Review

Interplay between the gut microbiota and epithelial innate signaling in colitis-associated colon carcinogenesis

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Abstract

Intestinal microbiota is involved in the maintenance of gut homeostasis as well as the regulation of colitis-associated colorectal tumorigenesis. The aberrant host immune signaling and the presence of opportunistic commensals with potential pathogenic characteristics (pathobionts) have been suggested to be incorporated into the genetic paradigm of colon carcinogenesis. The reciprocal relationship between innate immune response and microbial composition in tumorigenesis is highlighted in this article. A two-hit theory is proposed here that dysregulated host epithelial signaling and dysbiotic microbiota are synergistic factors to drive malignant transformation. Innate immune receptors such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors are involved in colitis-associated carcinogenesis through the regulation of epithelial cell death and proliferation, as well as the shaping of microbial community. From the microbial side, *Escherichia coli*, *Fusobacterium nucleatum*, enterotoxigenic *Bacteroides fragilis,* are identified as pro-tumorigenic pathobionts in colitis-associated tumor models. Probiotics such as *Lactobacillus, Bifidobacterium,* and butyrate-producing bacteria displayed tumor-suppressing effects. The Gram-negative characteristics of the mucosa-associated pathobionts indicate the involvement of lipopolysaccharide–dependent epithelial CD14/TLR4 signaling in cancer development. Virulence factors of the pathobionts were also identified in causing epithelial genotoxicity and signaling. The mechanistic insights of the interplay between host innate immunity and bacterial composition, and the understanding of how the dysfunction of one impacts on the other, will shed light to the development of novel strategies for the clinical management of inflammatory bowel disease and colon cancers.

Keywords: commensal bacteria, tumor biology, epithelial cells, Toll-like receptors, NOD-like receptors, virulence factors

INTRODUCTION

The gastrointestinal tract is a unique internal organ with a densely populated microbial ecosystem, in contrast to other aseptic viscera, in the human body (1, 2). Adult human intestine is inhabited by approximately 10^{14} bacterial cells, with the highest amount in the colon (3, 4). Over 1000 bacterial species mainly belonging to four phyla were identified in a cohort study with each individual harboring at least 160 species (5). A large inter-individual diversity was found and about 30-40

species are shared among individuals (5-8). The number of bacterial genes are estimated to be 100-fold higher than those of human genes (3, 5, 9). Besides the commensal bacteria, virus and fungi also exist in the intestine and are collectively defined as the gut microbiome (6, 10).

In the post-human genome era, much attention is now focused on this complex gut ecosystem. Advances in DNA sequencing and bioinformatics have fostered progress in human microbiome research. The explosion of knowledge in environment-diet-microbe-host interactions has greatly re-shaped our view of human physiology (5, 6, 11). Currently, enteric dysbiosis (a term that describes the condition of having microbial compositional, spatial, or number change within the body) is regarded not only as a key component of gastrointestinal diseases but also of extraintestinal and systemic disorders.

Dysbiosis has been reported in inflammatory bowel disease (IBD), colorectal cancer (CRC), atherosclerosis, obesity, type II diabetes, non-alcoholic liver diseases, multiple sclerosis, and chronic fatigue syndrome (12-15). A reduction of fecal bacterial diversity is found in patients with Crohn's disease and ulcerative colitis (16-18) and colonic carcinoma (19, 20), which indicates that even fewer species could be making up the majority of a disease-associated microbial population. Recently, bacteria with colitogenic and pro-tumorigenic characteristics are suggested to play critical roles in the pathogenesis of colitis-associated CRC (21-23).

Patients with Crohn's disease and ulcerative colitis are at higher risk of CRC (24, 25). A link between inflammation and cancer were also observed in gastritis-associated gastric carcinoma, hepatitis-associated hepatocellular carcinoma, and cholangitis-associated bile duct cancer (26, 27). Besides genetic instability mediated by inflammatory free radicals (26, 28, 29), the presence of disease-associated bacteria with virulence factors (21-23) and the aberrant innate immune responses to gut microbial products (30-32) are also involved in the multifaceted pathogenesis of CRC.

Taken into account the juxtaposition of bacteria and mucosa, microbial dysbiosis and dysregulated innate signals derived from intestinal epithelium are the focus of this review (33-36). A two-hit theory was proposed that aberrant host epithelial signaling and dysbiotic microbiota are co-existing factors that synergistically drive colitis-associated carcinogenesis (Figure 1). In this article, we aimed to highlight bidirectional evidence of epithelial innate signaling affecting the microbes and vice versa, and to discuss how aberrant interaction between bacteria and epithelium may contribute to tumor development and progression.

HOST-MICROBE CROSSTALK AND EPITHELIAL INNATE IMMUNITY

Innate immune signaling are actively involved in microbial recognition and colitis-associated CRC development. A long line of evidence for IBD-associated polymorphisms in Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (37-40) implicate that aberrant innate responses to their own microbial products is involved in disease pathogenesis. For information on the adaptive aspect of immunopathogenesis of IBD, other reviews are recommended (40, 41). Gene polymorphisms in lipopolysaccharide (LPS) receptors CD14 and TLR4 are observed in patients with Crohn's disease and ulcerative colitis, and the polymorphisms are correlated with a higher risk of CRC (42-45). Gene polymorphisms in TLR2 are also linked with susceptibility of IBD and higher risks of CRC (46-49). NOD2 was the first gene to be identified with Crohn's susceptibility; variants of NOD2 was found in a subset of patients with fibrostenosing Crohn's disease (50-54). Although NOD2 mutation was used as a predictor for aggressive diseases in Crohn's patients (55, 56), no correlation was found with CRC development (39, 57).

These innate receptors were originally identified in monocytic cells for induction of proinflammatory responses following binding to bacterial products. The TLRs are known to be expressed on the cell surface, whereas NLRs are mostly recognized in the cytosols of immune cells (58, 59). The LPS receptor CD14/TLR4 activates a myeloid differentiation factor (MyD88)-dependent proinflammatory signaling (e.g. mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NFκB)) for production of proinflammatory cytokines in monocytes (Figure 2A) (60, 61). TLR2 (a bacterial peptidoglycan and lipoteichoic acid receptor) was shown to complex with TLR1, TLR6, or CD14, and to induce MyD88-dependent signals (62, 63). Moreover, NOD2 after binding to a peptidoglycan component, i.e. muramyl dipeptide (MDP), activates inflammasome pathways and NFκB signaling in immune cells (58, 59).

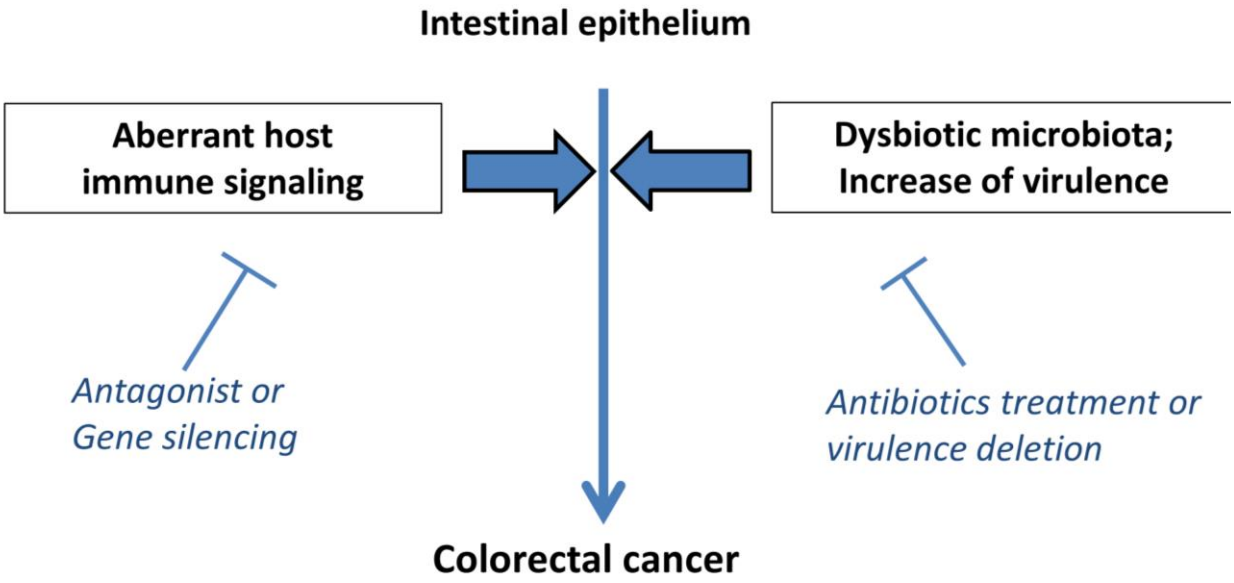

Figure 1. Schema of a two-hit theory of synergistic host and microbial factors involved in colon carcinogenesis. Aberrant innate signaling by host intestinal epithelium and immune cells to bacterial products has been demonstrated to alter the susceptibility of tumorigenesis. Enteric dysbiosis including microbiota changes and virulence increase also play crucial roles in the development of colorectal tumors. Modulation of host immune factors by antagonists or bacterial factors by antibiotics and virulence deletion are potential therapeutic strategies to reduce tumor growth.

A weak expression of TLR2/4 (64-67) and NOD2 (68, 69) was found in the intestinal epithelium of healthy individuals, and was traditionally considered a means to tolerate gut commensals. Constitutive CD14 expression was noted in the cell surface of normal intestinal epithelium (34, 64). In IBD and CRC patients, increased expression of CD14 and TLR4 was reported in the mucosal tissues and epithelial layers (Table 1) (64-66). Overexpression of TLR2 and NOD2 was also found in the epithelial cells of inflamed colon in Crohn's disease (68, 70, 71). In addition, membrane recruitment of wild type NOD2 in contrast to the cytosolic presence of mutant NOD2 (R702W and G908R) have been reported in human intestinal epithelial cell lines (72, 73). Accumulating evidence indicate that the aberrant innate receptor expression and signaling on intestinal epithelium are involved in tumor progression.

The cause-and-effect relationship between innate responses and carcinogenesis was first implicated by the observation of diminished tumor formation in APC(Min/+) mice when TLRs or MyD88 signaling was ablated (32, 74). Spontaneous intestinal tumor development is seen in the multiple intestinal neoplasia (Min) mice, which carry a heterozygous mutation in the adenomatous polyposis coli (*Apc*) gene (75). Further evidence was shown in experimental models that epithelia-specific or systemic knockout of TLR4 display reduced colon tumor numbers and sizes (33, 76, 77), whereas mice with genetic deficiency in NLRs, such as NOD1, NOD2, NLRC4, NLRP3, and NLRP6, demonstrated higher susceptibility to CRC (78-83); inconsistent data were observed for the role of TLR2 in colon tumorigenesis (84-86). So far, TLR4 is the best characterized innate receptor expressed on intestinal epithelium for promoting colon tumorigenesis (33, 76, 77).

The opposite effects of TLR4 and NLRs on regulation of CRC growth are striking cause both types of innate receptors are known to activate NFκB signals (58, 59). A number of features have been proposed to explain the discrepancy between the two receptors in colitis-associated tumor formation. One of the possible reasons is that dysregulated epithelial cell death and proliferation mediated by imbalances in epithelial CD14/TLR4 signaling (uncoupled to proinflammatory responses) serves as a key mechanism in LPS-induced CRC progression

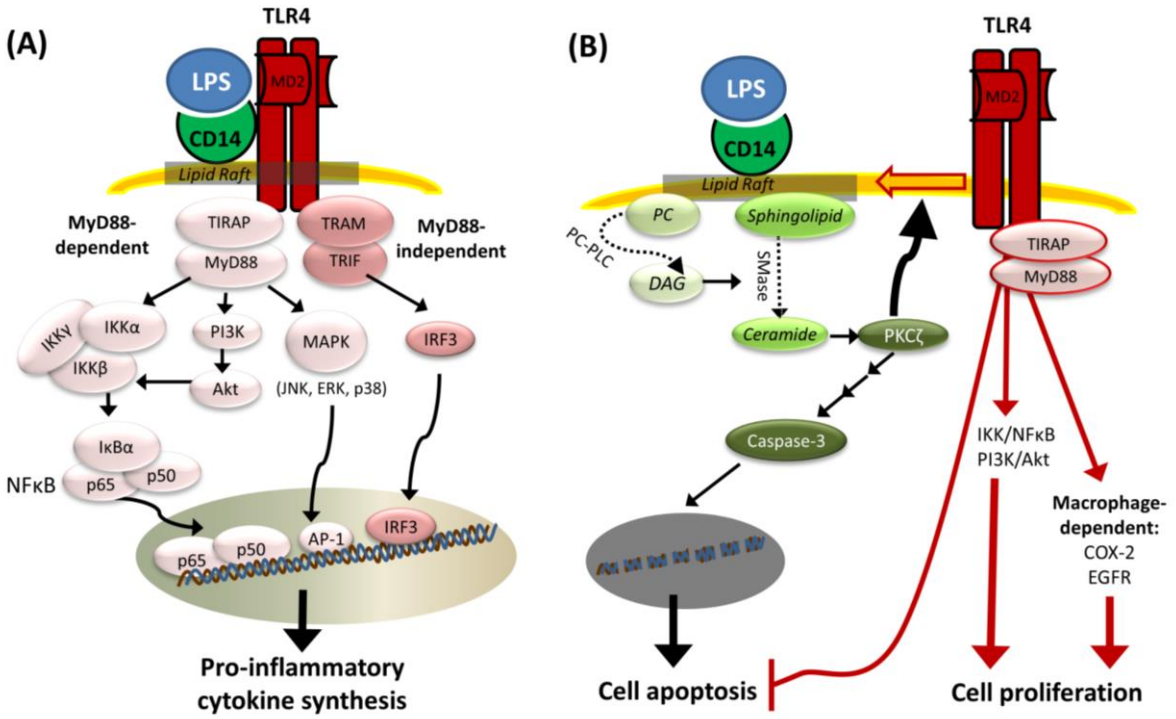

Figure 2. Bacterial LPS receptor subunits (CD14 and TLR4) are involved in proinflammatory signaling and regulation of cell death and proliferation in intestinal epithelium. (A) Binding of LPS to the CD14/TLR4 complex on lipid raft triggers myeloid differentiation factor (MyD88)-dependent and -independent signaling for proinflammatory cytokine production in intestinal epithelial cells. Early studies show that TLR4 activates MyD88-dependent pathways, including inhibitor of κB kinase (IKK)/inhibitor of κB (IκB)/nuclear factor-kappa B (NFκB), phosphatidylinositide- 3 kinase (PI3K)/Akt, and mitogen-activated protein kinases (MAPK) such as JNK, ERK, and p38. The TLR4-mediated MyD88-indepent pathway includes interferon regulatory factor 3 (IRF3). Nuclear translocation of NFκB subunits (p65 and p50), AP-1, or IRF3 cause the transcription of proinflammatory cytokines. **(B)** Recent findings indicate that LPS/CD14 binding on lipid raft triggers a number of lipid messengers to induce epithelial cell apoptosis which is counteracted by upregulation of TLR4. The cascade of lipid signaling involves conversion of membranous phophatidylcholine (PC) to diacylglycerol (DAG) by PC-specific phospholipase (PC-PLC), activation of sphingomyelinase (SMase) for sphingolipid metabolism and ceramide production, and phosphorylation of protein kinase C ζ (PKCζ). In absence of TLR4, the activation of PKCζ leads to caspase-dependent cell apoptosis in intestinal epithelial cells. However, upregulation of TLR4 serves as a antagonizing signal to inhibit epithelial cell apoptosis following PKCζ-dependent recruitment of TLR4 onto raft domains, acts as hyperproliferative signals through IKK/NFκB and PI3K/Akt molecules, and is involved in tumorigenesis via macrophage-associated cyclooxygenase-2 (COX-2) and epidermal growth factor receptor (EGFR)-dependent pathways.

(33-35, 87). On the other hand, inflammasome-dependent autophagy pathways (80, 88) and shaping of the microbiome (79, 89) are involved in the mechanisms of NLR-dependent suppression of tumorigenesis. The role of TLR4 in CRC development are described in this section, whereas the role of NLRs are discussed in relation to dysbiotic microbiota in the next section.

Previous studies using bone marrow chimera have demonstrated that epithelial TLR4 overexpression plays a more dominant role than the receptor expression on myeloid cells in driving colon tumor growth (33, 76, 87). Intestinal epithelial cell studies had shown that downstream signals of TLR4 such as NFκB and Akt were involved in the epithelial hyperproliferative responses *in vitro* (36, 90, 91). Moreover, upregulation of TLR4/MyD88 promotes colon carcinogenesis via cyclooxygase-2 (COX-2) and

Table 1. Expression of LPS receptors in primary human intestinal epithelial cells

Receptor subset	Intestinal samples	Expression & Location	Techniques	Ref.
CD14				
protein	Colonic epithelial cells isolated from healthy subjects	Epithelial expression	Flow	64
	Colonic normal and tumor tissues in CRC patients	Apical expression in normal epithelium and increased levels in tumors	IF	34
TLR4				
protein	Colonic normal and tumor tissues in CRC patients and healthy subjects	Undetectable in normal tissues, and increased apical and cytoplasm expression in tumors	IF, IHC	34,66,264
	Colorectal tissues in IBD patients and healthy subjects	Undetectable in tissues of healthy subjects, and increased expression in apical membrane of crypt cells in IBD patients	IHC	265,266
mRNA	Colonic epithelial cells isolated from healthy subjects	Low levels in epithelial cells of healthy subjects	qPCR, RT-PCR	67,256,267
	Colonic mucosal biopsies from IBD patients and healthy subjects	Low levels in mucosal tissues of healthy subjects and increased expression in IBD patients	RT-PCR	70

Note: CRC, colorectal carcinoma; IBD, inflammatory bowel disease; Flow, flow cytometry; IF, immunofluorescent staining; IHC, immunohistochemistry; qPCR, real time quantitative polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction.

epidermal growth factor receptor (EGFR)-dependent pathways in mouse models of colitis-associated CRC (Figure 2B) (74, 76, 92, 93). Our recent studies showed that TLR4 played an antagonistic role against its co-receptor CD14 in regulation of epithelial cell survival. Normal colonocytes respond to bacterial LPS through the constitutively expressed CD14 (34, 35). The intestinal epithelial cells undergo apoptosis following LPS/CD14 activation via lipid messengers and protein kinase C ζ (PKCζ) signals in the absence of TLR4, whereas upregulation of TLR4 expression inhibited CD14-mediated epithelial cell death and promoted tumor development (Figure 2B) (34, 35). Use of eritoran, which is a LPS mimicking molecule that acts as a CD14 agonist and TLR4 antagonist, caused an increase of cell death and a decrease of cell proliferation in tumor cells and significantly reduced tumor burden in a mouse CRC models (34, 35). Overall, functional antagonism between CD14 and TLR4 was identified in the bacterial regulation of epithelial apoptosis and proliferation, and the imbalance between the receptor subunits on epithelial cells plays a critical role in promoting tumorigenesis (34, 35, 94).

In keeping with early studies showing that commensal bacterial products are actively involved in the regulation of epithelial turnover and restitution (30, 95-97), our studies support the concept that aberrant epithelial signaling tips the balance toward malignancy. These findings provided novel information on the bacteria-regulated malignant transformation through innate signaling; however, the question remains as to what roles enteric dysbiosis play.

ENTERIC DYSBIOSIS

Alterations in the intestinal microbiota (such as changes in bacterial population or distribution) were documented in patients with IBD (98, 99), and CRC (100-102). Reduced microbial diversity was found in mucosal biopsies of patients with Crohn's disease (16, 17) and ulcerative colitis (18). Lower bacterial diversity was also reported in biopsy tissues and stool samples of carcinoma patients compared to controls (19, 20). However, colonic adenoma biopsies showed higher diversity and greater numbers of bacteria compared to healthy individuals (103, 104). It is noteworthy that live bacteria reside in gut mucosa of IBD and CRC patients, in contrast to the mostly lumen-dwelling commensals in normal subjects (105, 106).

A role of bacteria in intestinal carcinogenesis was first suggested in 1978 by Reddy et al (107), based upon the observation of a lower incidence of chemically induced duodenal and colonic tumors in germ-free rats than in conventional rats. Reduced severity and delayed onset of chemically or genetically induced colitis was later reported in germ-free mice (108-110). Nevertheless, a causative role of bacteria was challenged by the notion of the lack of immune maturation and/or tolerance (which is dependent on commensal colonization) in germ-free intestine (111-113). Additional studies showed that bacterial depletion by antibiotics significantly reduced tumor burden in the mutagen-induced wild type mice (114, 115), as well as in the tumor-susceptible NOD1(-/-), NOD2(-/-) and NLRP6(-/-) mice (78, 79, 82), providing direct evidence of bacterial involvement in tumorigenesis.

The existence of pathobionts (opportunistic pathogenic bacteria converted from commensals) with colitogenic and pro-tumorigenic abilities was not confirmed until clear evidence of 'transmissible' colitis and CRC was demonstrated through fecal microbial transplantation and co-housing experiments (79, 82, 114). Previous studies have shown that the severe colitis and high tumor susceptibility in NOD2(-/-) or NLRP6(-/-) mice are 'communicable' through fecal transplantation to the recipients of wild type mice (79, 82). Indeed, the fecal microbial composition was altered in NOD2(-/-) and NLRP6(-/-) mice compared to their wild type counterparts through imbalance in the inflammasome-mediated regulation in antimicrobial peptide (AMP) profiles (89, 116-118). The findings indicate the emergence of dysbiotic microbiota as a result of the host genetic deficiency in NLRs. In addition, changes in mucosal defensin levels were also documented after TLR4 signaling (119-121), implicating AMP-dependent modulation in microbial ecology by TLR4. The increase of tumor burden in NLR-deficient mice strongly supported that dysbiotic microbiota plays an active role in colitis and carcinogenesis. Clinical observation showed beneficial effects of antibiotic therapy in the induction of remission in IBD patients (122-124). Overall, these studies suggested that host NLRs were essential in the shaping of gut microbiota, and the lack of NOD1, NOD2, or NLRP6 might alter the microbial community to a disease-associated profile.

Although the presence of pathobionts (such as colitogenic bacteria and infectious carcinogens) was confirmed in rodent models by mouse to mouse fecal transplantation (79, 82), a recent study transferring stool samples from CRC and healthy patients to germ-free mice before mutagen exposure had shown surprising results (125). Mice receiving human CRC-associated bacteria developed fewer tumors than those given bacteria from tumor-free subjects (125). The authors concluded that the initial microbiome structure developed by the recipient mice following fecal transplantation, but not the cancer status of the human donors, was the main factor determining tumor incidence in the recipient mice. They also found that Gram-negative bacteria such as *Bacteroides* are positively correlated with increased tumor burden, whereas Gram-positive bacteria such as *Clostridiales* are negatively associated with tumor growth (125). In spite of the unexpected results, a crucial role of gut bacteria in the regulation of cancer formation is supported by this study. More importantly, the exact strains and composition of gut microbiota with beneficial or detrimental effects on CRC development remain to be elucidated.

PATHOBIONTS AND PROBIOTICS

The presence of pathobionts and/or a shortage of probiotics (beneficial bacteria to the host) both serve as key factors for disease development. Clinically, bactericidal antibiotic treatment is recommended for the management of ulcerative colitis if infectious complications are suspected (126). Moreover, antibiotics that increase the abundance of beneficial bacteria, the so-called 'eubiotics', are emerging as a new treatment option (127). The good and the evil of gut microbiota are equivocal aspects in deciphering the bacterial strains for regulation of colitis-associated CRC.

Particular bacterial strains were characterized in germ-free and antibiotic-depleted mice by monoassociation experiments. These studies offered pivotal evidence supporting the presence of bacteria with pro-tumorigenic or colitogenic ability. Nevertheless, it should be kept in mind that the majority of monoassociation studies have utilized cancer-prone or immune-compromised mice with genetic defects to identify the bacterial strains (79, 82, 128, 129). The findings therefore support the idea that disease progression in patient subsets with genetic predispositions is partly attributable to pathobionts. However, this remains uncertain for individuals in the general heterogeneous population who have chronic inflammation and sporadic cancers but lack particular genetic traits. The pathobionts (Table 2) and probiotics with either direct or causal links to colitis and CRC are summarized below.

Escherichia coli

Enrichment of mucosa-associated or internalized *Enterobacteriaceae* family or *Escherichia coli* was long observed in biopsy samples of IBD and CRC patients (18, 130-133). Increased *Escherichia* genus was also identified in fecal bacterial population in Crohn's disease, ulcerative colitis, and CRC patients compared to healthy individuals (101, 134). The levels of *E. coli* colonization appear to correlate positively with the proliferation index of colorectal tumor cells (130).

Diffusely adherent *E. coli* found in IBD and CRC patients possess a number of virulence genes such as afimbrial adhesin (*afa*), long polar fimbriae (*lpf*), fimbrial adhesin or type-1 pili (*fim*) and polyketide synthase gene complex (*pks*) (131, 132, 135). A subpopulation of *E. coli* originally identified in the ileal mucosa of Crohn's disease patients, termed adherent-invasive *E. coli* (AIEC), is well-characterized for its mucosal attachment and ability to survive intracellularly in epithelial cells and macrophages (136, 137). Although the adherent-invasive ability was observed in these types of *E. coli*, they were not categorized as pathogens according to the classical definition due to their lack of known genetic invasive or toxigenic determinants (138, 139).

Recent studies indicated that pks-positive *E. coli* encoding a genotoxin (colibactin) increased the susceptibility to colorectal cancer in mutagen-induced IL-10(-/-) mice (128, 140). DNA damage and cell cycle arrest were noted in epithelial cells and mouse crypts after exposure to these pks-positive *E. coli,* implicating a pro-tumorigenic mechanism (128, 140). Colibactin-producing *E. coli* also indirectly enhance tumor growth by inducing the emergence of senescent cells that secrete hepatocyte growth factors in models of mutagen-induced IL-10(-/-) and wild-type mice (141).

In addition, colitogenic and pro-tumorigenic characteristics of AIEC were observed in transgenic mice expressing the human-specific carcinoembryonic antigen-related cell adhesion molecules 6 (CEACAM6) receptors on epithelial cells (142, 143). The epithelial CEACAM6 allowed bacterial colonization via type 1 pili (fimbriae)(142, 143). The lipid A moiety of Gram-negative bacteria also plays a role in preventing epithelial CEACAM shedding and in facilitating mucosal colonization by bacteria (144, 145). AIEC owes its pathogenicity to its active invasion, which is associated with sustained macrophage-derived cyclooxygenase-2 production, which promotes mucosal inflammation and epithelial proliferation (135, 146). Other studies using *in vivo* and *in vitro* models have shown that AIEC colonization increased mucosal permeability and tight junction disruption, implicating a direct role of bacteria in triggering gut leakiness, which might be another factor leading to chronic inflammation (138, 147-149). Further investigation of AIEC-induced epithelial innate signaling in barrier regulation and cell proliferation is warranted. In sum, virulence factors in *E. coli* conferring mucosal adherence/invasion and genotoxicity properties are relevant to disease progression in colitis and CRC.

Fusobacterium nucleatum

Fusobacterium species are commonly found in the oral cavity but rarely in the intestinal tract of healthy individuals (150, 151). However, abundance of *Fusobacterium* spp. and *F. nucleatum* were reported not only in fecal samples but also in

Table 2. Potential pathobionts involved in colon carcinogenesis

Bacterial family, genus, and species	Virulence factors	Suggested mechanisms	Ref.
Enterobacteriaceae			
Escherichia coli	pks	Production of genotoxic colibactin that causes DNA damage and promotes tumor growth and cell senescence.	128, 140, 141
	afa, lpf, fim	Adherence and invasive characteristics that induce gut leakiness and macrophage-derived cyclooxygenase-2 production.	138, 147-149
Fusobactericeae			
Fusobacterium nucleatum	FadA	Binding to E-cadherin for adherence and invasion, and stimulation of β-catenin signaling for NFκB and oncogene production in adenocarcinoma cell lines.	158, 159, 162
	Fap2	Binding to a polysaccharide, Gal-GalNAc, on tumor tissues.	156, 161, 164
Bacteroidaceae			
Bacteroides fragilis	*B. fragilis* enterotoxin	Enterotoxin induces oxidative DNA damage, epithelial E-cadherin cleavage for increased permeability and cell proliferation, and activation of Stat3 and Th17 immune response.	170-172

Note: pks, polyketide synthase gene complex; afa, afimbrial adhesin; lpf, long polar fimbriae; fim, fimbrial adhesin or type-1 pili.

inflamed mucosa of Crohn's disease patients and in tumor specimens of CRC patients (19, 102, 152-157). The presence of mucosa-associated *Fusobacterium* in biopsy specimens of IBD and CRC has sparked interest in the emergence of possible invasive strains (99, 154, 158). *Fusobacterium* recovered from inflamed tissues of IBD patients displayed higher invasive ability to human carcinoma Caco-2 cell lines, compared to strains isolated from healthy tissues or control patients (158, 159). Moreover, the amount of *Fusobacterium* DNA in tumor tissues was found to be positively associated with poor prognosis in cancer patients (160).

In animal studies, eight weeks of daily feeding of human isolates of *F. nucleatum* accelerated the onset of cancer formation, increased tumor multiplicity, and selectively recruited tumor-infiltrating myeloid cells in APC(Min/+) mice (161). This observation of increased tumor burden by *F. nucleatum* is not associated with the exacerbation of colitis in APC(Min/+) mice (161). Further experiments were conducted in colitogenic mouse strains such as IL-10(-/-) and T-bet(-/-)/Rag2(-/-) mice to elaborate on the dissociation between colitis and tumors, and it was demonstrated that inoculation of *F. nucleatum* did not aggravate intestinal inflammation nor induce tumors in these colitic mice (161). These elegant studies suggested that *F. nucleatum*, albeit with protumorigenic potential under conditions of oncogenic mutation, did not possess colitogenic characteristics or the ability to trigger cancer in a colitis background. Moreover, *in vitro* studies had shown that *F. nucleatum* increased cell hyperproliferation in adenocarcinoma cell lines with APC mutation (e.g. HT29, DLD1, and SW480) or with β-catenin mutation (e.g. HCT116), but not in noncancerous HEK293 cells (162). Taken together, the findings suggested that pre-existing oncogenic mutation precede the *F. nucleatum*-driven

tumorigenesis.

Several virulence factors of *F. nucleatum* have been implicated in colon tumorigenesis. A recent study demonstrated that FadA adhesin via binding to E-cadherin induced nuclear translocation of β-catenin for oncogene transcription in human adenocarcinoma cell lines (162). Indirect evidence of a role of FadA in promoting tumor growth was demonstrated by xenograft studies (162). Moreover, FadA also binds to vascular endothelial cadherin and helps *F. nucleatum* to adhere and breach endothelial cells to enhance the penetration of *E. coli* in *in vitro* transwell assays (163). A report has identified a novel lectin-like outermembrane protein Fap2 expressed on *F. nucleatum* that binds to a polysaccharide, Gal-GalNAc, on mouse CRC, suggesting another potential pro-tumorigenic virulence factor for epithelial anchoring and signaling (164). In addition, it was shown that bacterial surface protein Fap2 and RadD facilitated the adherence of *F. nucleatum* to lymphocytes for contact-dependent immune cell apoptosis (165). However, the association of these *F. nucleatum* proteins with *in vivo* orthotopic CRC has not yet been documented.

Bacteroides fragilis

A subclass of the human commensal *Bacteroides* species, enterotoxigenic *Bacteroides fragilis* (ETBF), was associated with acute inflammatory diarrheal disease and CRC in patients (155, 166, 167). Presence of *B. fragilis* and ETBF was found in the stool and biopsy specimens of both normal and CRC patients, but the amount of bacteria and toxin was significantly higher in late-stage CRC samples (101, 102, 155, 167, 168). One report has shown inconsistent data of decreased abundance of *Bacteroides* genus in stool specimens of CRC patients compared to healthy volunteers (101).

Experimental models of colitis were used for the assessment of proinflammatory and pro-tumorigenic ability of ETBF. Orogastric administration of ETBF following antibiotic disruption of normal flora to promote colonization had caused acute colitis that persisted up to one year in wild-type mice (169-171). Moreover, ETBF worsened the severity of colitis induced by dextran sodium sulfate (169). Recent reports demonstrated that colonization by ETBF but not its non-toxigenic counterpart induced colitis and promoted colon tumorigenesis in APC(Min/+) mice (129, 172). This observation is different from the solely pro-oncogenic role of *F. nucleatum* (161). Several mechanisms have been proposed of its virulence factor, *B. fragilis* enterotoxin (also known as fragilysin) which acts as a metalloprotease. The pathogenic mechanisms include a direct cytotoxic effect by causing oxidative DNA damage, induction of epithelial E-cadherin cleavage for increased mucosal permeability and cell proliferation, and activation of Stat3 with a Th17 immune response (170-172). These studies indicated that adaptive T cell responses, beyond innate signaling in epithelial and immune cells, may also contribute to infection-induced carcinogenesis by ETBF.

Helicobacter species

Helicobacter pylori is classified as a class I carcinogen by the World Health Organization for its role in gastric cancer. Two of the extensively studied virulence factors cytotoxin-associated gene A (CagA) and vaculating cytotoxin A (VacA) have been associated with precancerous gastric lesions, through activation of epithelial proinflammatory and hyperproliferative signaling, and disruption of epithelial barrier (for a complete review, please see other articles (173, 174)). Although a relationship between *H. pylori* and CRC has been proposed, the evidence falls short of a definitive causal link due to conflicting results (175-180).

Infection with *H. hepaticus* has been shown to promote intestinal inflammation and CRC development in immunocompromised, colitogenic, or tumor-prone mouse models, such as Rag2(-/-), Rag2(-/-)APC(Min/+), mutagen-induced IL-10(-/-) mice (181-184). Although chronic life-long infection of *H. hepaticus* in the liver and colonic crypts are seen in immunodeficient mice, the bacteria do not colonize well nor cause disease in immunocompetent wild type animals (185, 186). In addition, there is no evidence of *H. hepaticus* infection on colorectal tumor samples in patient studies. The relevance of helicobacter species as a pathogen or pathobiont in promoting human CRC needs further investigation.

Lactobacillus and *Bifidobacterium*

Probiotics as dietary supplements have been investigated for their anti-inflammatory and anti-tumorigenic effects in experimental models. Numerous studies have demonstrated that a single species or mixtures of probiotics (such as

Lactobacillus and *Bifidobacterium*) prevent intestinal inflammation in chemical-induced colitis models or in IL-10(-/-) mice (187-191). Other reports had shown that administration of *Lactobacillus* and *Bifidobacterium* spp. suppressed tumor formation in mutagen-induced CRC and APC(Min/+) mice models (84, 192-195). The beneficial effects of probiotics in the prevention of colitis have been generally attributed to their immunoregulatory and barrier-fortifying actions (188, 189). However, the anti-cancer mechanisms of *Lactobacillus* and *Bifidobacterium* are suspected to be either related to their anti-inflammatory effects or to the modulation of epithelial turnover. *In vitro* data have shown direct inhibition of proliferation and induction of apoptosis, and strengthening of barrier integrity, in intestinal epithelial cell lines by multiple strains of *Lactobacillus* (*e.g. L. acidophilus, L. fermentum, L. reuteri, L. caseri, L. rhamnosus,* and *L. gasseri*) (196-201) and *Bifidobacterium* (e.g. *B. lactis* and *B. bifidum* (202, 203)). A complete review of the beneficial effects of probiotics against cancer can be found in the literature (204, 205).

Nevertheless, there are conflicting data regarding the abundance of *Lactobacillus* and *Bifidobacterium* in inflamed and non-inflamed mucosa in patients with IBD (206-209). In addition, there is no evidence to support the efficacy of probiotics in CD patients, while improvement in disease activity is observed only in subsets of UC patients (210). In cancer patients, one report has revealed lower counts of *Bifidobacterium* in mucosal samples (208), whereas another report found no difference in *Lactobacillus* and *Bifidobacterium* abundance compared to normal individuals (100).

Butyrate-producing bacteria

Short-chain fatty acids, including acetate, propionate, and butyrate, are important fermentative metabolites produced from dietary fibers by anaerobic commensals in the colon. Butyrate is utilized by normal colonocytes as the primary energy source through mitochondrial oxidation, where its consumption is greater than that of glucose or glutamine (211-215). Moreover, butyrate is well known for its inhibitory actions on histone deacetylase (HDAC) (216, 217). Butyrate treatment induces histone hyperacetylation and transcriptional activation of pro-apoptotic genes such as Fas and the cell-cycle regulator p21(Waf1/Cip1), thereby stimulating cell death and arresting the cell cycle (216, 217).

Mounting evidence indicates that butyrate-producing bacterial genera such as *Faecalibacterium*, *Eubacterium,* and *Roseburia* are significantly less abundant and the amount of butyrate is decreased in fecal samples of IBD and CRC patients (101, 152, 218-220). A reduction in other butyrate-producing bacteria, such as *Lachnospiraceae* and *Ruminococcaceae* at the family levels, were also found in biopsy and surgical specimens of IBD patients (18, 221).

A tumor-suppressing effect of butyrate-producing bacteria was observed in early nutritional studies in mouse models by repeated oral administration of *Butyrivibrio fibrisolvens* one week before and during chemical induction of CRC (222). *B. fibrisolvens* is a ruminant bacterium, which also resides in human intestine in low numbers. Other reports have shown that a high fiber diet, which causes a large amount of butyrate production, decreases the rate of aberrant crypt foci formation in rats (223). A recent study using a gnotobiotic mouse model polyassociated with four commensal bacteria demonstrated that supplementation with high dietary fiber and *B. fibrisolvens* significantly decreased tumor growth (224). These findings support a role for butyrate-producing bacteria in the prevention of tumorigenesis and provide novel insights into the differential usage of butyrate between normal and tumor cells. Butyrate, a preferential energy fuel for normal colonocytes (212, 214, 225), is less utilized in tumor cells which perform aerobic glycolysis (so called the “Warburg effect”) (224, 226). The colonization of the mouse intestine by butyrate-producing bacteria prior to the chemical induction of CRC caused intracellular accumulation of butyrate and lowered HDAC activity, leading to increased histone acetylation and the expression of specific tumor-suppressor genes in cancer cells (224). Further investigation into the therapeutic effect of butyrate-producing bacteria in tumor-bearing mice is needed to verify the potential of butyrate as a treatment for CRC.

CHARACTERISTICS OF GRAM STAINING AND AEROTOLERANCE OF BACTERIA

The aforementioned pathobionts including *E. coli*, *F. nucleatum*, and *B. fragilis* are Gram-negative rod-shaped cells. Among these bacteria, *E. coli* is a well-known facultative anaerobe, and numerous studies showed that *E. coli* is capable of adhering and

invading into intestinal epithelial cells and macrophages in oxygenated conditions for triggering innate signaling (138, 227, 228). Although *F. nucleatum* and *B. fragilis* are reported obligate anaerobes, a few reports have shown that *F. nucleatum* may grow as monoculture and even support other strict anaerobic bacteria in co-cultures in aerated environments (229, 230). Invasive strains of *Fusobacterium* were found in gut mucosa biopsies of IBD and CRC patients, and were able to survive and activate signals in epithelial cell lines (99, 154, 158, 159). Moreover, clinical strains of *B. fragilis* isolated from intestinal, blood and peritoneal specimens can be grown in oxygenated conditions (231, 232), and are capable of activating innate signaling (233, 234).

In contrast, the probiotic families such as *Lactobacillaceae, Bifidobacteriaceae, Clostridiaceae* (*e.g. Faecalibacterium* genus), *Lachnospiraceae* (*e.g. Lachnospira, Roseburia and Butyrivibrio* genus), and *Ruminococcaceae* are all Gram-positive rod-shaped cells. These probiotic bacterial strains are known as obligate anaerobes, except *Lactobacillus* being a facultative anaerobe.

A dichotomy seems to exist that Gram-negative bacteria plays a detrimental role in tumorigenesis whereas Gram-positive bacteria appears to be beneficial. It would be plausible to suspect that in addition to specific virulence factors, the outer lipid membranous product LPS of Gram-negative bacteria might be partly involved in its pro-tumorigenic properties through activation of epithelial and monocytic TLR4 signaling. On the other hand, MDP (a constituent of the peptidoglycan wall) which is in large quantities in Gram-positive bacteria and a lesser content in Gram-negative bacteria may be associated with NOD2 signaling for tumor-suppressive effects by probiotics. Together with the evidence of microbiome shaping by innate immune receptors (89, 116-118), a proposed model of the reciprocal relationship between innate immune responses and bacterial composition in carcinogenesis is depicted in Figure 3.

Other bacterial characteristics such as the ability to survive in close proximity to the oxygenated mucosa should also be considered as an advantage to increase its chance to cause pathology. However, solid tumor core is known to be relatively hypoxic (226, 235) and anaerobic bacteria may survive in oxygenated milieu with surrounding oxygen-consuming bacteria or in a biofilm (229, 236). Therefore, there is insufficient evidence to claim the necessity of oxygen-tolerance or -intolerence to be a basic requirement for bacteria to act as opportunistic pathogens.

UNANSWERED QUESTIONS, EXISTING CHALLENGES, AND FUTURE DIRECTIONS

The pathobionts were generally identified by their dominance on inflamed mucosa and cancerous tissues, and their pro-tumorigenic roles supported by evidence of increased tumor burden after inoculating large numbers of bacteria in chemically induced or genetically prone animal models of CRC. On the other hand, previously identified or widely ingested dietary probiotics are tested for their beneficial role in preventing cancer in animal models, but with limited evidence in patient fecal studies. While the search of individual bacterial species with essential roles in intestinal carcinogenesis could be a start for teasing out this complex host-microbe interplay, several fundamental questions remain unanswered.

First, the immunocompromised status or genetic mutation (either engineered or chemically induced) of the host seems to be a prerequisite for the suspected pathobiont to aggravate tumor development. The transplantation of dysbiotic microbiota or the inoculation of pathobionts only exacerbated diseases under pre-existing stimuli (e.g. colitogenic and carcinogenic agents, or genetic abnormality), but did not initiate lesions in untreated wild type conditions. It is noted that *E. coli* and *B. fragilis* are commonly seen in normal gut microbiota, while *F. nucleatum* mainly resides in the oral cavity of healthy individuals. Therefore, is host immune defect or early malignancy driving the emergence of disease-associated bacteria that further fuels the tumor growth? This hypothesis is in agreement with our proposed two-hit theory of host and bug, and further suggests that host abnormality may come first but may not act alone in tumorigenesis (as in germ-free condition). Although some may argue that increase of tumor susceptibility in wild type mice following fecal transplantation of the dysbiotic bacteria from NOD2(-/-) and NLRP6(-/-) mice (79, 82) is sufficient evidence for the existence of pathogenic bacteria uncoupled to host genetics, it should be kept in mind that the pro-tumorigenic stool bacteria were harvested from genetic deficient mice. Whether the pathobionts colonized preferentially in fecal contents and malignant niches are clonally developed or are orally acquired are still unknown.

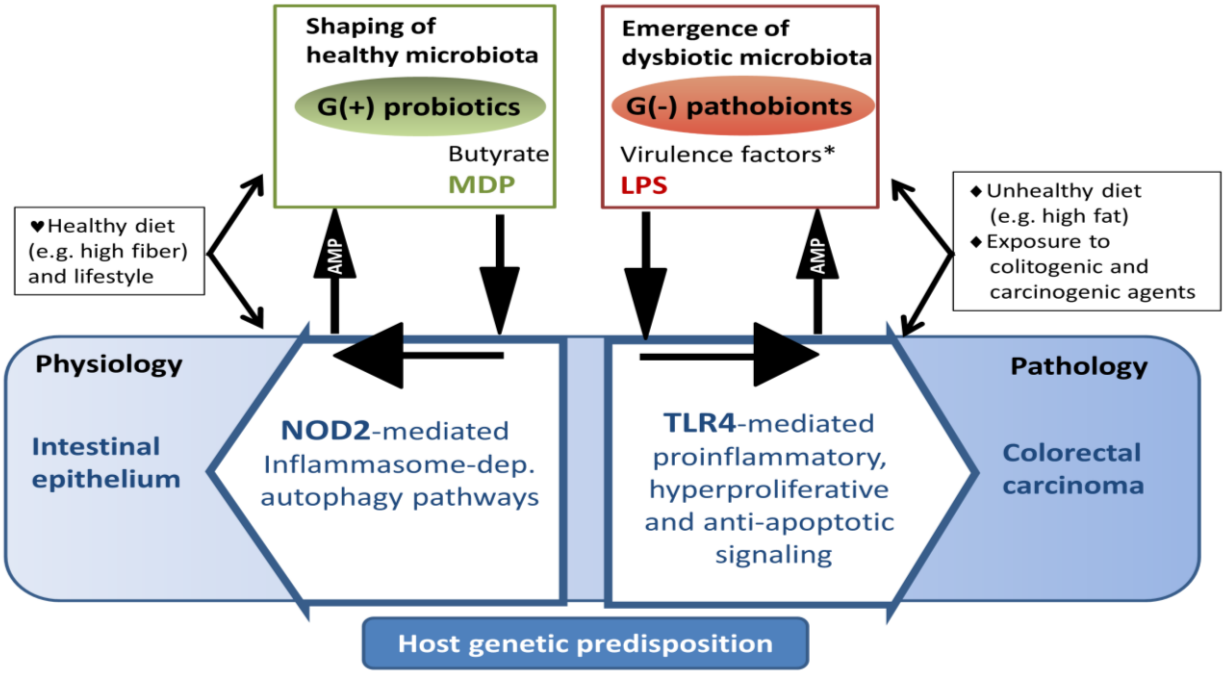

Figure 3. A proposed model of the reciprocal relationship between innate immunity and microbiota in the pathogenesis of colon cancer. During the transition from physiological intestinal epithelium to pathological colorectal carcinoma, two co-existing factors (i.e. innate immune response and microbial composition) synergistically determine the fate of malignant transformation on top of host genetic predisposition. Under a healthy diet and lifestyle, nucleotide-binding oligomerization domain 2 (NOD2) shapes a healthy microbiome via inflammasome-mediated regulation of antimicrobial peptides (AMP). The healthy microbiota contains Gram-positive (G(+)) bacteria as probiotics that produces butyrate and large quantities of muramyl dipeptide (MDP). MDP binding to NOD2 induces inflammasome-dependent autophagy pathways which are involved in the maintenance of epithelial homeostasis. However, with an unhealthy diet and after exposure to colitogenic and carcinogenic agents, overexpression of Toll-like receptor 4 (TLR4) instigates proinflammatory, hyperproliferative and anti-apoptotic signals in colonic epithelial cells after lipopolysaccharide (LPS) binding, and also alters the mucosal defensin level and causes dysbiosis. The dysbiotic microbiota contains Gram-negative ((G(-)) pathobionts with virulence factors and outer lipid membranous product LPS. Binding to LPS further increases TLR4 expression on cells, leading to a viscous cycle of activation. The list of virulence factors (*) with genotoxic, adherence, and invasive properties in the pathobionts is shown in Table 2. The bidirectional aggravation between pathobiont LPS and epithelial TLR4 further contributes to colon tumor development.

Considering that the presence of virus and bacteriophage is common in the gut and multiplying bacteria react to environmental cues rapidly, clonal lineages of gut commensals are perhaps more likely to make an opportunistic pathobiont in the stressed intestine.

Second, the majority of studies use fecal material for microbiome analysis whereas tissue biopsy data are mostly for identifying particular mucosa-associated bacteria. Inconsistent data regarding the abundance of *Bacteroidetes* phylum in fecal and mucosal samples of CRC patients were reported (103, 152), leading to the question of whether changes in stool or mucosal microbiota represent the disease-associated pattern. So far, a positive correlation between the abundance of fecal and mucosa-associated bacteria in terms of CRC risk are seen with the aforementioned pathobionts, i.e. *Escherichia* (101, 130-133) and *Fusobacterium* (19, 152-156), and ETBF (155, 167, 168). Whether fecal bacterial population simply reflects the counterbalance of space and nutrient demand between the mucosa-docking and free-floating bacteria remains to be determined. Since *E. coli* (138,

227, 228) and *F. nucleatum* (99, 154, 158, 159) adhere to or intracellularly survive in epithelial and tumor tissues, and aerotolerant *B. fragilis* are isolated from clinical peritoneal samples suggesting bacterial translocation (231, 232), the mucosal anchoring of bacteria could potentially increase its percentage in the fecal population. We believe that the mucosa-associated bacteria populated in vast numbers adjacent to epithelium and immune cells would be more relevant to disease progression, by which the virulence factors facilitating bacterial adherence and survival might be recognized by pattern recognition receptors for consequences of inflammation or tumorigenicity. Another line of evidence is that the amount of disease-associated bacteria in stool samples of CRC patients (e.g. *Escherichia spp.*, *Fusobacterium spp., and B. fragilis*), although increased compared to healthy individuals, are still a minor component (<3%) of fecal microbiota in disease states (101, 102, 152). In contrast, when tumor tissues were used for microbiome analysis, the abundance of *Fusobacterium* genus jumps up to ~10% (154, 157). Therefore, the stratification of bacteria by radial locations rather than by numbers in fecal contents may be more important in terms of host interaction. Furthermore, mucosal bacterial taxa derived from pyrosequencing should be cross-validated by the culturing of viable internalized bacteria to rule out passive uptake of dead bacterial residues which might confound the microfloral data.

Third, whether the wax and wane of particular bacterial species are influencing the viability of other microbes or even the whole microbiota population to impact on tumorigenesis is unclear. A bacterial driver-passenger model was proposed by Tjalsma et al indicating that particular species may play an active role (by initiating or aggravating lesions) or a passive role (as a bystander) in tumorigenesis, and the concept was suggested to be incorporated into the genetic paradigm of cancer progression (237). To answer this question, *in vitro* testing of a single bacterial strain to modulate proliferative and death response in epithelial cells would support a driver role of the microbe on epithelial-derived cancers. However, the possibility of this particular strain of bacteria acting on other members of the microbiota (as an assistant in altering tumorigenesis) is not mutually exclusive from its direct role and cannot be ruled out in *in vivo* settings. It is well known that maximized mutual fitness and bacteriocin-mediated competition co-exists among related species of *Escherichia* (238, 239). Uni- or bi-directional enhancement of bacterial growth with *Fusobacterium, Porphyromonas,* and *Bacteroides* species has been reported in *in vivo* subcutaneous abscess models and *in vitro* microbial co-cultures (229, 240). Moreover, probiotic mixture and eubiotic/antibiotic studies have shown that interaction among bacteria plays a key role in shifting the microbial community for suppression of cancer growth (115, 241, 242). Furthermore, the use of a combination of bacterial operational taxonomy units as a screening tool was shown to improve the probability of identifying adenoma and the prognosis of aggressive malignant transformation (156, 243, 244). These observations suggest that a consortium of bacterial complex instead of one particular species is in control of tumor progression. Employing large numbers of the suspected bacteria for a long-term repeated inoculation might overrule the necessity of supportive microbes for nutrient sharing and species competition, or mask the need of prebiotics and dietary metabolism that are otherwise important in microbiota shaping in normal conditions. The dynamics between particular bacteria and related species in the microbial community could be investigated through biofilm or mixed infection studies to provide a more holistic view of this complex interaction. We believe that although the presence of some bacterial taxa may not seem to be crucial in tumor-prone or tumor-inducing experimental settings, they may play regulatory roles in shaping a “healthy” intestinal microbiota and in maintaining epithelial and immune homeostasis to suppress the transition to malignancy. To date, no common species can be conclusively ruled out as having roles in intestinal cancer.

Fourth, the time-dependent change of genetic signatures of a particular bacteria clone throughout the course of tumorigenesis, or the temporal profile of genetic diversity of intestinal microbiota with the development of pathological conditions may clarify the ‘snapshot’ observation in cancer which is widely used in current studies and may help differentiate the driver or passenger role of bacteria. Moreover, employing antibiotic mixtures for bacterial depletion at various times to modulate tumor growth would be an efficient reductionist strategy. The finding of a critical period for bacteria-regulated tumorigenesis may justify the application of large scale metagenomics to decipher key molecules in host-microbial interaction and to speed up the search of potential therapeutic targets.

Fifth, the effect of diet either directly or

indirectly on bacterial composition adds another element of complexity in the quest of determining disease-associated bacteria. Dietary substances may indirectly modulate the bacterial community through endocrine and immune regulation. Other than fibers being the fermentative source of bacteria-derived butyrate with a clear tumor-suppressing role, high fat diet is known to increase the level of bacteria-derived secondary bile acid (e.g. deoxycholic acid) which shows a positive correlation to tumor growth (245, 246). Further information on diet in relation to dysbiosis and CRC risk could be found in recent articles (247-249), and will not be discussed in details here. While a direct link between diet and bacterial composition is irreputable, it should be kept in mind that dietary metabolites by affecting gut-brain-liver axis for glucose, lipid, and energy homeostasis (250, 251) have direct effects on the host systemically, with or without the involvement of secondary bacterial factors.

CONCLUDING REMARKS

Harnessing the aberrant signaling of the host epithelium and correcting the virulence of pathobionts as a two-hit intervention could be an effective strategy for the treatment of colitis-associated CRC. The appropriate timing, dosage, duration, and combination of therapeutic antibiotics or eubiotics to abort disease progression has yet to be determined. The impact of antibiotics on host innate signaling which might further modulate the course of colitis and tumorigenesis needs to be clarified. Binding of LPS and MDP has been previously shown to elicit positive or negative feedbacks for surface and vesicle expression of CD14, TLR4, or NOD2 (252-255). The phenomena of cross-tolerance or costimulation of TLRs and NLRs by agoinsts have also been documented (256-258). Hence, the effect of antibiotic treatment on mucosal levels of TLRs and NLRs will provide additional information on the microbial regulation of tumor growth. Bacterial engineering would be another approach to manipulate cancer progression either by directly killing pathobionts, by colonization of targeted bacteria to outgrow their parent strains, or by improvement of probiotics with higher synthesis of beneficial metabolites and more stable colonization (259-263). In summary, manipulation of the gut microbiota to alter the epithelial response or vice versa is considered new therapeutic strategies for cancer treatment beyond gene-related therapy. The understanding of host and microbial interplay would benefit the development of novel strategies for disease intervention in patients with IBD and CRC.

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Abbreviations:

afa, afimbrial adhesin;
AIEC, adherent-invasive *Escherichia coli*;
AMP, antimicrobial peptide;
APC, adenomatous polyposis coli;
CagA, cytotoxin-associated gene A;
CEACAM6, carcinoembryonic antigen-related cell adhesion molecules 6;
COX, cyclooxygenase-2;
CRC, colorectal cancer;
DAG, diacylglycerol;
EGFR, epidermal growth factor receptor;
ETBF, enterotoxigenic *Bacteroides fragilis*;
fim, fimbrial adhesin;
HDAC, histone deacetylase;
IBD, inflammatory bowel disease;
IKK, IκB kinase;
IRF3, interferon regulatory factor 3;
IκB, Inhibitor of κB;
lpf, long polar fimbriae;
LPS, lipopolysaccharide (LPS);
MAPK, mitogen-activated protein kinase;
MDP, muramyl dipeptide;
Min, multiple intestinal neoplasia;
MyD88, myeloid differentiation factor;
NFκB, nuclear factor-kappa B;
NLR, nucleotide-binding oligomerization domain-like receptor;
NOD, nucleotide-binding oligomerization domain;
PC, phophatidylcholine;
PC-PLC, PC-specific phospholipase;
PI3K, phosphatidylinositide-3 kinase;
PKCζ, protein kinase C ζ;
pks, polyketide synthase gene complex;
SMase, sphingomyelinase.
TLR, Toll-like receptors;
VacA, vaculating cytotoxin A;

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