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#### **ABOUT COVER**

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REVIEW

## Microbiome and colorectal carcinogenesis: Linked mechanisms and racial differences

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#### Abstract

Various studies have shown the interplay between the intestinal microbiome, environmental factors, and genetic changes in colorectal cancer (CRC) development. In this review, we highlight the various gut and oral microbiota associated with CRC and colorectal adenomas, and their proposed molecular mechanisms in relation to the processes of "the hallmarks of cancer", and differences in microbial diversity and abundance between race/ethnicity. Patients with CRC showed increased levels of Bacteroides, Prevotella, Escherichia coli, enterotoxigenic Bacteroides fragilis, Streptococcus gallolyticus, Enterococcus faecalis, Fusobacterium nucleatum (F. nucleatum) and Clostridium difficile. Higher levels of Bacteroides have been found in African American (AA) compared to Caucasian American (CA) patients. Pro-inflammatory bacteria such as F. nucleatum and Enterobacter species were significantly higher in AAs. Also, AA patients have been shown to have decreased microbial diversity compared to CA patients. Some studies have shown that using microbiome profiles in conjunction with certain risk factors such as age, race and body mass index may help predict healthy colon vs one with adenomas or carcinomas. Periodontitis is one of the most common bacterial infections in humans and is more prevalent in Non-Hispanic-Blacks as compared to Non-Hispanic Whites. This condition causes increased systemic inflammation, immune dysregulation, gut microbiota dysbiosis and thereby possibly influencing colorectal carcinogenesis. Periodontal-associated bacteria such as Fusobacterium, Prevotella, Bacteroides and Porphyromonas have been found in CRC tissues and in feces of CRC patients. Therefore, a deeper understanding of the association between oral and gastrointestinal bacterial profile, in addition to identifying prevalent bacteria in patients with CRC and the differences observed in ethnicity/race, may play a pivotal role in predicting incidence, prognosis, and lead to the development of new treatments.



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**Core Tip:** In this review, we describe oral and gut microbiome associated with colorectal (CRC) carcinogenesis in relation to the "hallmarks of cancer" and microbial diversity and abundance between races/ethnicities. CRC patients showed increased levels of *Bacteroides, Prevotella, Escherichia coli,* enterotoxigenic *Bacteroides fragilis, Streptococcus gallolyticus, Enterococcus faecalis, Fusobacterium nucleatum* (*F. nucleatum*) and *Clostridium difficile.* Higher levels of *Bacteroides, F. nucleatum* and *Enterobacter* species have been found in African American (AA) compared to Caucasian American (CA) CRC patients. Also, AA patients had decreased microbial diversity compared to CA patients. Periodontal-associated bacteria, *Fusobacterium, Prevotella, Bacteroides* and *Porphyromonas,* have been found in CRC tissues and in feces of CRC patients.

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#### INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the third leading cause of cancer death[1] with higher incidence and mortality rates for African Americans (AA) among general population[2]. The incidence rates are 24% higher in Non-Hispanic (NH) black males and 19% higher in NH black females, while the death rates are 47% higher in NH black men and 34% higher in NH black women compared to NH white men and women[3]. This significant impact underscores the importance of further understanding the mechanisms and factors that influence the progression of CRC so as to alter the disease process before it has progressed to cancer or improve outcomes in those with a CRC diagnosis. The microbiome and its potential role in colorectal carcinogenesis is a newly emerging yet important field of study.

Current evidence indicates a complex interplay between the gut microbiome, genetic alterations and environmental factors. The gut microbiome is highly diverse and compared to the human genome it contains approximately 100 times the number of genes[4]. There are vast differences found in the microbiota of apparently healthy individuals. Variables such as differences in host genetics, antibiotics usage, environmental and lifestyle factors, including ethnicity, geographic location, and urbanization may modify the gut microbiome[5]. The epithelial surface and mucus layer are enriched with Clostridium, Lactobacillus and Enterococcus and the intestinal lumen is enriched with Bacteroides, Bifidobacterium, Streptococcus, Enterobacteriaceae, Enterococcus, Clostridium and Lactobacillus<sup>[6]</sup>. Certain microorganisms could protect against pathogens that promote carcinogenesis by competing for attachment sites and thus preventing the development of CRC[7]. Probiotic strains of Lactobacillus and Bifidobac*terium* are thought to play a protective role by competing for adhesion sites, secreting antibacterial peptides and displacing the enteropathogens, Salmonella typhimurium and Escherichia coli (E. coli), as demonstrated in an enterocyte-like Caco-2 cell layer[8]. In CRC patients, a significantly reduced level of Bifidobacterium has been found[7]. In contrast, several studies have reported increased levels of Bacteroides, Prevotella, E. coli, enterotoxigenic Bacteroides fragilis (B. fragilis), Streptococcus gallolyticus (S. gallolyticus), Enterococcus faecalis (E. faecalis), Fusobacterium nucleatum (F. nucleatum) and Clostridium difficile in CRC subjects[9-15]. Additional human studies also have confirmed that F. nucleatum is associated with other Gram-negative bacteria, such as Streptococcus, Campylobacter and Leptotrichia, and synergistically promotes CRC[14].

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Recent epidemiological studies have examined the association between periodontal diseases and CRC risk. Periodontitis is one of the most common bacterial infections in humans. In periodontitis, pathogenic opportunistic microorganisms in the oral cavity damage the integrity of the tooth-supporting tissues causing increased systemic inflammation, immune dysregulation, gut microbiota dysbiosis and thereby possibly influencing colorectal carcinogenesis[16,17]. F. nucleatum is one of the most prevalent species found in extra-oral sites. This bacterium regulates biofilm organization and interacts with the host cells by producing various adhesins and associates with other bacteria through cross-feeding and metabolic interactions[18]. As such, F. nucleatum has been suggested to be a "driver bacterium" with pro-carcinogenic characteristics that contribute to tumor development by facilitating "passenger bacteria" to continue the progression of CRC[19]. Periodontal-associated bacteria such as Fusobacterium, Prevotella, and Bacteroides have been found in CRC tissues[9] and Fusobacterium and Porphyromonas in feces of CRC patients[19,20]. Half of Americans age 30 or older have periodontitis and this increases to 70% for adults aged 65 years and older[7]. Moreover, the prevalence in NH blacks is 59.1% as compared to 40.8% in NH whites [7].

Race/ethnicity also has been associated with variations in microbial abundance. Analysis of the gut microbiota by 16S in 1673 participants in the United States reported 12 microbial genera and families that vary by race/ethnicity. This suggests that the gut microbiota could be inherited and associated with human genetic variation<sup>[21]</sup>. Farhana et al<sup>[22]</sup> analyzed microbial communities in colonic effluents using 16SRNA profiling from AA and Caucasian American (CA) patients scheduled for an outpatient screening colonoscopy. The results showed higher levels of Bacteroides in AAs compared to CAs. Pro-inflammatory bacteria such as F. nucleatum and Enterobacter species were significantly higher in AAs. Also, AA patients had decreased microbial diversity compared to CA patients[22]. A study conducted in Malaysia reported that Parvimonas micra, F. nucleatum, Peptostreptococcus stomatis and Akkermansia muciniphila were enriched in colon tissue of CRC patients[23]. Another study described four periodontal pathogens, Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola, and Filifactor alocis, to be more prevalent among AAs than among CAs[24]. Significant differences in oral and gut microbial diversity and abundance between AA and CA may play a role in the CRC disparity observed between the populations.

The "Hallmarks of Cancer," proposed by Hanahan and Weinburg[25] organize the fundamental processes involved in the complex progression from normal cell to a tumorigenic state within a neoplastic environment. During carcinogenesis, various changes affect the host environment processes such as cellular metabolism and immunological function. Several intestinal microbes may influence the initiation and progression of tumorigenesis by modulating host factors that comprise the hallmarks of cancer[26]. This influence may occur locally and distantly through infection and microbial products, by changing the metabolism of the products produced by host and microbes or by modulating tumor immunosurveillance, which in turn alters the balance between the rate of cell proliferation and apoptosis, triggering chronic inflammation and immunosuppression[27].

Here, we summarize the current knowledge on how specific members of the microbiota and their bacterial machinery influence the hallmarks of cancer in the initiation and progression of CRC (Table 1). Each listed bacterial species is systematically presented according to the following scheme: (1) Tumor-promoting inflammation; (2) Avoiding immune destruction; (3) Deregulating cellular energetics; (4) Sustaining proliferative signaling; (5) Inducing angiogenesis; (6) Resisting cell death; and (7) Genome instability and mutations.

#### TUMOR-PROMOTING INFLAMMATION

A progressive interplay between tissue cells, microbiota and immune cells has been described. T and B cells present in the intestinal mucosa have location-specific phenotypes and functions that can be modified by the microbiota[28]. Commensal microbiota can modulate innate immune cells to release pro-inflammatory cytokines such as interleukin 6 (IL-6), IL-23 and IL-1β, which stimulate the expansion of Thelper-17 (Th17) cells. Th17 cells are a unique CD4<sup>+</sup>T-helper subset that secrete the cytokine IL-17. IL-17 increases Paneth cell production of anti-microbial peptides and promotes inflammation by the recruitment of polymorphonuclear neutrophils from the bloodstream[29]. Th17 have pro-tumorigenic effects and it has been associated with worse prognosis in CRC, as shown in Figure 1[30]. While Th17 immune



#### Table 1 Gut and gastric microbiota associated with cancer development

Gut bacteria	Bacterial machinery	Hallmarks of cancer including enabling characteristics	Outcome	Methods	Ref.
		affected			
Fusobacterium nucleatum	FadA	Tumor-promoting inflammation	Expression of NF-кВ and pro- inflammatory cytokines IL-6, 8, and 18	HCT116 cells (expressing E-cadherin)	[56, 57]
	Unknown	Tumor-promoting inflammation	Infiltration of specific myeloid cell subsets and an NF-ĸB proinflammatory signature (shared with human CRC tissue with a high Fusobacterium abundance)	Apc(Min/+) mice fed <i>F. nucleatum</i>	[39]
	Unknown	Tumor-promoting inflammation	TNF- $\alpha$ and IL-10 abundance	Rectal biopsies of adenoma cases compared to controls	[59]
	Unknown	Tumor-promoting inflammation	Cytokine production, which is mediated by the p38 MAPK signaling but independent of TLRs, NOD-1, NOD-2 and NF- ĸB signaling	HEK293T cells, (which lack endogenous TLRs)	[58]
	Fap2	Avoiding immune destruction	Fap2 interacted with TIGIT, leading to the inhibition of NK cell cytotoxicity	Various BW cells	[31]
	Unknown	Avoiding immune destruction	MicroRNA-21 increases the levels of IL-10 and prostaglandin E2, which suppress antitumor T-cell- mediated adaptive immunity	Colorectal carcinoma tissues (stages I- IV) from Japanese patients	[66]
	Generation of formyl- methionyl-leucyl- phenylalanine and SCFAs from dietary amino acids	Deregulating cellular energetics	Chemoattract myeloid cells	ApcMin/+ mouse model of intestinal tumorigenesis	[ <mark>39</mark> ]
	Adhesin FadA	Sustaining proliferative signaling	FadA binds to E-cadherin and activates β-catenin signaling	HCT116 cells (expressing E-cadherin)	[ <mark>56</mark> ]
	Unknown	Genome instability and mutations	CpG island methylating phenotype (CIMP), microsatellite instability (MSI), and MLH1 hypermethylation	Colorectal carcinoma tissue	[82]
Streptococcus galloyticus (S. bovis)	Unknown	Tumor-promoting inflammation	Increase in the production of IL- 8 in the colonic mucosa. Study suggests that bacteria act as a promoter of early preneoplastic lesions in the colon of rats	Male rats pre-treated with the carcinogen azoxymethane (AOM)	[64]
	Unknown	Tumor-promoting inflammation	Induce mRNA expression of proinflammatory cytokines, IL-1	Colorectal mucosa and tumors of CRC patients with and without a history of <i>S. gallolyticus</i> bacteremia in the last 2 years	[87]
	Wall extracted antigens (WEA) and whole bacteria	Sustaining proliferative signaling	MAPKs activation which up- regulate the expression of COX- 2	Human colonic epithelial Caco-2-cells	[ <mark>36</mark> ]
	Unknown	Inducing angiogenesis	Induce mRNA expression of angiogenic chemokine, IL-8	Feces and colorectal tissue of CRC patients with and without a history of <i>S. gallolyticus</i> bacteremia in the last 2 years	[87]
	WEA and whole bacteria	Inducing angiogenesis	Over-expression of COX-2	Human colonic epithelial Caco-2-cells	[ <mark>36</mark> ]
	Unknown	Resisting cell death	mRNA expression of proinflammatory cytokines, IL-1 and COX-2, as well as angiogenic chemokine, IL-8	Feces and colorectal tissue of CRC patients with and without a history of <i>S. gallolyticus</i> bacteremia in the last 2 years	[87]
	Unknown	Resisting cell death	Higher IL-8 mRNA and NF-ĸB mRNA in tumorous than non-	Serum and tissue of CRC, CRA and healthy volunteers	[ <mark>88</mark> ]



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			tumorous tissue sections of adenoma and carcinoma.		
	WEA and whole bacteria	Resisting cell death	Over-expression of COX-2	Human colonic epithelial Caco-2-cells	[ <mark>36</mark> ]
Enterotoxigenic Bacteroides fragilis	<i>B. fragilis</i> toxin (BFT)	Tumor-promoting inflammation	Activation of STAT3 initiates a Th17 mucosal immune response	ApcMin/+ mouse model of intestinal tumorigenesis	[ <mark>53</mark> ]
	BFT	Sustaining proliferative signaling	E-cadherin cleavage then β- catenin nuclear signaling is expressed and induces c-Myc translation	HT29/C1 cells	[94]
	BFT	Sustaining proliferative signaling	Induces E-cadherin cleavage, interleukin-8 secretion, and epithelial cell proliferation	Specific pathogen-free (SPF) C57BL/6J or germfree mice	[74]
	BFT	Genome instability and mutations	NF-кB and mitogen-activated protein kinases (MAPKs)	HT29/C1 cells	[ <mark>94</mark> ]
	BFT	Genome instability and mutations	SMO-dependent generation of ROS and induction of γ-H2A.x, a marker of DNA damage	HT29/c1 and T84 colonic epithelial cells	<b>[98]</b>
E. coli	Cyclo-modulins (CM)	Sustaining proliferative signaling	Increases in proliferating cell nuclear antigen (PCNA) mRNA levels	CEACAM-expressing mice	[80]
	Colibactin-producing (pks+)	Sustaining proliferative signaling	Accumulation of SUMO- conjugated p53 and production of hepatocyte growth factor (HGF) by targeting targets SENP1 (senescence-associated secretory phenotype)	AOM/IL-10-/- (azoxymethane/interleukin) mouse model	[ <mark>81</mark> ]
	СМ	Genome instability and mutations	genotoxin-encoding genes in mucosa	Analysis of mucosa of patients with CRC	[ <b>79</b> ]
Enterococcus fecaelis	Unknown	Genome instability and mutations	Macrophage COX-2 is induced by superoxide and propagate genomic instability	Hybrid hamster cells [A(L)N] containing human chromosome 11 and a dual-chamber tissue culture model	[ <mark>100</mark> ]
	Enterococcus faecalis-infected macro-phages, or purified trans-4-hydroxy-2-nonenal (4-HNE)-an endogenous mutagen and spindle poison produced by macrophages	Genome instability and mutations	Double-stranded DNA breaks, tetraploidy and chromosomal instability (CIN)	Primary murine colon epithelial cells growth as allografts in immunodeficient mice	[ <del>99</del> ]
	Unknown	Genome instability and mutations	Epithelial cell DNA damage through the production of extracellular O <sup>2-</sup>	HT-29 intestinal epithelial cells and a rat intestinal colonization model	[12]
H. pylori	cagA	Tumor-promoting inflammation	Upregulation of COX-2 and prostaglandin E2	Analysis of serum IgG antibodies against <i>H. pylori</i> (ELISA) and cagA protein (Western blot assay) in patients with colon cancer	[ <mark>62</mark> ]

COX-2: Cyclooxygenase-2; H. pylori: Helicobacter pylori; CIN: Chromosomal instability; CRC: Colorectal cancer; HGF: Hepatocyte growth factor; BFT: Bacteroides fragilis toxin; CM: Cyclo-modulins; SATA3: Signal transducer and activator of transcription 3; MSI: Microsatellite instability; PCNA: Proliferating cell nuclear antigen; TLRs: Toll-like receptors; cagA: Cytotoxin-associated gene; S. gallolyticus: Streptococcus gallolyticus; S. bovis: Streptococcus bovis.

> responses promote tumor development, other cytotoxic immune cells, such as natural killer (NK) and CD8+ T cells, are essential for recognizing and eliminating cancer cells [31].

> One commonality across many diseases in which microbiota contribute to progression is the disruption of the mucosal/epithelial layers of organs, allowing bacteria and their metabolites to enter compartments that are not normally in close proximity to microbes[32]. This can trigger a local chronic inflammatory response, due to perpetually injured tissues and thus a constant stream of infiltrating microbes/ microbial products. Resident commensal bacteria may trigger exaggerated immune responses (colitis) when key components of immune tolerance are broken and/or modify the general immune response upon entering systemic circulation[33-35]. Such disruption may allow some non-native bacterial species to colonize the gut and adapt to the new environment, including oral bacterium. For example, Fusobacterium, Peptostreptococcus, and Lactococcus access and adhere to the basement membrane of the

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Figure 1 Tumor-promoting inflammation. TLRs: Toll-like receptors; BFT: Bacteroides fragilis toxin; MAPK: Mitogen-activated protein kinase; ETBF: Enterotoxigenic Bacteroides fragilis; IL: Interleukin; TNF-a: Tumor necrosis factor a; COX-2: Cyclooxygenase-2; SATA3: Signal transducer and activator of transcription 3; Th17: T-helper-17.

gut in setting of CRA and CRC[9].

F. nucleatum is an obligate anaerobic gram-negative bacteria commonly present in the mouth and typically a poor colonizer of healthy and intact intestinal mucosa[9]. Elevated F. nucleatum colonization in the normal tissues may predispose to the development of colorectal adenoma (CRA). Its virulence factor FadA adhesion gene ( fadA) has been found in the colon tissue from patients with CRA and CRC in > 10-100 times higher compared to healthy individuals[36]. Other studies using metagenomic and transcriptomic analyses also have shown an enrichment of Fusobacterium species in CRA compared with adjacent normal tissue[7,37-39]. Infections of Streptococcus galloyticus (S. galloyticus) have been associated with CRC and CRA. S. galloyticus, formerly known as Streptococcus bovis (S. bovis), bacteremia has been associated with colon cancer in 25% to 80% of cases and S. galloyticus endocarditis has been associated with colon cancer in 18% to 62% of cases [11,40-45]. S. galloyticus has shown a specific association with CRC and CRA when compared with the more dominant intestinal bacteria, B. fragilis[46]

Enterotoxigenic Bacterioides fragilis (ETBF) is an anaerobic gram-negative rod that is known to have an affinity for colonizing the colonic mucosa[47]. Asymptomatic carriage can be seen in up to 40% of healthy children and adult fecal samples[48]. The pathogenicity of ETBF is a result of the B. fragilis toxin (BFT), which has 3 isotypes (BFT-1, BFT-2, BFT-3). BFT-1 is believed to more commonly colonize stool and BFT-2 more commonly colonizes the mucosa[49]. An association between ETBF and CRC is emerging. ETBF enhances Th17-driven inflammation and colonic tumor development. *B. fragilis* preferentially colonize the epithelial crypts of the colonic mucosa and thus evade the host immune response leading to a more stable colonization in CRC[10,50]. In general, ETBF in CRC patients has been more commonly found on the colonic mucosa as opposed to stool samples<sup>[51]</sup>. It has been hypothesized that the human colon's exposure to BFT may lead to a chronic, possibly focal, inflammation of colonic



mucosa thus creating sites susceptible to carcinogenesis. BFT induces both acute and chronic colitis and carcinogenesis mediated by IL-17[52]. In multiple intestinal neoplasia (Min) mice, Wu *et al*[53] described a signal transducer and activator of transcription 3 that led to a pro-carcinogenic Th17-dependent pathway for inflammation-induced cancer by *ETBF*.

Some bacterial species, such as *Proteobacteria*, *E. coli* and *Bacteroides thetaiotamicron*, have evolved to survive amidst harsh conditions of immune activation[54,55]. *E. coli*, which is benign under homeostatic conditions, possesses a significant growth advantage as it utilizes inflammatory nitric oxides as an energy source[54]. In the absence of IgA, the commensal bacterium *Bacteroides thetaiotaomicron* expresses high levels of gene products that are involved in the metabolism of nitric oxide and generates pro-inflammatory signals in the gut[55].

*F. nucleatum* is capable of affecting both innate and adaptive immune responses[7]. *F. nucleatum* enhances inflammation through engagement of its adhesin FadA. The host endothelial receptor for FadA is the vascular endothelial cadherin (CDH5), which is a member of the cadherin family[15]. FadA adheres to and invades epithelial and endothelial cells and activates inflammatory cytokines (IL-6, IL-8, IL-10, IL-18, TNF- $\alpha$  and NF- $\kappa$ B levels) that create a pro-inflammatory environment which accelerates the progression of CRC (Table 1)[15,56,57].

Within the host cytoplasm, F. nucleatum may release its RNA, leading to detection by cytosolic retinoic acid-inducible gene I (RIG-I), a cytosolic pattern recognition receptor (PRR) responsible for the type-1 interferon (IFN1) response, thereby stimulating cytosolic NF-kB and promoting inflammation. It generates a pro-inflammatory microenvironment outside the tumor cell through recruitment of tumor-infiltrating immune cells as the primary mechanism[15]. The ability of F. nucleatum to invade HEK293T cells, human embryonic kidney cells, which lack endogenous Tolllike receptors, allows the bacteria to activate a pro-inflammatory response through cytosolic pattern recognition receptors, NOD-1, NOD-2 and NF-кВ signaling. This proinflammatory response is mediated by the p38 MAPK signaling pathway[58]. In a mouse model of intestinal cancer, introduction of F. nucleatum to ApcMin/+ mice resulted in accelerated small intestinal and colonic tumorigenesis, infiltration of specific myeloid cell subsets into tumors, and an NF-KB proinflammatory signature. This proinflammatory signature is shared with human CRC tissues with a high Fusobacterium abundance[39]. Additionally, a positive correlation has been found between the bacterial concentration in human tissues, for adenoma and non-adenoma controls, and TNF- $\alpha$  and IL-10 abundance [59]. Unlike other bacteria associated with CRC, however, F. nucleatum does not exacerbate colitis, enteritis, or inflammation-associated intestinal carcinogenesis. This suggests that F. nucleatum may drive non-colitis-associated intestinal tumorigenesis (Table 1).

Helicobacter pylori (H. pylori) is a small, spiral, gram-negative bacillus that has a wellestablished association with the development of gastric cancer and is considered a carcinogen by the World Health Organization[60]. There are conflicting data on the correlation of *H. pylori* as an etiological factor of CRC. The production of oxidative stress involves alteration of the intragastric environment through bacterial and neutrophilic production of ROS, pro-inflammatory cytokines, and upregulation of cyclooxygenase-2 (COX-2)[61]. This includes excessive production of ROS by neutrophils in an effort to eradicate the bacteria. The bacterial infection causes inflammation, leading to increased production and activity of COX-2 and prostaglandin E2, a biomarker associated with inflammation and CRC risk. Some evidence has been reported to support a potential association between H. pylori and CRC. Shmuely et al[62] described that cag-positive *H. pylori* strains were associated with a 10.6-fold increased risk of CRC compared to cagA negative strains. A systematic review with a meta-analysis found a moderate correlation between *H. pylori* infection and the risk of CRC[63]. Further investigations should be conducted to determine the role of cagA, and the mechanism by which H. pylori induces gastric carcinogenesis and potentially CRC.

*S. gallolyticus* produce a similar effect as *H. pylori. In vitro* experiments have shown that the binding of *S. gallolyticus* to intestinal cells leads to production of cytokines[36, 46,64]. It has been described that treatment with *S. bovis* or wall-extracted antigens in adult rats promoted the progression of preneoplastic lesions through the increased formation of hyperproliferative aberrant colonic crypts, and increased the production of IL-8 in the colonic mucosa[64].

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#### AVOIDING IMMUNE DESTRUCTION

F. nucleatum directly interacts with the host immune system. Fap2, an autotransporter domain found in the bacterial outer membrane protein, facilitates F. nucleatum to adapt to different body habitats. In the oral cavity, Fap2 attaches to neighboring bacteria by co-adhering to different microorganisms, increasing the diversity and the stability of the developing dental biofilm[65]. Fap2 protein adhesion directly interacts with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) expressed in tumor-infiltrating lymphocytes, leading to the inhibition of NK cell cytotoxicity (Figure 2)[31]. TIGIT is an inhibitory receptor present on human NK cells and on various T cells. The interaction between F. Nucleatum, Fap2 and TIGIT induces lymphocytes apoptosis and generates an immuno-suppressive microenvironment that promotes the progression of colorectal tumors[15]. Fap2 protein is believed to directly interact with TIGIT, leading to the inhibition of NK cell cytotoxicity[31]. These results identify a bacterium-dependent, tumor-immune evasion mechanism in which tumors exploit the Fap2 protein of *F. nucleatum* to inhibit immune cell activity via TIGIT[31]. Several clinical and animal studies have correlated the abundance of *F. nucleatum* with suppression of antitumor T cell response by affecting the enhancement of myeloid-derived suppressor cells and tumor-associated macrophages (Table 1).

Furthermore, various microRNAs are induced during the macrophage inflammatory response and modulate host-cell responses to pathogens. MicroRNA-21 increases the levels of IL-10 and prostaglandin E2, which suppress antitumor T-cellmediated adaptive immunity through the inhibition of the antigen-presenting capacities of dendritic cells and T-cell proliferation in CRC cells (Figure 2). F. nucleatum can expand myeloid-derived immune cells, which inhibits T cell proliferation and activation resulting in tumor cell growth by blocking the middle (G1) phase of the cell cycle and attracting myeloid-derived suppressor cells to the tumor site. F. nucleatum also induces T-cell apoptosis in CRC (Table 1)[66].

#### DEREGULATING CELLULAR ENERGETICS

Fermentation of dietary fibers leads to the production of short-chain fatty acids (SCFAs), such as butyrate, which serve as the primary energy source for intestinal cells (Figure 3). The presence of butyrate has an anticancer effect by starving cancer cells. Additionally, it produces epigenetic modifications by inhibiting cell proliferation and promoting apoptosis by inhibiting histone deacetylase[67]. Non-cancerous colonocytes utilize butyrate as their primary energy source in contrast with CRC cells which primarily use glucose and undergo increased glycolysis, a phenomenon known as the Warburg effect or aerobic glycolysis, decreasing mitochondrial oxidative metabolism [55,68].

Fusobacteria species also participate in the metabolism of amino acids ingested in the diet, generating formyl-methionyl-leucyl-phenylalanine and SCFAs that chemoattract myeloid cells. This explains the intratumoral expansion of myeloid cells that interconnect tumor, bacterial and immune cells metabolism (Table 1)[39]. In addition, F. nucleatum is an asaccharolytic bacterium, a competitive advantage in the tumor milieu; therefore, it will not compete for glucose, a preferred substrate for tumor metabolism[69].

Some bacterial communities could protect intestinal cells from inflammation and tumorigenesis. SCFAs function as signaling molecules between gut epithelia and immune cells modulating changes in the gene expression and providing nutrition to colonocytes. The three major SCFAs produced by bacterial fermentation of carbohydrates are acetate, propionate, and butyrate<sup>[70]</sup>. Published evidence supports the idea that butyrate is tumor-suppressive by inhibiting the proliferation of CRC cell lines while stimulating their apoptosis and/or differentiation (Figure 3)[40,54,55]. A Western diet slows mucus growth rate and increases penetrability of the colonic mucus barrier, and this effect co-occurs with the shifts in microbial community characterized by gradual decrease of SCFA-producing bacteria, such as Bifidobacterium and Bacteroidales family and increases in Firmicutes[71].

A higher prevalence of Fusobacterium and Porphyromonas in feces of CRC patients has been reported [19,20]. An increase in glutamate levels by 76% in fecal samples from colon cancer patient samples was reported but there was no increase in glutamine levels. The authors hypothesized that tumor cells may exhibit an increase of glutaminase activity, which results in the conversion of glutamine to glutamate. This





Figure 2 Avoiding immune destruction. TIGIT: T-cell immunoglobulin and ITIM domain; NK: Natural killer.

supports the theory of the role of certain bacteria as "driver bacteria" with procarcinogenic characteristics that contribute to tumor development and then a transition to "passenger bacteria" that contribute to an environment conducive to cancer<sup>[19]</sup>.

Hester et al[72] compared bacteria and SCFA in stool samples of AA and CA in a small pilot study. They found lower acetate, butyrate, total SCFA content and a higher pH in AA compared to the other racial groups. Similar results reported in another study where AA had increased levels of SCFAs in stool than other racial/ethnic groups and significantly lower intake of non-starchy vegetables[73]. Wnt/B-catenin signaling plays a fundamental role in several biological processes such as development and cell proliferation related to tumorigenesis. Butyrate has beneficial effects in reducing colon cancer risk with anti-inflammatory, immunomodulatory effects and down regulating Wnt signaling, which inhibits cell proliferation and migration. In addition, AA had higher levels of Firmicutes bacteria compared to CA and Hispanics. Moreover, the ratio of Firmicutes compared to Bacteriodes, which has been associated with obesity, was higher in AA. These results continue to suggest that AA have higher risk of developing colon cancer[72].

#### SUSTAINING PROLIFERATIVE SIGNALING

E-cadherin is a type of cell adhesion molecule and usually is targeted by various intestinal bacteria promoting epithelial proliferation by activating the Wnt/ $\beta$ -catenin pathway. ETBF, an enterotoxin-producing bacterium, is involved in the initiation and progression of CRC by not only modulating the mucosal immune response, but also inducing epithelial cell changes. BFT promotes cleavage of E-cadherin (Table 1). This produces nuclear translocation of β-catenin and subsequent transcription of the c-Myc proto-oncogene causing hyperplasia due to proliferation of colonocytes[74]. After treatment of HT29/C1 human colon cancer cells with BFT, cleavage of membraneassociated E-cadherin and loss of intercellular adhesion occurs. This in turn leads to subsequent expression of β-catenin nuclear signaling and induction of c-Myc translation resulting in persistent cell proliferation[75]. The presence of ETBF may contribute to chronic colon diseases, including oncogenic transformation, intestinal inflammation, chronic colonic dysfunctions, and colorectal precancerous and cancerous lesions[75].



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Figure 3 Deregulating cellular energetics. SCFAs: Short chain fatty acids.

The mucosa associated/internalized E. coli have been shown to occur more frequently in patients with CRC than healthy controls[76-78]. Pathogenic E. coli produces virulence factors called cyclomodulins (CM). These CMs can modulate cell cycle progression, apoptosis, cell differentiation, and proliferation (Table 1)[79,80].

Senescent cells secrete growth factors that increases cell proliferation resulting in tumor growth. Colibactin-producing (pks+) E. coli promote CRC cancer in a murine AOM/IL-10-/-(azoxymethane/IL) mouse model by expression of SENP1, microRNA-20a-5p, hepatocyte growth factor (HGF) and phosphorylation of HGF receptor. In addition, senescence-associated secretory phenotype induces epithelial cell proliferation via the production of growth factors by senescent cells. SENP1 downregulation and p53 SUMOylation are key features of pks+ E. coli-induced senescence as result of modifying p53 function[81].

F. nucleatum has shown a propensity to adhere to mucosa enabling it to invade human epithelial and endothelial cells[7]. The percentage of F. nucleatum-enriched CRC gradually increases from rectum to cecum, suggesting that the rate of bacteria proliferation differs among the intestinal sites [82]. F. nucleatum enhances epithelial proliferation through engagement of its adhesin FadA. FadA modulates E-cadherin, a tumor suppressor gene, and activates  $\beta$ -catenin signaling, leading to increased expression of oncogenes, Wnt genes, and inflammatory genes as well as growth stimulation of CRC cells (Figure 4 and Table 1)[56]. The FadA binding site on Ecadherin has been mapped to an 11-amino-acid region. The experimental use of an 11amino-acid inhibitory synthetic peptide has been shown to inhibit F. nucleatum from binding and invading the epithelial cells and abolishing all subsequent host responses, including tumor growth and inflammatory responses (Table 1)[56].

S. gallolyticus-induced mucosal inflammation may lead to enhanced mucosal permeability and increased entry for S. gallolyticus into colonic cells. S. gallolyticus in vitro also has shown strong adherence to the proteins of the extracellular matrix, collagen I, collagen II and collagen IV, enabling it to have easy entry into cells and successfully colonize both colonic and vascular tissues [46,83]. S. gallolyticus is able to grow in bile and can easily bypass the hepatic reticulo-endothelial system and access the systemic circulation[84]. S. gallolyticus endocarditis infections also have been associated with increased hepatic dysfunction[85]. It is hypothesized that underlying colonic disease or S. gallolyticus's effects on the liver's production of immunoglobulins

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Figure 4 Sustaining proliferative signaling.

and bile acids may promote S. gallolyticus overgrowth and thus altering the colonic microbiome[85]. Although the mechanism is unclear, S. gallolyticus whole bacteria and wall extracted antigens have shown greater propensity towards colonizing colonic tumor cells compared to normal mucosa (Table 1)[36]. S. gallolyticus also may induce uncontrolled cell proliferation by triggering proteins known as mitogen activated protein kinases that promote cellular transformation and genetic mutations[36].

#### INDUCING ANGIOGENESIS

S. gallolyticus is believed to promote the advancement of preneoplastic lesions to neoplastic lesions through the increased formation of aberrant colonic crypts that show increased expression of cytokines such as IL-8 (Table 1)[64]. IL-8 is a cytokine that stimulates angiogenesis which in turn also may promote carcinogenesis[86]. The pattern of IL-8 mRNA expression in the tumor microenvironment may function as a significant regulatory factor rather than a promoter for the adenoma progression and the adenoma-carcinoma transition. This might be attributed to the angiogenic role of IL-8 by which new blood vessels are formed to meet the increasing demands of cancer growth[46]. Moreover, S. gallolyticus-induced overexpression of COX-2 via prostaglandins acts as a promoter of carcinogenesis by inducing angiogenesis[36].

#### **RESISTING CELL DEATH**

S. gallolyticus plays an essential role in the oncogenic progression through different factors that cause an anti-apoptotic effect in colorectal mucosa as shown in Figure 5. In Abdulamir et al[46], S. gallolyticus appeared to induce mRNA expression of proinflammatory cytokines, IL-1 and COX-2 which induce transformation of normal or premalignant colorectal tissues into malignant status. After analysis of mRNA expression of the oncogene c-Myc and antiapoptotic Bcl-2 were not linked to



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Figure 5 Resisting cell death. WEA: Wall extracted antigens; PGE2: Prostaglandin E2; IL: Interleukin; COX-2: Cyclooxygenase-2.

colonization by these bacteria, but were associated with CRC transformation. These results may suggest that S. gallolyticus does not induce oncogenic changes or suppress cellular apoptosis, and might instead have a role as a propagator for premalignant or oncogene-positive tissues to enter the transformation cycle through inflammatory and angiogenic microclimates (Table 1)[87]. The release of PGE2-mediated by S. gallolycticus is correlated with the overexpression of COX-2, which is seen in about 85% of colon cancers, and through its association with enhanced angiogenesis and inhibition of apoptosis, is favorable to the development and progression of CRC[36]. In addition, this group also found S. gallolyticus-seropositive CRC patients were significantly associated with higher mRNA expression of both NF-kB and IL-8 that play an integrated role in a series of steps to escape cell death signals[88].

#### GENOME INSTABILITY AND MUTATIONS

A study comparing microbiota from more than 1000 fecal samples including 416 pairs of twins identified numerous microbial taxa whose abundance was influenced by host genetics. In the case of monozygotic twins, a more similar microbiota was observed than in dizygotic twins. However, it is unclear whether the host's genetic variation shapes and interacts with the gut microbiome to affect the host's phenotype[89]. The analysis of gut microbiota in stool of 2084 participants in the Healthy Living in an Urban Environment Study described that people who live in the same city tend to show similar gut microbiota with other people of their ethnic origin[90]. Ethnic differences in alpha diversity and inter-individual differences were independent of metabolic health and were only partially explained by ethnic characteristics, including sociodemographic, lifestyle, or dietary factors. Therefore, the ethnicity of individuals may be an important factor to consider in the research of microbiome and cancer CRC [90]

Sulfidogenic bacteria, such as Fusobacterium, Desulfovibrio and Bilophila wadsworthia, have been implicated in CRC development through the production of hydrogen sulfide (Figure 6)[91]. Hydrogen sulfide is a genotoxic compound that has been shown to damage DNA leading to genomic or chromosomal instability (CIN), effecting DNA repair in a multistep carcinogenic process. One hypothesis is that hydrogen sulfide diffuses into intestinal epithelial cells and interferes with mitochondrial function, ultimately leading to hyperproliferation via the Ras/MAPK pathway[92]. The hyperactivation of the Ras/MAPK pathway is a known mechanism of carcinogenesis in CRC. A study described the concentration of specific bacterial DNA in colonic tissue biopsies, and showed that AA with CRC had higher concentrations of sulfidogenic





Figure 6 Genome instability. Colibactin is a genotoxin associated with particular strains of Escherichia coli. Sulfidogenic bacteria referred to in this diagram are Fusobacterium, Desulfovibrio and Bilophila wadsworthia. ROS: Reactive oxygen species; RNS: Reactive nitrogen species; H<sub>2</sub>S: Hydrogen sulfide; CIN: Chromosomal instability; BFT: Bacteroides fragilis toxin; MSI: Microsatellite instability; MAPK: Mitogen-activated protein kinase; COX-2: Cyclooxygenase-2.

bacteria compared to NH whites. At the same time, AA with CRC had increased levels of sulfidogenic bacteria compared to AA without CRC[93].

Some bacterial products, such as colibactin or BFT, may damage the genetic information inside the nucleus, and actively induce DNA damage in organs that are in direct contact with the microbiome (Figure 6 and Table 1)[94]. These genotoxins may directly promote the release from macrophages and other inflammatory cells of reactive oxygen species (ROS), reactive nitrogen species (RNS) and hydrogen sulfide (H<sub>2</sub>S) from the bacterial microbiota products [95]. ROS and RNS inhibit the activity of T cells, including antitumor cytolytic CD8+ T cells. An abundance of myeloid-derived suppressor cells also leads to increased production of ROS and RNS and subsequent tumor-supporting inflammation and neoangiogenesis<sup>[70]</sup>. Hydrogen sulfide has been shown to damage DNA leading to genomic or CIN, affecting DNA repair in a multistep carcinogenic process. One hypothesis is that hydrogen sulfide diffuses into intestinal epithelial cells and interferes with mitochondrial function, ultimately leading to hyperproliferation via the Ras/MAPK pathway[92]. Furthermore, metabolic actions of the microbiome may promote the development of CRC by activation of other genotoxins such as acetaldehyde, dietary nitrosamine and other carcinogens[95].

As shown in Figure 6, various gut microbes and their bacterial products can cause DNA mutations. E. coli contribute to the accumulation of mutations resulting from DNA damage induced by genotoxins, or by downregulating host DNA mismatch repair proteins (Table 1)[96]. One cyclomodulin is a hybrid polyketidenonribosomal peptide called colibactin, encoded by the polyketide synthase (pks) genomic island. Colibactin possesses genotoxic properties that result in CIN and double-strand breaks in the DNA of human eukaryotic cells. E. coli strains harboring the pks genotoxic island, which are found in a significantly high percentage of inflammatory bowel disease and CRC patients<sup>[79]</sup>. In vitro studies using different mammalian cells, including normal intestinal cells, showed that pks+ E. coli produce DNA double-strand breaks affecting the normal cellular division with the consequent cell cycle arrest and aneuploidy[97]. Conversely, different commensal bacteria could harm DNA strands by stimulating host inflammation and producing a pro-oxidant microenvironment. ETBF causes DNA damage by peroxide that comes from the colonocyte expression of enzyme spermine oxidase[98].

E. faecalis may have a microbiome driven bystander effect that leads to increased COX-2 expression in macrophages leading to ROS formation, which in turn promotes CIN in intestinal epithelial cells. Primary colonic epithelial cells can have induction of CIN or malignant tumor aneuploidy via macrophages that have been polarized by E. faecalis[99]. These results validate a novel mechanism for CRC that involves endogenous CIN and cellular transformation arising through a microbiome-driven bystander effect (Figure 6)[100].



Enterococci have increasingly been shown to cause infections in the elderly. They are gram positive, facultative anaerobe, diplococci that grow as short chains. E. faecalis has been found to aggregate at higher levels in stool samples in CRC patients than in healthier controls [101,102]. It also has been shown to be in greater abundance in the adjacent tissues of CRC when compared to healthy mucosa in controls[103]. It has been postulated that *E. faecalis* can damage colonic DNA and cause genomic instability via its ability to generate ROS that predisposes to mutations leading to CIN and subsequent carcinogenesis (Figure 6)[12].

A large abundance of F. nucleatum has been shown to induce a series of tumorspecific molecular events, including the CpG island methylating phenotype (CIMP), microsatellite instability (MSI), and genetic mutations in BRAF, CHD7, CHD8 and TP53. A higher abundance of F. nucleatum DNA in CRC tissues has been associated with an increased CRC-specific mortality, evidence that suggests F. nucleatum may potentially serve as a prognostic biomarker (Figure 6)[82].

Several etiological mechanisms of H. pylori in CRC pathology have been hypothesized. One alternative is that chronic *H. pylori* infection can lead to hypergastrinemia, which is considered to be a nutrient factor in the colorectal mucosa and may lead to the promotion of mutagenesis. In addition, this bacterial infection and bacterial CagA protein lead to chronic gastritis with an increase in gastrin production (Figure 6) [62]. Ammonia produced by *H. pylori* might also act as an endogenous carcinogen. More studies are needed to investigate the potential role of gastrin in the mechanisms of metastasis of the tumor cells[63].

#### CONCLUSION

In this review, we highlight the various gut and oral microbiota associated with CRC and CRA, and their proposed molecular mechanisms in relation to the processes of "the hallmarks of cancer." Common oncogenic mechanisms include disruption of mucosal/epithelial layer of organs, promotion of inflammation and neoangiogenesis, use of genotoxins by bacteria, altering of genetic expression, and modification or weakening of the existing immune system.

To understand whether host genetics play a role in the associations between race/ethnicity, and oral and gut microbiota, it is essential to perform genome-wide association studies with microbial data among diverse populations. In 2016, 81% of existing genome-wide association study data was generated from individuals of European descent where the proportion of samples from individuals of African descent only increased by 2.5% and that of ancestry Hispanic or Latin American by about 0.5% [104]. There are huge gaps in knowledge related to understanding the underlying causes of racial/ethnic differences in the gastrointestinal microbiota and their possible role in colon cancer. Therefore, it is essential to be able to generate new knowledge by generating large and representative cross-sectional studies with gut, oral and fecal samples in populations that include individuals with various social determinants of health (for example, NHANES). Variables that could cause these racial/ethnic differences, such as diet, habits, socioeconomic status and oral health status should also be further studied. Genetic factors may contribute to biological reasons for CRC disparity. Diverse studies described somatic alterations in wellknown CRC genes (APC, BRAF, KRAS, and PIK3CA) and lower frequency of MSI, a good prognostic biomarker, among AA patients[105,106]. F. nucleatum levels have been found to be significantly higher in AAs[22] and has been shown to induce a series of tumor-specific molecular events, including CIMP, MSI, and genetic mutations in oncogenes and tumor suppressors[82].

Differences in the immunological profiles of colon tumors from AA compared to CA suggested a deficiency of appropriate immune defense mechanisms in terms of gene expression, recruitment of immune cells and systemic secretion of cytokines. As such, these immune differences could be mitigated through population-specific therapeutic approaches[106]. Studies of associations between specific taxa in microbiome and race/ethnicity could provide an insight for examining specific bacterial members as mediators of health disparities. Defining the composition of a "healthy microbiota" is one of the challenges in the field of microbiome research. Our review reveals that unique opportunities exist in targeting racial/ethnic differences in oral and gut microbiome for a greater understanding of the complexity of CRC and CRA etiology and carcinogenesis.

As knowledge is gained regarding the microbiome as it pertains to CRC, the clinical implications will continue to grow and hopefully come to the forefront in the



prevention, detection, and treatment of CRC in clinical practice. Current non-invasive screening methods for CRC include FIT and Cologuard. However, their ability to detect precancerous lesions is not entirely reliable, thus creating a void for superior noninvasive screening methods that microbiome studies could likely one day fill[107]. When combining testing for oral bacteria *F. nucleatum* with FIT, the combination showed superior sensitivity than FIT alone in detecting CRC, and additionally increased the performance of adenoma detection, suggesting the potential of bacterial biomarkers as more useful diagnostic tools over current diagnostic strategies[108]. In addition, the ratio *F. nucleatum/Bifidobacterium* showed superior sensitivity of 84.6% and specificity of 92.3% for diagnosing CRC in comparison with the use of a single fecal bacterial biomarker candidate[109].

The deficit in the number of butyrate-producing bacteria can have detrimental consequences in the progression of the disease, hence the screening of SCFA and microbial-derived metabolites have potential as biomarkers and diagnostic tools for CRC. Some studies already have shown that using microbiome profiles in conjunction with certain risk factors such as age, race and body mass index can help predict healthy colon vs one with adenomas or carcinomas[110]. While detection of CRC and precancerous lesions is our current goal in preventing CRC mortality, the microbiome also provides promise into potentially preventing CRC by inhibiting colorectal tumorigenesis. A recent study by Li et al[111] aimed to look at the role of depleted bacteria, specifically Streptococcus thermophilus (S. thermophilus), in CRC to see if when used as a probiotic that it could prevent CRC. They showed in a mouse model that tumor formation could be reduced using S. thermophilus by oral gavage, and it was specifically the β-Galactosidase secreted by S. thermophilus that was critical to retarding the growth of CRC cells. S. thermophilus also was able to increase other known probiotics, including Bifidobacterium and Lactobacillus, via β-Galactosidase. Albeit, just in a mouse model, it highlights the potential for possible prevention and reversal of CRC by use of the microbiome.

Additional prospective human studies must be undertaken to determine the role of the microbiome in CRC therapy and in the reliability of certain profiles for screening and prevention. Furthermore, when certain microbiome signatures that predispose risk for CRC do arise, the age at which one is to start looking for these predispositions also needs to be established to enable clinical use. The heterogeneity of CRC could be related to different microbiota communities that either predispose or provide resistance to the disease, and the profile analysis of the oral microbiome may offer an alternative screen as a biomarker for detecting CRC[112]. Only single studies detected associations with *Fusobacterium* or *Porphyromonadaceae* and CRC[110,113]. Further studies with a larger sample size are needed to confirm the identified associations and estimate the potential utilization of the oral microbiota and periodontal diagnosis and treatment for use in CRC early detection or prevention.

The gut microbiome and its metabolites have therapeutic implications for CRC and other cancers. It has been postulated that therapeutic response to immune checkpoint inhibitors (ICI) may be influenced by presence of the gut microbiome. In 100 patients diagnosed with non- small cell lung cancer and on ICI therapy, the stool of patients responding to ICI therapy was rich in *Akkermansia mucinphilia* compared to nonresponders[114]. The baseline microbiome or its modulation using antibiotics, probiotics or FMT have influenced treatment efficacy in numerous cancers[115]. For example, patients with non-small cell lung cancer, renal cell carcinoma or urothelial cancer treated with antibiotics for routine indications shortly before, during, or shortly after treatment with anti-PD1/PD-L1 mAB had significantly lower progression-free survival and overall survival rates compared to patients who had not received antibiotics. This suggests that disrupting the gut microbiota (*via* antibiotic use) could potentially impair anti-tumor immune responses as well as response to immune checkpoint blockade[114,115].

The gut microbiome is a dynamic meditator of immune and cellular response to cancer and influences the efficacy of cancer therapies. Manipulating the gut microbiome will likely emerge as a viable option of modulating the responsiveness of cancers to immune mediated and other therapies. In addition, other decisions regarding the use of antibiotics with cancer and other therapies should be weighed carefully considering their impact on the gut microbiome. Large prospective studies on the impact of dietary interventions (prebiotics), antibiotic use and the influence of environmental pollutants are needed to clarify many unanswered questions on the factors that impact the gut microbiome and the durability of that effect. Lastly, the price and availability of microbiome analysis will have to come to a point where it is widely available and accessible to make it mainstay in the clinical realm.

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