diagnostics and therapeutics tailored to improve CRC outcomes [34,47]. This review aims to elucidate the mechanisms by which the microbiome contributes to treatment resistance in colorectal cancer, exploring potential therapeutic strategies that leverage microbial modulation as a pathway to overcoming resistance and enhancing patient care.

Methods

This review was undertaken to systematically evaluate the gut microbiome's influence on treatment resistance in colorectal cancer (CRC), examining mechanisms that affect therapy, including chemotherapy, immunotherapy, and targeted therapies. A structured and comprehensive literature search was conducted across prominent scientific databases, namely PubMed, Scopus, Embase, Web of Science, SciELO, and Google Scholar (included as a source of gray literature). Search terms were carefully selected to encompass key MeSH (Medical Subject Headings) and relevant terms, such as "Colorectal Neoplasms," "Microbiota," "Drug Resistance, Neoplasm," "Immunotherapy," "Short-Chain Fatty Acids," and "Dysbiosis." They were used with Boolean operators (AND, OR) to optimize retrieval of relevant studies. The review encompassed a range of study designs, including randomized controlled trials, cohort studies, case-control studies, cross-sectional analyses, case series, systematic reviews, and meta-analyses. Studies were selected based on their focus on CRC and microbiota interactions, specifically those that addressed the relationship between dysbiosis and treatment resistance mechanisms, the modulation of immune response by microbial metabolites, and the roles of short-chain fatty acids in influencing CRC treatment outcomes. Two reviewers initially screened Titles and abstracts independently to ensure an objective and comprehensive selection. Any discrepancies during the selection process were resolved through discussion or consulting a third reviewer.

The reviewers were blinded to study authorship and institutional affiliations during the screening to reduce potential bias. Data extraction was conducted following a standardized format to gather essential information from each study, including design, population demographics, primary findings, and specific microbiome-related factors associated with CRC resistance, with particular attention to immunotherapy and the metabolic role of short-chain fatty acids. The findings were organized using a thematic approach and grouped into key topics: the impact of dysbiosis on CRC progression, microbiome-induced modulation of drug resistance pathways, the influence of microbiota diversity on immunotherapy response, and the molecular pathways involved in microbial contributions to CRC resistance. Additionally, the review considered implications for microbiome-targeted strategies and highlighted the potential for integrating microbiota modulation in CRC treatment plans, especially as adjuncts to conventional therapies. This review aims to present an integrated summary of current research findings, identify critical knowledge gaps, and propose directions for future studies to enhance our understanding of microbiome-driven CRC treatment resistance. By synthesizing this information, the study aspires to support advancements in personalized cancer treatment that leverage the therapeutic potential of microbiome modulation in CRC.

Results and Discussion

Therapies Targeting the Microbiome in CRC

The gut microbiome plays an increasingly recognized role in colorectal cancer (CRC) treatment resistance, profoundly impacting the efficacy of chemotherapy, immunotherapy, and targeted therapies. This complex microbial ecosystem within the gastrointestinal tract contributes to CRC progression and influences how tumors respond to various treatments (Table 1) [8,9]. *Fusobacterium nucleatum*, frequently found in CRC tumors, interferes with chemotherapeutic agents like 5-fluorouracil (5-FU) and oxaliplatin, weakening their apoptosis-inducing effects on cancer cells [10]. This interference, resulting from microbial enzymatic activities that alter drug metabolism, highlights the importance of characterizing and targeting microbial interactions to improve treatment outcomes. Personalized approaches that address microbial-driven resistance could lead to more effective therapeutic strategies [14]. The intestinal microbiota plays a crucial role in maintaining gut homeostasis, immune modulation, and the integrity of the epithelial barrier. However, specific alterations in the gut microbiome's composition and function—called dysbiosis—are associated with an increased risk of colorectal cancer (CRC) [16,44]. Dysbiosis involves an imbalance where pathogenic bacteria outnumber beneficial species, leading to an inflammatory and pro-carcinogenic environment in the colon. This imbalance disrupts normal gut functions and contributes to tumor initiation and progression through various mechanisms, including microbial metabolite production, immune modulation, and direct interactions with the gut epithelium [29,48].

Table 1: Microbiome and Treatment Resistance in Colorectal Cancer.

Author	Study	Results
Rebersek M [1]	Review Study	This study underscores the role of *Fusobacterium nucleatum* in CRC, particularly in promoting immune evasion and resistance to chemotherapy. By fostering a pro-inflammatory environment, *F. nucleatum* impairs immune responses, complicating treatment outcomes.
Song M, et al. [2]	Cohort Study	Identified specific microbiome profiles associated with increased CRC risk. These profiles exhibit immune modulation and metabolic disruptions that favor tumorigenesis, suggesting that certain microbiota compositions can predispose individuals to CRC.
Cheng Y, et al. [3]	Case-Control Study	Demonstrated that *Fusobacterium nucleatum* interacts with chemotherapeutic agents, reducing their effectiveness by activating immune evasion pathways. This bacterium hinders immune-mediated cancer cell clearance, compromising overall treatment response.
Liu Y, et al. [3]	Meta-Analysis	Demonstrated that gut microbiota can metabolize chemotherapy drugs, rendering them less effective. Certain bacteria metabolize drugs into inactive forms, directly impacting CRC treatment outcomes and indicating that microbiome-targeted interventions could enhance efficacy.
Wang Z, et al. [9]	Prospective Study	Investigated the role of dysbiosis in CRC recurrence, showing that an imbalance in gut microbiota fosters a pro-inflammatory state, making patients more susceptible to tumor relapse post-treatment. Findings suggest dysbiosis as a key factor in recurrence.
Zhang T, et al. [56]	Experimental Study	Explored the microbiome's effect on immunotherapy, showing that beneficial bacteria can enhance checkpoint inhibitor efficacy by promoting immune cell activation and infiltration. Findings suggest microbiota composition as a key factor in immunotherapy success.
Zhou H, et al. [90]	Cross-Sectional Analysis	This study highlights that certain bacteria can induce epigenetic changes, such as DNA methylation, in CRC cells. These alterations can upregulate genes associated with drug resistance, indicating that epigenetic modulation via microbiota may impact treatment outcomes.
Pan C, et al. [30]	Clinical Trial	Evaluated fecal microbiota transplantation (FMT) and SCFA-producing bacteria in CRC patients. Results indicated that these interventions could stabilize immune checkpoints and enhance treatment efficacy, reducing tumor growth rates significantly.
Santiago-Lopez L, et al. [31]	Longitudinal Study	Investigated the impact of dietary habits on CRC-related microbiota, revealing that high-fiber diets support SCFA production and reduce pro-inflammatory bacterial populations, aiding in the efficacy of chemotherapy and immunotherapy by promoting a favorable microbiota profile.
Han J, et al. [73]	Observational Study	Established a link between dysbiosis and CRC metastasis, demonstrating that certain bacterial populations promote epithelial-mesenchymal transition (EMT) and cell migration, increasing metastatic potential and complicating treatment.
Li X, et al. [61]	Randomized Control Trial	Assessed the effect of probiotic supplementation in CRC patients undergoing chemotherapy. Probiotics improved immune responses and decreased treatment-related dysbiosis, potentially enhancing chemotherapy outcomes by promoting a balanced gut environment.
Murphy N, et al. 2022	Systematic Review	Summarized the relationship between diet and CRC, emphasizing that high dietary fiber and reduced red meat intake favorably modulate gut microbiota, potentially lowering CRC risk and recurrence rates through microbiota-mediated immune modulation.
Yu T, et al. 2021	*In Vivo* Study	Explored Akkermansia muciniphila's role in enhancing immunotherapy effectiveness in CRC models. Findings indicate that higher levels of this bacterium correlate with improved immune checkpoint responses, suggesting its potential as a biomarker for treatment efficacy.

Ahmed S, et al. 2023	Case Series	Reported on the beneficial effects of FMT in CRC patients, particularly those resistant to checkpoint inhibitors. FMT improved responses by restoring beneficial bacteria that support immune function and reduce inflammation, enhancing response rates in refractory cases.
Zhang L, et al. 2023	Genomic Analysis	Analyzed bacterial genomes associated with CRC, identifying specific genes involved in drug metabolism. Findings suggest that targeted microbiome interventions could counteract microbial drug inactivation, improving chemotherapy efficacy.
Kim Y, et al. 2021	Cross-Sectional Study	Demonstrated that advanced CRC stages are associated with reduced microbiota diversity, which is linked to poorer prognosis and treatment resistance, indicating microbiome diversity as a potential prognostic marker.
Johnson CH, et al. 2021	Translational Research	Investigated microbiota-produced SCFAs and their dual role in chemoresistance. While SCFAs support immune modulation, high levels in dysbiotic environments can enhance tumor growth, suggesting the need for precise SCFA modulation in CRC treatments.
Smith RA, et al. 2022	Cohort Study	Examined post-surgical recurrence rates in relation to microbiota composition. Findings showed that patients with balanced microbiota post-surgery exhibited lower recurrence rates, suggesting that microbiota composition may predict recurrence risk.
Patel KK, et al. 2022	Case-Control Study	Compared microbiome profiles in chemoresistant vs. non-chemoresistant CRC patients. Identified unique microbial patterns associated with resistance, suggesting that specific microbiota profiles could serve as predictive biomarkers for treatment outcomes.
Zhao F, et al. 2021	*In Vitro* Study	Examined the role of certain bacterial strains in upregulating NF-κB signaling, a key pro-survival pathway in CRC cells. Results indicate that bacterial influences on NF-κB contribute to chemoresistance, supporting targeted microbiome interventions.
Martinez J, et al. 2022	Prospective Cohort	Showed that dietary polyphenols modulate microbiota composition favorably, suggesting a protective effect against CRC progression. Polyphenol supplementation improved chemotherapy outcomes by reducing pro-inflammatory bacteria and enhancing SCFA levels.
Tan S, et al. 2022	Meta-Analysis	It is concluded that SCFA levels correlate with improved chemotherapy responses, indicating a role in immune modulation and tumor suppression. Findings highlight SCFAs as potential adjuncts in CRC treatment, particularly in immune-compromised patients.
Rodriguez K, et al. 2023	Randomized Trial	Found that probiotic supplementation enhances checkpoint inhibitor efficacy in CRC. Results showed reduced inflammation and increased T-cell infiltration in tumors, supporting probiotics as an adjunct to immunotherapy in enhancing immune responses.

Alterations in the intestinal microbiota that predispose individuals to colorectal cancer (CRC) are driven by various environmental, dietary, lifestyle, and medical factors that disrupt the balance of microbial populations within the gut. This imbalance, or dysbiosis, is characterized by decreased beneficial bacteria and increased pathogenic or pro-inflammatory bacteria, creating a gut environment that fosters inflammation, genetic damage, and carcinogenesis [30,45].

Epigenetic Modulation by Microbial Interactions

One of the primary factors leading to dysbiosis is diet, particularly Western-style diets high in fat, red and processed meats, refined sugars, and low in fiber. Such diets favor the growth of bacteria that produce harmful metabolites. Diets rich in red and processed meats can increase the production of N-nitroso compounds (NOCs) and secondary bile acids [21,49]. Certain bacteria, such as Bilophila wadsworthia, thrive in high-fat conditions and contribute to increased production of secondary bile acids. These bile acids can irritate the colonic lining, damage DNA, and promote cell proliferation, setting the stage for cancer initiation. Additionally, red and processed meats contribute to forming NOCs, carcinogenic compounds linked to DNA mutations in colonic cells [39,50]. A low-fiber diet also has significant implications for gut health, as it deprives beneficial bacteria of the necessary substrates to produce short-chain fatty acids (SCFAs), such as butyrate. Butyrate is a crucial SCFA that provides energy to colon cells, promotes anti-inflammatory pathways and supports healthy epithelial barrier function [17]. When fiber intake is reduced, butyrate-producing bacteria like Bifidobacterium and Lactobacillus diminish, weakening the gut barrier and reducing butyrate availability. This depletion allows pathogenic bacteria to thrive and encourages an inflammatory environment, increasing the risk of CRC [47,51].

Antibiotic use is another significant factor contributing to dysbiosis, as it can lead to a rapid and profound alteration in microbial diversity by indiscriminately killing both beneficial and harmful bacteria. The frequent or prolonged use of antibiotics can reduce beneficial bacteria, allowing pathogenic or opportunistic bacteria to overgrow and dominate the gut environment [4,52].

This shift reduces the production of SCFAs and creates gaps in the microbial ecosystem, facilitating the establishment of pathogenic strains like Escherichia coli and Clostridium difficile, which can disrupt gut integrity and contribute to inflammation. Furthermore, some antibiotic-resistant bacteria may persist and complicate the re-establishment of a healthy microbiota [26,53]. Chronic stress and psychological factors can also influence the gut microbiota through the gut-brain axis. Stress has been shown to alter gut motility, immune function, and mucosal barrier integrity, impacting microbial composition and function. Stress-induced changes can decrease the abundance of beneficial bacteria and promote the growth of pro-inflam-

matory bacteria [10,48]. This shift contributes to a leaky gut barrier, allowing bacterial endotoxins like lipopolysaccharides (LPS) to enter the bloodstream and induce systemic inflammation. This inflammation is associated with various chronic conditions, including CRC, as chronic inflammation creates an environment conducive to DNA damage and cellular mutations [49,54]. Another factor that disrupts gut microbiota is exposure to environmental toxins, including pesticides, heavy metals, and artificial food additives. These substances can selectively harm beneficial bacteria while promoting the growth of more resilient, pathogenic bacteria [5-7]. Emulsifiers and artificial sweeteners in processed foods have been shown to alter gut microbiota by enhancing the growth of bacteria associated with inflammation and breaking down the gut's protective mucous layer.

This breakdown increases intestinal permeability, allowing harmful microbes and inflammatory molecules to interact more directly with gut epithelial cells, promoting conditions favorable to CRC [13,55]. Sedentary lifestyles and lack of physical activity negatively affect the gut microbiome. Regular exercise has increased microbial diversity and a higher abundance of beneficial bacteria, such as Akkermansia muciniphila, linked to gut barrier integrity and anti-inflammatory effects [42]. On the other hand, physical inactivity is correlated with reduced microbial diversity and a more significant presence of bacteria associated with inflammation and dysbiosis, thereby increasing the risk of CRC [38]. Aging naturally alters the gut microbiome. As people age, there is a decline in microbial diversity, with beneficial bacteria like Bifidobacterium species decreasing and potentially pathogenic bacteria increasing [46,50]. The immune system also weakens with age, reducing the capacity to control harmful bacteria and maintain balanced gut microbiota. This immune aging can contribute to a pro-inflammatory gut environment, making the elderly more susceptible to dysbiosis-related diseases, including CRC [52]. Alterations in the intestinal microbiota that predispose individuals to CRC are primarily driven by dietary choices, antibiotic use, chronic stress, environmental toxins, lack of physical activity, and aging. Each of these factors disrupt the average balance of the gut microbiome, promoting an increase in pro-inflammatory and pathogenic bacteria while reducing beneficial species [38-40]. This imbalance weakens the gut barrier, induces chronic inflammation, and leads to the production of carcinogenic compounds and genetic mutations in colonic cells, all of which contribute to an increased risk of colorectal cancer.

Addressing these contributing factors through dietary changes, lifestyle modifications, and mindful medical practices may be essential in reducing CRC risk associated with microbiome dysbiosis [44,56]. One of the primary microbial changes observed in dysbiosis related to CRC is an increased abundance of certain pathogenic bacteria, including *Fusobacterium nucleatum*, Escherichia coli, and Bacteroides fragilis. These bacteria produce toxins and virulence factors that can damage the intestinal epithelium, induce inflammation, and promote genetic mutations in colon cells [11-13]. *Fusobacterium nucleatum* is known to adhere to and invade colonic epithelial cells. It triggers inflammatory responses and impairs cell signaling pathways that regulate apoptosis, allowing mutated cells to survive and proliferate. Additionally, *F. nucleatum* can modulate the immune response by attracting myeloid cells that suppress anti-tumor immunity, creating a microenvironment that supports tumor growth [52,53]. Pathogenic strains of Escherichia coli associated with CRC frequently possess a polyketide synthase (pks) genomic island, which enables them to produce colibactin, a genotoxin capable of causing DNA double-strand breaks in host cells [30]. This DNA damage increases the likelihood of mutations in essential tumor suppressor genes (such as p53) and oncogenes, which are crucial steps in transforming normal cells into cancerous ones. Over time, these cumulative genetic mutations contribute to cellular dysregulation and malignant transformation, accelerating the progression of CRC [45,56].

Bacteroides fragilis, particularly enterotoxigenic strains, also contribute to CRC by releasing a toxin known as Bacteroides fragilis toxin (BFT). BFT induces inflammation and disrupts the E-cadherin protein in epithelial cells, weakening cell adhesion and increasing intestinal permeability [18-20]. This compromised barrier function allows for the translocation of other bacteria and microbial products into the bloodstream and surrounding tissues, intensifying the inflammatory response and promoting carcinogenic changes in the colonic epithelium. BFT further stimulates the release of cytokines, such as IL-17 and IL-6, which drive chronic inflammation and enhance cellular proliferation, supporting an environment that favors CRC development [3-5,57]. Another significant factor in CRC-associated dysbiosis is the depletion of beneficial bacteria, such as Bifidobacterium and Lactobacillus species, which play protective roles in the gut. These commensal bacteria produce short-chain fatty acids (SCFAs), such as butyrate, which have anti-inflammatory and anti-carcinogenic properties [14-16]. Butyrate mainly serves as an energy source for colonocytes, promoting healthy cell differentiation and apoptosis in abnormal cells. It also has anti-inflammatory effects, inhibiting NF-κB signaling, a pathway frequently associated with inflammation and cancer. With the reduction of butyrate-producing bacteria in dysbiotic microbiomes, the protective effects of SCFAs are diminished, weakening the colon's defenses against tumorigenesis [53,58].

Dysbiosis disrupts the immune system's balance, creating an environment that supports CRC development. The gut microbiota is vital in educating the immune system, promoting tolerance to harmless antigens, and mounting responses to harmful pathogens. When dysbiosis occurs, pro-inflammatory immune cells, such as Th17 cells, and a decrease in regulatory T cells (Tregs) that maintain immune homeostasis often increase [27,59]. Elevated levels of pro-inflammatory cytokines, including IL-6, IL-17, and TNF-α, contribute to chronic inflammation, which has been widely linked to CRC. This inflammatory environment leads to the recruitment of immune cells that produce reactive oxygen and nitrogen species, which can damage DNA and further promote mutations in colonic cells [49,60]. Microbial

metabolites also contribute to CRC risk. Specific bacterial enzymes convert dietary components, mainly red and processed meats, into carcinogenic compounds like N-nitroso (NOCs) and secondary bile acids. Bilophila wadsworthia increase in response to diets high in fat and animal protein, leading to elevated production of secondary bile acids [20-22]. These bile acids have been shown to damage the colonic epithelium and promote cell proliferation, contributing to an environment conducive to cancer. The accumulation of carcinogenic compounds and altered bile acid metabolism in dysbiosis further underscores the role of the microbiota in predisposing individuals to CRC [56,61]. Dysbiosis in the gut microbiota predisposes to colorectal cancer through various mechanisms, including the proliferation of pathogenic bacteria that cause direct DNA damage, depletion of beneficial SCFA-producing bacteria, immune system dysregulation, and the production of carcinogenic microbial metabolites [58-60].

Together, these factors create a pro-inflammatory, genotoxic environment that promotes the initiation and progression of CRC. Dysbiosis through dietary interventions, probiotics, and potentially microbiome-modulating therapies may offer promising strategies for reducing CRC risk and supporting colon health [33,34]. In addition to *Fusobacterium nucleatum*, several other bacterial species play critical roles in colorectal cancer (CRC) progression and treatment resistance. Bacteroides fragilis, for instance, is known to drive inflammation in the gut and release toxins that directly damage the DNA of epithelial cells. These toxins can initiate inflammatory responses that promote cellular proliferation and treatment resistance, creating an environment conducive to CRC progression [45-47]. Pathogenic strains of Escherichia coli, particularly those producing colibactin, are also implicated in CRC. Colibactin is a genotoxin that causes DNA damage in intestinal cells, potentially driving carcinogenesis and supporting tumor growth by creating conditions favorable for treatment resistance [32-35]. Another bacterium, Enterococcus faecalis, generates reactive oxygen species (ROS) and other toxic compounds that induce DNA damage, promoting genetic instability and inflammation. This chronic inflammatory environment can enhance tumor cell survival and increase resistance to conventional CRC treatments [58,62]. Certain species within the Clostridium genus also impact CRC outcomes, primarily by producing short-chain fatty acids (SCFAs) such as butyrate.

While butyrate typically has anti-inflammatory properties, its role in the tumor environment is more complex; it may exhibit tumor-promoting effects in CRC cells already predisposed to resistance [44,60]. Akkermansia muciniphila, generally considered a beneficial bacterium, has also shown a dual impact in cancer patients. Emerging research indicates that its presence in CRC patients may correlate with reduced efficacy of immunotherapies like immune checkpoint inhibitors, though the mechanisms are not fully understood [40,41].

While Helicobacter pylori is more commonly associated with gastric cancer, certain strains have been implicated in colorectal carcinogenesis, particularly in individuals with chronic inflammation and dysbiosis. H. pylori can contribute to CRC by releasing toxins and sustaining chronic inflammatory states, creating a pro-carcinogenic environment [62,63]. Porphyromonas gingivalis, primarily associated with periodontal disease, has been linked to CRC. This bacterium promotes inflammation and immune modulation, both of which support a tumor-friendly microenvironment and may play a role in facilitating resistance to treatment [20]. Together, these bacterial species contribute to CRC treatment resistance through various mechanisms, including inflammation, DNA damage, production of pro-tumor metabolites, and immune modulation. A deeper understanding of these interactions may help develop microbiome-targeted interventions to overcome resistance and improve therapeutic outcomes for CRC patients [24].

In colorectal cancer (CRC), genetic alterations are central to disease initiation, progression, and treatment resistance. They occur in a stepwise accumulation of mutations and epigenetic changes that transform normal epithelial cells into malignant ones. These genetic alterations typically involve mutations in several key genes, including tumor suppressors, oncogenes, and genes involved in DNA repair mechanisms, each contributing uniquely to the cancerous phenotype observed in CRC [64,65]. The genetic landscape of CRC patients further complicates treatment response, particularly when mutations in immune-regulatory genes, such as MSH2 and MLH1, affect microbiome composition. These genetic predispositions foster a microenvironment conducive to CRC progression and shape microbial profiles that may enhance resistance [19,52]. The interaction between genetics and the microbiome opens new possibilities for dual-modality interventions targeting genetic and microbial components, optimizing therapeutic efficacy. Integrating genetic profiling with microbiome analysis could lead to a multi-layered approach to treatment, potentially transforming outcomes for patients with CRC [27,66]. One of the most mutated genes in CRC is the APC gene (adenomatous polyposis coli), which plays a crucial role in regulating the Wnt signaling pathway. Mutations in APC lead to uncontrolled activation of Wnt signaling, driving cellular proliferation and reducing cell adhesion. This mutation often represents an early event in CRC development, creating a pro-proliferative environment that facilitates the accumulation of additional genetic alterations [38,46].

Another critical gene involved is KRAS, a proto-oncogene that, when mutated, stimulates downstream signaling pathways such as the MAPK/ERK pathway, which promotes cell growth and survival [29-31]. Mutations in KRAS not only accelerate tumor progression but also contribute to treatment resistance, particularly to anti-EGFR therapies. KRAS mutations are often associated with poor prognosis due to the gene's role in activating growth-promoting signals, even in the presence of therapeutic agents [60,67]. Loss of function in TP53, the gene encoding the p53 tumor suppressor protein, is another significant genetic alteration in CRC. Known as the "guardian of the genome," p53 prevents genomic instability by initiating DNA repair mechanisms or inducing apoptosis in response to DNA damage

[40]. Mutations in TP53 disrupt these protective functions, allowing cells with extensive genetic damage to survive and proliferate. In CRC, TP53 mutations are commonly observed in the later stages of tumor progression, contributing to both malignancy and resistance to treatments, as cells lose the ability to undergo apoptosis in response to chemotherapy or radiation therapy [27,68]. Mutations in DNA mismatch repair (MMR) genes, such as MLH1, MSH2, MSH6, and PMS2, lead to microsatellite instability (MSI), characterized by frequent mutations in short repetitive DNA sequences. MMR deficiency allows mutations to accumulate rapidly across the genome, contributing to a hypermutated state that fosters tumor heterogeneity [64-66].

Microsatellite instability is a hallmark of approximately 15% of CRC cases. It has implications for treatment response, as tumors with MSI-high status may respond differently to immunotherapies, such as immune checkpoint inhibitors, compared to microsatellite-stable tumors [41-13]. Epigenetic changes, such as DNA methylation, also play a significant role in CRC. Promoter hypermethylation in genes involved in cell cycle regulation, apoptosis, and DNA repair silences their expression, effectively shutting down tumor-suppressive pathways [54,69]. Hypermethylation of the MLH1 promoter is commonly observed in sporadic CRC cases with microsatellite instability, contributing to the inactivation of this critical MMR gene. This type of epigenetic silence can support tumor progression similarly to mutations by removing essential regulatory proteins from cellular processes [62,70]. Additional mutations in genes like SMAD4 and PIK3CA further contribute to CRC progression. SMAD4 mutations affect TGF-β signaling, a pathway involved in cell growth inhibition, immune response, and apoptosis, while mutations in PIK3CA activate the PI3K/AKT pathway, promoting cell survival, proliferation, and metabolism. These mutations create a complex network of dysregulated pathways that enable CRC cells to grow, evade apoptosis, and resist therapy [17-19,71]. CRC development and progression are driven by genetic alterations affecting multiple cellular pathways, from Wnt and MAPK signaling to DNA repair and epigenetic regulation [35,36].

These alterations enable the transition from normal cells to malignant ones and contribute to treatment resistance by disrupting apoptosis, enhancing cell survival, and allowing rapid mutation accumulation. These genetic changes provide insights into potential therapeutic targets and help develop personalized treatment strategies that address the unique genetic landscape of each CRC tumor [63,64].

Microbiota's Influence on Tumor Immunotherapy

The microbiome's extensive influence on CRC progression and resistance, highlighting its role as a significant factor in patient prognosis. Specific microbial species like *Fusobacterium nucleatum* are known to promote tumor growth and immune evasion, thus reducing the effectiveness of standard therapies [25-27]. In contrast, beneficial bacteria, including Bifidobacterium and Lactobacillus, support anti-inflammatory pathways, creating an environment less favorable to tumor progression and enhancing treatment efficacy. Beyond the presence of specific species, the metabolic activities of microbiome play a fundamental role in CRC treatment resistance [46,72]. Short-chain fatty acids (SCFAs) produced by certain gut bacteria exhibit dual roles in the tumor microenvironments, supporting immune function in some conditions while promoting tumor growth in others. Dysbiosis, the imbalance in microbial composition commonly seen in CRC patients, further disrupts immune and inflammatory responses, fostering an environment that promotes tumor survival and treatment resistance [58-60,73]. In immunotherapy, the microbiome's role is equally profound. Immunotherapies like checkpoint inhibitors, which have shown great promise in other cancers, are often less effective in CRC, particularly in microsatellite-stable (MSS) tumors. Certain bacterial strains modulate immune checkpoint pathways, such as PD-1 and PD-L1, altering the immune system's response to tumor cells [49-51,74]. Research into microbiome modulation to enhance the efficacy of CAR-T cell therapy in CRC patients highlights the potential of combination therapies that integrate microbiome-targeted interventions with immunotherapy.

The microbiome's role in antigen presentation, immune cell infiltration, and critical factors in immunotherapy efficacy could further expand treatment options for CRC patients [70]. Immunotherapy in colorectal cancer (CRC), particularly in cases with genetic mutations and microsatellite instability (MSI), harnesses the immune system's natural ability to recognize and destroy cancer cells. The primary approach to immunotherapy in CRC involves immune checkpoint inhibitors, which target regulatory pathways that cancer cells exploit to evade immune detection [67,75]. In MSI-high (MSI-H) CRC cases, where DNA mismatch repair genes are mutated, tumors acquire a high mutational burden, creating numerous neoantigens that make them more immunogenic and, thus, more visible to the immune system [13,49]. Immune checkpoint inhibitors, particularly those targeting PD-1 (Programmed Death-1) and CTLA-4 (Cytotoxic T-Lymphocyte-Associated Protein 4), enhance the immune response by blocking inhibitory signals, allowing T cells to recognize and attack tumor cells more effectively [68-71]. At the molecular level, the PD-1/PD-L1 pathway is a crucial target for immunotherapy in CRC. Typically, PD-1 is a checkpoint protein expressed on T cells that, when engaged by its ligand PD-L1 on other cells, transmits an inhibitory signal, reducing T cell activity. Tumor cells overexpress PD-L1 to "hide" from immune surveillance by binding to PD-1 receptors on T cells, effectively deactivating them. Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, block the interaction between PD-1 and PD-L1 [74-76].

This blockade prevents the inhibitory signaling, allowing T cells to remain active and target the tumor cells. CTLA-4 inhibitors, on the other hand, block the CTLA-4 pathway that regulates T cell activation in early immune responses. By inhibiting CTLA-4, drugs like ipilimumab enhance T-cell priming and increase the number of active T cells available to attack tumor cells [50-52]. The immune response in CRC cases involving immunotherapy is mediated by various cytokines and

interleukins that critically orchestrate the anti-tumor response. Interleukin-2 (IL-2) promotes the growth and activation of T-cells, enhancing their cytotoxic activity against cancer cells [65-67]. IL-12 is another key cytokine that stimulates the production of interferon-gamma (IFN-γ) and activates natural killer (NK) cells and T-cells, further supporting the immune response against CRC. IFN-γ, produced by T-cells and NK cells, is essential for enhancing antigen presentation on tumor cells, making them more recognizable to the immune system. This cytokine stimulates immune cells and upregulates the expression of MHC (Major Histocompatibility Complex) molecules on tumor cells, increasing their visibility to T-cells [39,77]. Tumor necrosis factor-alpha (TNF-α) also plays a dual role in immunotherapy. TNF-α has pro-inflammatory effects that can help to recruit immune cells to the tumor microenvironment and promote T-cell activation [54]. However, in some cases, TNF-α may also contribute to immune suppression within the tumor if excessively produced, highlighting the complexity of cytokine interactions in CRC immunotherapy [16].

Interleukin-6 (IL-6), often upregulated in the tumor microenvironment, can promote inflammation and tumor progression, representing a challenge for immunotherapy as it may counteract the anti-tumor immune response. Targeting IL-6 alongside immune checkpoint inhibition is currently under investigation as a combined approach to optimize therapeutic outcomes [74,76]. The success of immunotherapy in CRC is highly dependent on the immunological characteristics of the tumor microenvironment. The high mutational burden in MSI-H tumors leads to an abundance of neoantigens that attract immune cells, including CD8+ cytotoxic T cells, which are essential for targeting and killing tumor cells. These T-cells are supported by the actions of helper T-cells (CD4+), which secrete cytokines to sustain the anti-tumor immune response [78-80]. However, immunotherapy is often less effective in microsatellite-stable (MSS) CRC tumors, which lack a high neoantigen load. MSS tumors tend to have a lower infiltration of T-cells and an immune-suppressive microenvironment dominated by regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which inhibit anti-tumor immune activity [33,49]. To overcome the immune-suppressive microenvironment in MSS CRC, research explores combination therapies that include immune checkpoint inhibitors with agents targeting other immune-regulatory molecules. Some studies investigate the combination of checkpoint inhibitors with IL-2 or IL-15 agonists, which can promote the expansion and activation of effector T cells [66,81].

Others are examining therapies targeting tumor-associated macrophages (TAMs) and MDSCs, which release factors like IL-10 and TGF-β that suppress T-cell responses. Blocking these factors or reprogramming these cells can potentially enhance the immune response in MSS CRC, making immunotherapy more effective [57-59]. Immunotherapy in CRC leverages immune checkpoint inhibitors to activate T cells by blocking inhibitors used by tumor cells to evade immune detection. This process is intricately supported by cytokines like IL-2, IL-12, and IFN-γ, which promote T-cell activation and enhance antigen presentation [31,74]. Cytokines like IL-6, IL-10, and TGF-β can inhibit immune response, presenting challenges in CRC treatment. The molecular interplay of these cytokines and the immunological profile of the tumor microenvironment largely determine the success of immunotherapy in CRC, and current research is focused on overcoming resistance by combining immunotherapy with other immunomodulatory agents [79,82].

Angiogenesis via Microbiota Modulation

Microbial influence extends beyond immune modulation, affecting angiogenesis within the tumor microenvironment. Certain bacteria promote blood vessel formation within tumors, supporting tumor growth and metastasis and complicating drug delivery [78-80]. Targeting these bacteria may limit CRC progression, optimize chemotherapeutic agent distribution, and enhance treatment efficacy. This aspect underscores the need for strategies targeting bacteria that contribute to tumor angiogenesis, as such approaches could simultaneously limit tumor growth and improve drug distribution within the tumor [9-11,83]. Microbial metabolites, such as SCFAs, add another layer of complexity to CRC treatment resistance. Butyrate demonstrates both pro- and anti-tumor effects, depending on the metabolic context within the tumor microenvironment. These metabolites influence signaling pathways that promote cancer cell survival, such as NF-κB and STAT3, which pathogenic bacteria activate [24-26]. Epigenetic modifications induced by microbiome activity further contribute to CRC resistance. Pathogenic bacteria like *Fusobacterium nucleatum* can induce DNA methylation and histone deacetylation, effectively silencing tumor suppressor genes and promoting cancer cell survival. Targeting these bacterial-driven epigenetic changes represents a promising avenue for novel therapies that could reverse resistance at the molecular level [36-38]. The impact of the microbiome on CRC recurrence and metastasis highlights the importance of microbial interventions in improving long-term outcomes. Specific microbial profiles associated with inflammation and immune suppression may increase recurrence risk following treatment [70,72].

By understanding and modifying these profiles, clinicians could develop strategies to reduce recurrence, thereby improving survival rates. This approach supports long-term interventions beyond initial treatment, addressing the potential for CRC recurrence through microbiome modulation [32,48]. The gut microbiota plays a crucial role in tumor recurrence after colorectal cancer (CRC) treatments, including surgical resection, radiotherapy, and adjuvant or neoadjuvant therapies. Post-treatment recurrence is a significant challenge in CRC management, and emerging evidence suggests that specific alterations in the gut microbiota can create a microenvironment conducive to tumor regrowth and resistance to therapies [4-6]. Dysbiosis, or the disruption of the average gut microbial balance, often occurs following CRC treatments, which can compromise immune responses, promote inflammatory pathways, and enhance cellular signaling

mechanisms that favor tumor survival and proliferation [65,84]. Following surgical resection, the gut microbiome often undergoes significant shifts due to physiological stress, alterations in gut motility, and exposure to perioperative antibiotics [11-13]. These changes can deplete beneficial microbial species, such as Bifidobacterium and Lactobacillus while allowing opportunistic pathogens, such as *Fusobacterium nucleatum* and Escherichia coli, to dominate [30]. *F. nucleatum* has been associated with increased tumor recurrence rates in CRC patients due to its ability to modulate the tumor microenvironment.

This bacterium promotes chronic inflammation by activating nuclear factor kappa B (NF-κB) and other inflammatory pathways, producing a pro-inflammatory milieu that encourages cancer cell survival and proliferation. *F. nucleatum* can bind directly to cancer cells through its FadA adhesion molecule, enhancing cancer cell proliferation and invasion and possibly accelerating recurrence [47-50]. Postoperative dysbiosis also influences immune modulation in ways that undermine effective antitumor responses. A disrupted microbiome reduces the diversity of microbial metabolites, such as short-chain fatty acids (SCFAs), which are essential for maintaining mucosal immunity and controlling inflammation [76]. Reduced SCFA levels can impair T-regulatory cells (Tregs) and other immune-regulatory cells, weakening the body's natural defenses against residual cancer cells and increasing the likelihood of recurrence [64]. The lack of SCFAs also leads to increased gut permeability, allowing bacterial endotoxins like lipopolysaccharides (LPS) to enter circulation, where they can stimulate systemic inflammation and further suppress immune responses that might otherwise control tumor cells [40]. Radiotherapy and chemotherapy can also induce significant alterations in the microbiota that contribute to recurrence. These treatments often reduce bacterial diversity and promote the overgrowth of inflammatory species. Clostridium difficile and other pathogenic bacteria tend to increase in response to the immunosuppressive effects of radiotherapy and chemotherapy [80,85].

This microbial shift leads to increased production of pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-17 (IL-17), which activate signaling pathways like STAT3 and MAPK in residual cancer cells. These pathways are implicated in cell survival, proliferation, and resistance to apoptosis, which are hallmarks of tumor recurrence and resistance [53-55]. Neoadjuvant and adjuvant therapies, including chemoradiation, can also disrupt the gut microbiota by reducing beneficial bacteria and enhancing antibiotic-resistant strains. Bacteroides fragilis, can produce toxins (e.g., B. fragilis toxin) that damage epithelial cells and create a pro-tumorigenic inflammatory environment [1,2,86]. B. fragilis can also activate Wnt/β-catenin and NF-κB signaling in host cells, pathways that are associated with cancer cell survival and metastasis. This microbial-driven inflammation supports an immune-suppressive tumor microenvironment, limiting the effectiveness of adjuvant therapies and facilitating recurrence [16-18]. The increase in microbial metabolites, such as secondary bile acids produced by dysbiotic bacteria, has been linked to DNA damage in colon epithelial cells, enhancing the potential for oncogenic mutations and contributing to the recurrence process [79-81]. The gut microbiota's role in resistance to therapies is also linked to its influence on drug metabolism and immune modulation. Escherichia coli can alter the metabolism of chemotherapeutic agents like 5-fluorouracil, reducing its cytotoxic effect on cancer cells [84,85].

Dysbiosis-induced inflammation suppresses the effectiveness of immune-based treatments, as inflammatory cytokines shift the immune response towards tumor-promoting Th17 cells and away from cytotoxic T cells essential for eliminating cancer cells. Thus, dysbiosis increases the likelihood of recurrence and drives resistance to further treatments [69,87]. Another crucial molecular alteration involves the epigenetic changes in both host and microbial genomes induced by dysbiosis. Pathogenic bacteria like Fusobacterium and Bacteroides have been shown to induce DNA methylation and histone modification in host cells, silencing tumor suppressor genes while activating oncogenes [59-61]. This epigenetic modulation creates a genetic environment in the host primed for cancer recurrence, as tumor cells with epigenetic alterations are more likely to survive and proliferate despite treatment [36]. Bacteria can also exchange genes involved in antibiotic resistance and virulence factors through horizontal gene transfer, making dysbiotic microbiota harder to control and potentially leading to multidrug-resistant bacterial populations that complicate recovery and post-treatment infection management [52]. The immune system's role in recurrence cannot be overstated. Dysbiosis skews the immune system towards a chronic, low-grade inflammatory state that supports tumor cell persistence and growth. Immune cells, such as tumor-associated macrophages (TAMs), can be polarized towards a pro-tumor M2 phenotype in the presence of specific bacterial populations, which secrete anti-inflammatory cytokines like IL-10, creating an environment that protects residual tumor cells.

Moreover, these immune changes reduce the effectiveness of immune checkpoint inhibitors, making it challenging to harness the immune system in the fight against recurring cancer [81,86-88]. Alterations in the gut microbiota play a substantial role in CRC recurrence by promoting inflammation, modifying immune responses, and influencing genetic and epigenetic pathways that encourage tumor survival and resistance [19]. Pathogenic bacteria reduce microbial diversity, and a shift in microbial metabolite production creates a favorable environment for cancer recurrence after treatment. A deeper understanding of these microbiota-related mechanisms in recurrence and resistance highlights the need for microbiome-targeted therapies alongside conventional treatments to improve patient outcomes and reduce the risk of CRC relapse [44,67,89].

Biomarker Development for CRC Microbiome Analysis

The microbiome's potential as a predictive biomarker for CRC treatment response has also garnered attention. Identifying microbial signatures linked to favorable or unfavorable outcomes could enable clinicians to tailor treatment plans, reduce resistance, and increase therapeutic precision [80-82]. Although promising, estab-

lishing standardized microbial biomarkers for clinical use is still underway, necessitating further research to validate these markers and integrate microbiome analysis into precision oncology [77]. Predictive biomarkers for colorectal cancer (CRC) treatment response and tumor recurrence are gaining recognition for their potential to guide personalized therapies, reduce resistance, and improve therapeutic outcomes. These biomarkers include microbial and molecular indicators that can help clinicians assess which patients are more likely to respond favorably or unfavorably to specific treatments, allowing for tailored interventions that maximize efficacy [89-91]. On the microbial level, certain bacterial species within the gut microbiota have been linked to favorable or adverse responses to CRC treatments. *Fusobacterium nucleatum*, commonly enriched in CRC patients, is associated with treatment resistance and higher recurrence rates [48-50]. Studies show that *F. nucleatum* promotes inflammation and immune evasion, compromising the efficacy of chemotherapy and immunotherapy [12]. Elevated levels of *F. nucleatum* in CRC patients have been correlated with poor prognosis and reduced responsiveness to drugs like 5-fluorouracil (5-FU) and oxaliplatin, primarily due to the bacterium's ability to inhibit apoptosis in cancer cells.

Thus, detecting *F. nucleatum* can serve as a predictive biomarker for potential chemoresistance and recurrence risk, suggesting alternative therapeutic strategies are needed in patients with high *F. nucleatum* levels [55-58,84].

Lifestyle and Microbiota: Reducing CRC Risk

Beneficial bacteria such as Bifidobacterium and Lactobacillus have shown promise as positive biomarkers, often linked to improved response to therapy and reduced risk of recurrence [42]. These bacteria produce short-chain fatty acids (SCFAs), such as butyrate, which have anti-inflammatory properties and support immune function. SCFAs enhance T-cell activity and promote a tumor-suppressive environment, making patients with higher levels of these bacteria more likely to respond well to treatments like immunotherapy [31]. Monitoring SCFA levels and Bifidobacterium and Lactobacillus abundance could thus serve as indicators of favorable treatment responses, and efforts to increase these bacteria through probiotics or diet may enhance therapeutic effectiveness [67]. On the molecular level, specific genetic and epigenetic alterations in CRC cells are critical predictive biomarkers for treatment outcomes. Mutations in DNA mismatch repair (MMR) genes, such as MSH2 and MLH1, are particularly significant. CRC patients with deficient MMR (dMMR) exhibit microsatellite instability-high (MSI-H) tumors, which respond better to immune checkpoint inhibitors like pembrolizumab [84,85]. This makes MSI-H a valuable biomarker for predicting responsiveness to immunotherapy. At the same time, patients with microsatellite stable (MSS) tumors may require alternative approaches as they often show resistance to these therapies [90,91]. Epigenetic changes driven by microbial interactions also contribute to biomarker potential. Certain bacteria, including Bacteroides fragilis, can induce DNA methylation and histone modifications that alter gene expression in CRC cells, creating a more aggressive phenotype prone to recurrence [23-26].

Elevated hypermethylation levels in tumor suppressor genes, such as p16 and APC, are linked to poorer outcomes, as these alterations drive tumor progression and chemoresistance. Thus, assessing methylation patterns in essential regulatory genes may offer predictive insights into a patient's likelihood of recurrence and resistance [64,65,92]. Cytokine profiles in the tumor microenvironment are another valuable set of biomarkers. Inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-17 (IL-17) are commonly elevated in CRC patients with adverse outcomes. High levels of these cytokines promote signaling pathways such as STAT3 and NF-κB, which enhance tumor cell survival, proliferation, and immune evasion [59-62]. Higher levels of anti-inflammatory cytokines like interleukin-10 (IL-10) may indicate a more favorable prognosis, as IL-10 promotes immune regulation and can mitigate chronic inflammation that fuels CRC progression. Monitoring these cytokine levels before and during treatment could inform clinicians about the tumor's inflammatory profile and predict treatment resistance or success [15-18]. Molecular markers like KRAS, NRAS, and BRAF mutations also offer predictive insights, particularly in targeted therapies. For instance, mutations in KRAS and NRAS genes confer resistance to anti-EGFR (epidermal growth factor receptor) therapies like cetuximab and panitumumab, meaning that patients with these mutations are unlikely to benefit from such treatments [78,93]. Testing for KRAS and NRAS mutations before initiating anti-EGFR therapy can prevent ineffective treatments and enable a shift to alternative therapies better suited to the patient's molecular profile. Similarly, BRAF mutations, especially V600E, are associated with aggressive disease and poor prognosis, and their presence may justify more intensive or combination therapies to counteract the high risk of recurrence [49-52].

Circulating tumor DNA (ctDNA) in the bloodstream has emerged as a non-invasive biomarker for detecting residual disease and predicting recurrence. High levels of ctDNA after surgery or chemotherapy are indicative of minimal residual disease (MRD) and are associated with an increased likelihood of recurrence [74,90]. Regular monitoring of ctDNA allows clinicians to detect early signs of recurrence and adjust treatment plans proactively, potentially initiating adjuvant therapies to reduce recurrence risk [28-30]. Combining microbial and molecular biomarkers provides a robust framework for predicting CRC treatment response and recurrence. Microbial biomarkers such as *F. nucleatum* and SCFA-producing bacteria offer insights into microbiota-driven resistance or sensitivity, while molecular biomarkers, including MSI-H status, gene mutations, and cytokine profiles, help refine treatment strategies [93,94]. Using these biomarkers in clinical practice can lead to more personalized, precise treatment plans, ultimately improving outcomes and reducing the incidence of CRC recurrence [80,81]. Carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) are valuable biomarkers in the management and monitoring of colorectal cancer (CRC), particularly in the

postoperative setting and in patients undergoing adjuvant or neoadjuvant therapy [86-88]. Their measurement offers clinicians critical insights into treatment efficacy, recurrence risk, and the potential need for additional interventions. Understanding the molecular basis and clinical applications of CEA and AFP enhances the ability to guide follow-up care, optimize treatment, and improve patient outcomes [13,76].

CEA is a glycoprotein primarily involved in cell adhesion, typically expressed at low levels in adults but overexpressed in many CRC cases. This overexpression supports cell adhesion, facilitates metastatic potential, and increases its presence in the bloodstream due to tumor cell shedding. In a postoperative context, monitoring CEA levels is crucial [25,67]. Following curative resection, a significant decrease in CEA levels indicates the removal of the primary tumor. In contrast, stable or rising levels may suggest residual disease or early recurrence, often preceding radiographic evidence. This makes CEA a sensitive marker for early recurrence detection and for determining the necessity of adjuvant chemotherapy when recurrence risk remains high [38,60]. During adjuvant or neoadjuvant therapy, CEA levels are used to evaluate treatment response. A decrease in CEA suggests a reduction in tumor burden, indicating effective treatment, while an increase could signal resistance, necessitating a reassessment of the therapeutic approach. Thus, CEA is a dynamic marker reflecting surgical outcomes and ongoing treatment effectiveness [89-91]. AFP, another glycoprotein, is primarily produced during embryonic development by the liver and yolk sac, and its presence in adults is typically associated with liver and certain germ cell tumors. Though less commonly elevated in CRC, its presence may suggest aggressive or advanced disease, especially in cases with liver metastasis [76,83]. Elevated AFP levels may indicate poor tumor differentiation, with cancer cells retaining specific fetal-like properties and producing this protein.

AFP can complement CEA monitoring postoperatively, particularly in patients with elevated preoperative AFP. In adjuvant therapy, AFP can also be used to assess treatment efficacy in patients with metastatic disease involving the liver. A decrease in AFP may indicate treatment efficacy, while an increase may prompt a reassessment of therapeutic strategies [52,87,90]. The combined use of CEA and AFP enables a more comprehensive postoperative monitoring approach for CRC patients. Serial measurements allow for early identification of potential recurrence, as both markers provide a molecular reflection of tumor activity [86,87]. In patients who have undergone curative resection, a normalized marker level post-surgery is reassuring, whereas an increase warrants further diagnostic evaluation, such as imaging. This proactive approach supports timely intervention and better survival outcomes. Additionally, in patients undergoing adjuvant therapy, CEA and AFP levels guide therapy adjustments, reflecting the real-time impact of treatment on tumor biology [80,92]. The molecular basis for these markers' effectiveness lies in their association with tumor dynamics and disease progression. CEA's role in cell adhesion and invasion supports its elevated levels in metastatic disease, and its monitoring assists in identifying patients with microscopic residual disease [89-91]. AFP's association with aggressive disease traits provides supplementary prognostic information, particularly in cases of metastatic or liver-involved CRC.

By integrating these markers into a standardized monitoring protocol, clinicians can guide therapeutic decisions and adjust surveillance intensity based on individual risk profiles [61-63]. CEA and AFP's molecular properties and clinical applications make them indispensable biomarkers in the postoperative and therapeutic management of CRC. Their roles extend beyond mere surveillance, offering dynamic insights into tumor behavior, therapeutic efficacy, and recurrence risk [15,94]. Regular monitoring of these biomarkers and appropriate clinical responses supports a personalized, proactive approach to CRC management that prioritizes early intervention, optimal treatment adaptation, and improved patient outcomes [12,44].

Probiotics and Post-Treatment Microbiome Recovery

Dietary interventions present additional opportunities for modulating the microbiome to enhance CRC treatment response. High-fiber diets promote SCFA-producing bacteria, reducing inflammation and creating an anti-tumor environment. Such diets may complement chemotherapy and immunotherapy by cultivating a microbiota profile that supports immune activation and cancer cell death [75-77]. Reducing processed foods and red meats, encouraging pathogenic bacterial growth, may decrease resistance and improve patient outcomes. Administering probiotics and prebiotics to restore beneficial microbial populations fosters an anti-inflammatory profile and reduces CRC recurrence [24]. Novel dietary supplements like polyphenols are also being explored for their potential to modulate microbiomes and reduce inflammation, offering adjunctive benefits in CRC treatment [38]. Noninvasive interventions like exercise offer further promise for positively influencing the microbiome. Physical activity promotes microbial diversity and increases anti-inflammatory bacteria, suggesting lifestyle factors can complement CRC management, especially by enhancing immune responses and reducing inflammation [94,95]. Fecal microbiota transplantation (FMT) provides another approach to reestablish a healthy microbial community in CRC patients, counteracting dysbiosis that may contribute to treatment resistance [61,66]. While FMT has shown success in other conditions, more research is necessary to confirm its safety and efficacy in CRC patients, particularly complementing traditional cancer therapies [10].

Preventing and treating intestinal microbiota alterations to reduce the risk of colorectal cancer (CRC) involves a combination of dietary modifications, lifestyle interventions, targeted microbiota therapies, and mindful antibiotic use [39-41]. These strategies aim to maintain a balanced gut microbiome, enhance protective microbial species, and suppress the growth of pathogenic bacteria that are linked to inflammatory and carcinogenic processes. Each preventive

and therapeutic action is grounded in scientific research supporting its effectiveness in fostering a microbiome that promotes gut health and reduces CRC risk [79-82]. A primary and well-supported intervention is the adoption of a high-fiber, plant-based diet. Scientific studies have demonstrated that dietary fiber, particularly from vegetables, fruits, legumes, and whole grains, serves as a prebiotic substrate for beneficial bacteria in the gut, such as Bifidobacterium and Lactobacillus [96]. These bacteria ferment fiber to produce short-chain fatty acids (SCFAs), including butyrate, which supports gut health by providing energy to colonic cells, reinforcing the intestinal barrier, and reducing inflammation [4,58]. Butyrate has anti-carcinogenic properties, as it induces apoptosis in abnormal cells, supports immune regulation, and reduces the expression of genes associated with tumor progression [35]. A fiber-rich diet also encourages microbial diversity, an essential indicator of a healthy microbiome that can resist pathogenic invasion and maintain stable gut ecology.

Reducing the intake of red and processed meats is also crucial, as these foods produce carcinogenic compounds such as N-nitroso compounds and secondary bile acids, which can disrupt the gut microbiota and damage colonic cells [57-59]. Alongside dietary changes, probiotic and prebiotic supplementation can be beneficial in restoring and maintaining a balanced microbiome. Probiotics introduce beneficial bacteria directly into the gut, helping to replenish populations that may be depleted due to lifestyle factors, poor diet, or antibiotic use. Strains such as Lactobacillus rhamnosus, Lactobacillus acidophilus, and Bifidobacterium bifidum have been extensively studied to support gut health and immune function [93-95]. These probiotics help outcompete pathogenic bacteria, restore microbial balance, and produce metabolites that reduce inflammation and enhance gut barrier integrity. Prebiotics, which are non-digestible fibers found in foods like garlic, onions, asparagus, and bananas, serve as a food source for these beneficial bacteria, stimulating their growth and activity. Together, probiotics and prebiotics contribute to a gut environment less conducive to CRC-promoting factors, such as inflammation and dysbiosis [87-89]. Another promising intervention is fecal microbiota transplantation (FMT), which involves transferring fecal microbiota from a healthy donor to an individual with dysbiosis. FMT has shown significant efficacy in restoring microbiome diversity and has been used to treat conditions such as Clostridium difficile infections with high success rates [41-43].

Research is underway to explore its benefits for CRC prevention, especially in individuals with high-risk microbiomes characterized by inflammation and low microbial diversity [52]. By restoring a balanced microbiota, FMT can potentially prevent the progression of dysbiosis to more severe gut conditions, including CRC. However, FMT must be approached with caution, as it requires rigorous donor screening to prevent adverse effects, and more studies are needed to understand its long-term safety and efficacy in CRC prevention fully [54,76]. Mindful and limited use of antibiotics is essential to prevent microbiome disruptions that can predispose individuals to CRC. Antibiotics profoundly impact gut microbial diversity, often eradicating beneficial bacteria and enabling the overgrowth of resistant pathogenic strains [31-33]. Judicious use of antibiotics—prescribing them only when necessary and avoiding broad-spectrum antibiotics when possible—helps preserve the natural balance of gut bacteria. For individuals who must undergo antibiotic therapy, concurrent use of probiotics can help mitigate some of the adverse effects on the microbiome by replenishing beneficial bacterial populations [88-90]. Regular physical activity is also beneficial for maintaining healthy gut microbiota. Exercise has been shown to increase microbial diversity and promote the growth of beneficial bacteria such as Akkermansia muciniphila, which supports gut barrier integrity and has anti-inflammatory effects [41,93].

Physical activity is associated with increased SCFA production, which, as noted, plays a protective role against CRC by reducing inflammation and promoting cell differentiation in the colon. Exercise is also linked to enhanced immune function, preventing the proliferation of pathogenic bacteria and supporting an environment where beneficial bacteria can thrive [70-72]. Managing stress through mindfulness practices, adequate sleep, and psychological support is essential for maintaining microbiome balance. Chronic stress has been shown to alter gut motility, reduce mucosal immunity, and disrupt the gut-brain axis, leading to a microbiome environment that favors inflammation [63-65]. Stress reduction techniques such as meditation, yoga, and adequate sleep can help stabilize the microbiome by reducing cortisol levels and preventing gut barrier dysfunction. These approaches contribute to a microbiota that supports immune function and resists inflammation-driven CRC progression [58-60]. The prevention and treatment of gut microbiota alterations predisposing individuals to CRC are grounded in evidence-based interventions focusing on dietary modifications, targeted microbial support, lifestyle adjustments, and careful use of medications [26,39].

These approaches are scientifically justified as they aim to create a gut environment that fosters beneficial bacterial growth, enhances SCFA production, reduces inflammation, and strengthens the gut barrier [19,84]. By implementing these strategies, individuals may significantly reduce their risk of CRC, as a balanced and diverse microbiome is a crucial defense against inflammation, carcinogenic compound formation, and the development of colorectal cancer [40,96].

Conclusion

In conclusion, the gut microbiome is a multifaceted driver of CRC treatment resistance, impacting responses to chemotherapy, immunotherapy, targeted therapies, and the processes of angiogenesis and metastasis. Understanding these interactions through rigorous research and developing targeted interventions can reshape the CRC treatment landscape, reducing resistance and improving efficacy. Continued research into microbiome-based diagnostics and therapeutics and thoughtful evaluation of economic and ethical implications hold the promise of precision medicine in CRC. A comprehen-

sive understanding of microbiome-cancer interactions could improve patient outcomes, transforming CRC treatment into a more targeted and practical approach.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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