Published in final edited form as:

Curr Opin Gastroenterol. 2017 November ; 33(6): 422–427. doi:10.1097/MOG.0000000000000399.

Novel Insights into Microbiome in Colitis and Colorectal Cancer

Ye Yang¹ and Christian Jobin^{1,2,*}

¹Department of Medicine, University of Florida, Gainesville, FL 32611, USA

²Department of Infectious Diseases and Pathology, University of Florida, Gainesville, FL 32611, USA

Abstract

Purpose of review—Microbiota is a major component of the etiology of inflammatory bowel diseases (IBD) and colorectal cancer (CRC). Here, we summarize key advances achieved the past 18 months (ending June 2017) toward a better understanding of the role of microbiota in colitis and CRC development.

Recent findings—Accumulating evidence shows the essential role of intestinal barrier function (e.g., mucus, IgA, LCN2, LYPD8) in protecting against bacteria-induced inflammation and tumor development. Numerous signaling pathways (e.g., TLRs, NLRs), metabolites (e.g., indole, bile acids, retinoic acid) and small non-coding RNAs (e.g., miRNA) have been identified as key mediators regulating host-microbe interactions in the intestine. Novel microbial drivers of colitis and tumorigenesis (e.g., *Alistipes finegoldii*, *Atopobium parvum*, *Peptostreptococcus anaerobius*) have been identified and their disease-promoting activities have been described.

Summary—IBD-associated colorectal cancer results from a complex breakdown of communication between the host and its microbiota, involving barrier function, immune signaling and metabolites.

Keywords

microbiota; inflammatory bowel disease (IBD); colorectal cancer (CRC); colitis-associated colorectal cancer (CAC)

Introduction

The intestinal microbiota encompasses microorganisms such as viruses, bacteria and fungi, and this community plays an essential role in modulating host metabolism and immunity (1). Although the intestinal microbiota is well integrated within host function, a series of mechanisms such as a functional intestinal barrier, mucosal immune surveillance and metabolic crosstalk are in place to maintain homeostasis. Breakdown of these various interactive processes have the potential to dysregulate host-microbe interactions, leading to intestinal pathologies such as inflammatory bowel diseases (IBD) and colorectal cancer

*Correspondence: Christian Jobin, Dept of Medicine, 2033 Mowry Rd, PO Box 103633, Gainesville, FL 32611-0882, Christian.Jobin@medicine.ufl.edu, Phone: 352-294-5148; Fax: 352-392-3944.

Conflicts of interest: There are no conflicts of interest.

(CRC) (2, 3). Recent studies have brought a more detailed understanding of how these regulatory mechanisms ensure optimal integration of host-microbe interactions and help maintain homeostasis. Here we summarize these findings and discuss their impact on IBD and CRC pathogenesis.

Barrier function

Interactions between the intestinal microbiota and the host mucosal compartment are tightly regulated by both a physical barrier and secreted molecules such as mucus, antimicrobial peptides (AMPs) and immunoglobulin A (IgA).

Goblet cells produce various mucins (MUC2, MUC3 and MUC4) that form a polymeric network of glycosylated proteins restraining physical interactions between microbes and the epithelia. MUC2 deficiency in mice leads to overexpression of the goblet cells-derived mucosal defense factor RELM- β , which induces colonic production of the antimicrobial lectins REGIII β and REGIII γ (4**). REGIII β predominantly targets *Lactobacillus* species, potent producers of beneficial short-chain fatty acids, and oral gavage of murine *Lactobacilli* isolates reduced RELM- β and REGIII β levels and ameliorated spontaneous colitis in *Muc2*^{-/-} mice (4**). In contrast, MUC4 appears to promote colitis and tumorigenesis as *Muc4*^{-/-} mice are more resistant to DSS colitis and AOM/DSS-induced tumorigenesis, which might be due to compensatory upregulation of MUC2 and MUC3 in mutant mice (5). In addition, intestinal mucin-type O-glycosylation is essential to prevent bacterial intrusion and caspase-1 inflammasome activation, thereby protecting against colitis and CRC (6).

Intestinal IgA serves as a defense mechanism against enteric microorganisms and toxins. Malik et al. showed that IL-33 modulates the IgA-microbiota axis to prevent IL-1 α -dependent colitis and tumorigenesis (7*). IL-33 synergizes with TGF- β to promote IgA production by B cells (7*). *Il-33*^{-/-} mice have reduced colonic IgA, altered microbiota characterized by expansion of the mucolytic *Akkermansia*, and are more susceptible to DSS colitis and AOM/DSS-induced CAC which can be rescued by inhibiting IL-1 α (7*). Cohousing with WT mice or metronidazole depletion of *Akkermansia* protects *Il-33*^{-/-} mice from DSS colitis (7*).

Lipocalin 2 (LCN2) is a siderophore-binding antimicrobial protein that limits bacterial iron acquisition. LCN2 is induced by microbiota in a MYD88-dependent manner and prevents formation of a colitogenic microbiota (8). *Lcn2*^{-/-} mice display microbial dysbiosis, characterized by higher bacterial load, increased relative abundance of *Bacteroidetes* and *Proteobacteria* and decreased *Tenericutes* (8). Cohousing *Lcn2*^{-/-} and *Il-10*^{-/-} mice exacerbated colitis in the latter (8). Consistently, Moschen et al reported that *Lcn2*^{-/-}/*Il-10*^{-/-} mice developed spontaneous colitis and invasive right-sided tumors due to dysregulated microbiota (9**). In particular, LCN2 inhibits growth of *Alistipes* spp. (9**), which are associated with human CRC (10). *Alistipes finegoldii* colonization induces CAC development via activation of IL-6/STAT3 signaling in *Il-10*^{-/-} mice (9**).

Ly6/PLAUR domain containing 8 (LYPD8) was recently identified by Okumura et al to segregate colonic mucosa from flagellated bacteria (11**). LYPD8 is a highly N-

glycosylated protein expressed by colonic epithelial cells and secreted into the lumen, where it binds to flagella, thereby inhibiting bacterial motility (11**). PCR-based microbial analysis using bacterial genus-specific primers showed that the colon tissue of *Lypd8*^{-/-} mice contains higher abundance of *Proteus*, *Helicobacter* and *Escherichia*. In particular, *Proteus mirabilis* was found in close proximity to the colonic epithelium as shown by culture assay and fluorescence-labeled bacteria *in vivo* (11**). Not surprisingly, *Lypd8*^{-/-} mice are highly susceptible to DSS colitis (11**). Interestingly, colonic expression of LYPD8 is decreased in UC and CRC patients, suggesting a potential role in human diseases (11**).

Aside from these barrier-modulating agents, the intestinal epithelium itself forms a physical barrier against invading microorganisms. Disruption of intestinal epithelial homeostasis leads to colitis and/or tumorigenesis which can be enhanced by microbiota. For example, mice with fucosylation deficiency (*Fx*^{-/-}) display loss of Notch activation and downregulation of the Notch target gene *Hes1* in the colonic epithelium, accompanied by a progressive increase in gut epithelial permeability (12). Consistent with the role of Notch in regulating epithelial cell lineage commitment, *Fx*^{-/-} mice show goblet cell expansion and aberrant crypt proliferation in the colon (12). Notably, *Fx*^{-/-} mice sequentially developed colitis, dysplasia and adenocarcinoma, which can be prevented by antibiotic treatment (12). Similarly, mice with IEC-specific deletion of the IBD susceptibility gene *Ptpn11* exhibit impaired goblet cell differentiation in the colon and dysbiotic microbiota which drive spontaneous colitis development (13).

At the basal side, the intestinal epithelium is connected to the basement membrane via hemidesmosomes where plectin links $\alpha6\beta4$ integrin to cytoplasmic keratin filaments. Mice with IEC-specific deletion of $\alpha6$ integrin developed spontaneous colitis and adenocarcinoma (14). Inflammation, which can be attenuated by antibiotic treatment, is driven by epithelium detachment-induced caspase-1 inflammasome activation and IL-18 secretion by epithelial cells, whereas tumorigenesis depends on IL-1 signaling and adaptive immunity (14). Liu et al showed that mice haplodeficient in keratin 8, a major intermediate filament protein in the intestinal epithelia, were more susceptible to DSS colitis and more prone to AOM/DSS-induced CAC, which could be attenuated by TLR4 inhibition and antibiotic treatment respectively (15). Together, the data suggest that compromised structural integrity of the epithelia increases the risk for inflammation and tumor development.

Tumor sites have impaired barrier which can further enhance carcinogenesis. One mechanism recently demonstrated by Peuker et al is that intruding bacteria activate TLR-dependent calcineurin/NFAT signaling in neoplastic cells, resulting in upregulation of stem cell-associated genes (e.g., *Cd44v6*, *Lgr5*, *Olfm4* and *Dclk1*) and thus tumor stem cell function (16*).

Innate sensors and immune signaling

The host recognizes microbial structures and components via pattern-recognition receptors (PPRs) such as Toll-like receptors (TLRs), Nod-like receptors (NLRs) and RIG-I-like receptors (RLRs) expressed by a variety of immune and non-immune cells.

Increased expression of TLR4 has been reported in the epithelium of patients with IBD, CAC and sporadic colon cancers. Overexpression of TLR4 in intestinal epithelial cells (IECs) results in disrupted barrier function and dysbiotic microbiota characterized by increased abundance of *Lachnospiraceae* (17). This altered microbiota is proinflammatory as cohoused WT mice exhibit increased sensitivity to DSS colitis (17).

NOD2 is an IBD susceptibility gene and has been linked to human CRC. Udden et al recently demonstrated that *NOD2* negatively regulates TLR/NF- κ B signaling to suppress tumorigenesis (18*). Cohousing and microbiota transfer experiments suggest that the microbiota enhances colitis but appears not to be the major driver of the increased CRC susceptibility observed in *Nod2*^{-/-} mice compared to WT mice (18*). Mechanistically, *NOD2* induces IRF4 which interacts with MYD88 and TRAF6 to suppress TLR/NF- κ B signaling in myeloid cells (18*).

Expression of NLRC3 is reduced in CRC tumors. Karki et al demonstrated that NLRC3 suppresses tumorigenesis by inhibiting PI3K-AKT-mTOR signaling in *Apc*^{min/+} mice and AOM/DSS-treated WT mice (19). At the molecular level, NLRC3 interacts with PI3K to block AKT activation and binds to TRAF6 to attenuate TLR/NF- κ B and mTOR activation (19, 20).

Activation of the NLRP6 inflammasome is modulated by microbiota-derived metabolites such as taurine and histamine, and regulates IL-18 and AMP production to maintain gut homeostasis (21). In addition, NLRP6-induced IL-18 cytokine expression prevents colitis in *Il-10*^{-/-} mice by limiting expansion of *Akkermansia muciniphila* (22**). *A. muciniphila* induces colitis in specific-pathogen-free (SPF) *Il-10*^{-/-} mice, likely owing to its ability to degrade mucus and activate TLR4/MYD88 signaling (22**). Similarly, Chen et al demonstrated that NLRP12, whose expression is downregulated in UC patients, prevents microbiota-driven colitis (23*). *Nlrp12*^{-/-} mice have a less diverse microbiota characterized by decreased abundance of *Lachnospiraceae* and increased *Erysipelotrichaceae*, and displayed higher susceptibility to DSS colitis which can be suppressed by oral supplementation of *Lachnospiraceae* (23*).

RIG-I recognizes double-stranded viral RNA and mediates antiviral immunity. Zhu et al found that RIG-I expression was downregulated in human CAC tumor sites and that *Rig-I*^{-/-} mice had reduced levels of intestinal IgA and REGIII γ , concurrent with disturbance in microbiota composition, compared to WT mice (24). *Rig-I*^{-/-} mice are more susceptible to AOM/DSS-induced tumorigenesis, which can be partially attenuated by antibiotic treatment (24), suggesting bacteria-dependent and -independent mechanisms contribute to the protective role of RIG-I against CAC.

IRAK-M is a negative regulator of TLR/NF- κ B signaling and found to be upregulated in IBD and CRC patients (25, 26). *Irak-m*^{-/-} mice showed enhanced colitis but reduced tumorigenesis following AOM/DSS treatment (25). Cohousing experiments suggest that inflammation, but not tumorigenesis, is microbiota-dependent in *Irak-m*^{-/-} mice (25). TLR and WNT activation in tumor cells drive IRAK-M expression, which promotes tumorigenesis by preventing STAT3 proteasomal degradation (25). Another study confirmed

the protective role of IRAK-M against AOM/DSS-induced tumorigenesis, although the authors reported resistance to DSS colitis and attenuation of intestinal microbial translocation in *Irak-m*^{-/-} mice (26).

NEMO is a component of the I κ B kinase complex which activates NF- κ B by phosphorylating I κ B proteins. Mice lacking NEMO in IECs develop spontaneous colitis in SPF but not germ-free conditions, supporting the critical role of microbiota (27). Further investigation reveals that NEMO prevents Paneth cell and colonic epithelial cell death by activating NF- κ B and inhibiting RIPK1 kinase activity respectively (27).

Metabolism

CARD9 is an IBD susceptibility gene involved in regulation of PPR-induced inflammatory responses and inflammasome activities. *Card9*^{-/-} mice have altered microbiota characterized by decreased abundance of *Adlercreutzia* (genus), Actinobacteria (phylum) and *Lactobacillus reuteri*, resulting in defective tryptophan metabolism into indole derivatives such as indole-3-acetic acid (28**). Therefore, these mice fail to activate aryl hydrocarbon receptor (AHR) to induce IL-22 expression (28**). Inoculating *Card9*^{-/-} mice with tryptophan-metabolizing *Lactobacillus* strains or treatment with an AHR agonist attenuated DSS colitis, suggesting CARD9 regulates the microbiota-tryptophan-AHR-IL-22 axis to affect colitis susceptibility (28**). Importantly, AHR activity and tryptophan metabolites are found to be reduced in IBD patients (28**).

Bile acids are end products of hepatic cholesterol catabolism and secreted into the gut lumen where they are transformed by bacteria into secondary bile acids including lithocholic acid and deoxycholic acid (DCA). Recent studies demonstrated bile acids can affect microbiota and development of colitis and CRC. For example, IEC-derived SIRT1, a NAD⁺-dependent protein deacetylase downregulated in UC patients, prevents age-dependent reduction of Bacilli/*Lactobacillus* partially via regulating bile acid metabolism (29). In addition, DCA administration accelerates tumorigenesis by inducing microbiota dysbiosis and inflammation in *Apc*^{min/+} mice (30*). Fecal transfer of DCA-treated but not untreated *Apc*^{min/+} mice induced low grade inflammation and activated M2 tumor-associated macrophages and the WNT/ β -catenin pathway in recipient *Apc*^{min/+} mice (30*).

Vitamin A metabolite all-trans-retinoic acid (atRA) is mainly produced by the epithelium and plays important physiological functions. In human sporadic CRC, UC and UC-associated CRC, the atRA-synthesizing enzyme ALDH1 is significantly decreased whereas the atRA-catabolizing enzyme CYP26A1 is increased, suggestive of common atRA deficiency in these pathologies (31*). Using the AOM/DSS CAC mouse model, Bhattacharya et al demonstrated that atRA protects against tumorigenesis by enhancing anti-tumor CD8⁺ T cell response and that microbiota-induced inflammatory cytokines promote differential expression of ALDH1 and CYP26A1 as observed in patients (31*). The microbiota metabolite butyrate was recently shown to stimulate ALDH1 expression, thereby increasing atRA levels in epithelial cells (32).

MiRNAs

Liu et al recently showed that miRNAs, mainly produced by IECs and Hopx⁺ cells, are abundantly present in the gut lumen and play a role in shaping the microbiota composition (33**). MiRNAs can enter bacterial cells and directly bind DNA based on sequence similarity to affect bacterial gene expression and growth, as demonstrated by the effects of human miR-515-5p on *Fusobacterium nucleatum* and miR-1226-5p on *Escherichia coli* (33**). Interestingly, germ-free mice or antibiotics-treated mice have more abundant and different profiles of fecal miRNAs compared to SPF mice, suggesting that the microbiota modulates miRNA expression in the gut (33**).

Activation of inflammatory responses appears to play a role in microbial regulation of miRNAs. *F. nucleatum* induces miR-21 in CRC cells by activating TLR4/MYD88/NF- κ B signaling, a process responsible for the enhanced CRC cell proliferation and invasion following infection (34*). Given that inflammatory responses are commonly associated with bacterial infection which likely occurs frequently in IBD and CAC where barrier function is impaired, microbe-miRNA reciprocal modulation might be a key component of the disease etiology.

Specific microbes

Enterotoxigenic *Bacteroides fragilis* (ETBF), *pks*⁺ adherent invasive *E. coli* and *F. nucleatum* have been shown to possess colitogenic and/or carcinogenic activities (2, 3). Duration of ETBF colonization positively correlates with tumorigenesis in Min^{Apc} 716 mice, suggesting that early ETBF acquisition is potentially carcinogenic and that depletion of this bacterium could prevent cancer (35). Abed et al demonstrated that *F. nucleatum* preferentially accumulates in colorectal adenocarcinomas via Fap2/Gal-GalNAc interaction (36). However, Tomkovich et al found that several *F. nucleatum* clinical isolates, although carrying putative carcinogenic genes such as *fap2* and *fadA*, failed to enhance tumorigenesis in 129/SvEv *Apc*^{min/+} and *Apc*^{min/+}; *Il-10*^{-/-} mice, suggesting that carcinogenic activities are strain- and model-specific (37).

Recent studies have identified new bacterial drivers of colitis and/or tumorigenesis in preclinical models. For example, Mottawea et al showed that abundance of H₂S-producing bacteria including *Atopobium parvulum* positively correlates with pediatric IBD disease severity (38*). *A. parvulum* promotes colitis in conventionalized *Il-10*^{-/-} mice, which can be attenuated by the H₂S scavenger bismuth (38*). Tsoi et al demonstrated that *Peptostreptococcus anaerobius*, which is increased in human colon tumors compared with non-tumor tissues, enhances AOM-induced tumorigenesis in mice by activating TLR2/4-ROS-cholesterol axis (39*).

Conclusion

These studies highlight the rapid pace of discoveries made in the field of microbiota and intestinal pathologies and specifically underscore the critical importance of proper integration of host-microbiota crosstalk. The signaling events initiated by host-microorganism communication through either structural proteins or small molecules offer

new perspectives for therapeutic intervention. For example, microbial components implicated in barrier function, metabolism and immune modulation could serve as therapeutic targets for management of inflammation and carcinogenesis. Although great progress has been made in this field of research, a number of challenges lie ahead. For example, big gap of knowledge exists about microbial interspecies communication and how this affects host homeostasis. Since IBD and CRC are diseases associated with not only breakdown of host-microbe interaction but also likely defective polymicrobial interplay, it is essential to decipher this complex communication network. Moreover, the literature on microbiota and IBD/CRC pathology is vastly dominated by research examining roles of bacteria, with little attention to other members of the community (viruses, fungi, etc). Although links have been made regarding the implication of these microorganisms in intestinal pathology (40), more research is needed to understand their functions and disease-modulating mechanisms, particularly trans-kingdom interactions. We expect that future studies will provide a comprehensive view of how the microbiota and its complex constituents interact with the host to influence health and disease.

Acknowledgments

We would like to thank Dr. Sarah Tomkovich and Rachel C. Newsome for help editing the review. Due to space restriction, we were not able to cite all scientists whose work has contributed to this field of research.

Financial support and sponsorship: This research was supported by National Institutes of Health grants RO1DK073338, RO1AT08623 and R21CA195226 to C. Jobin. Y. Yang was supported by the Crohn's & Colitis Foundation of America (CCFA) research fellowship award (CCFA Ref. #409472).

References

1. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol*. 2016; 16(6):341–52. [PubMed: 27231050]
2. Brennan CA, Garrett WS. Gut Microbiota, Inflammation, and Colorectal Cancer. *Annu Rev Microbiol*. 2016; 70:395–411. [PubMed: 27607555]
3. Kang M, Martin A. Microbiome and colorectal cancer: Unraveling host-microbiota interactions in colitis-associated colorectal cancer development. *Semin Immunol*. 2017
- 4**. Morampudi V, Dalwadi U, Bhinder G, et al. The goblet cell-derived mediator RELM-beta drives spontaneous colitis in Muc2-deficient mice by promoting commensal microbial dysbiosis. *Mucosal Immunol*. 2016; 9(5):1218–33. This study demonstrates that MUC2 deficiency in mice leads to overproduction of REGIII that predominantly targets *Lactobacilli* and that supplementation of *Lactobacilli* ameliorates spontaneous colitis MUC2-deficient mice. [PubMed: 26813339]
5. Das S, Rachagani S, Sheinin Y, et al. Mice deficient in Muc4 are resistant to experimental colitis and colitis-associated colorectal cancer. *Oncogene*. 2016; 35(20):2645–54. [PubMed: 26364605]
6. Bergstrom K, Liu X, Zhao Y, et al. Defective Intestinal Mucin-Type O-Glycosylation Causes Spontaneous Colitis-Associated Cancer in Mice. *Gastroenterology*. 2016; 151(1):152–64 e11. [PubMed: 27059389]
- 7*. Malik A, Sharma D, Zhu Q, et al. IL-33 regulates the IgA-microbiota axis to restrain IL-1alpha-dependent colitis and tumorigenesis. *J Clin Invest*. 2016; 126(12):4469–81. This study demonstrates that IL-33 deficiency leads to reduced colonic IgA levels, dysbiosis characterized by expansion of *Akkermansia*, and enhanced susceptibility to DSS colitis and AOM/DSS-induced CAC which can be attenuated by blocking IL-1α. [PubMed: 27775548]
8. Singh V, Yeoh BS, Chassaing B, et al. Microbiota-inducible Innate Immune, Siderophore Binding Protein Lipocalin 2 is Critical for Intestinal Homeostasis. *Cell Mol Gastroenterol Hepatol*. 2016; 2(4):482–98 e6. [PubMed: 27458605]

- 9**. Moschen AR, Gerner RR, Wang J, et al. Lipocalin 2 Protects from Inflammation and Tumorigenesis Associated with Gut Microbiota Alterations. *Cell Host Microbe*. 2016; 19(4): 455–69. This study demonstrates that LCN2 inhibits growth of *Alistipes* spp. and that *A. finegoldii* activates IL-6/STAT3 signaling to promote CAC development in *Il-10^{-/-}* mice. [PubMed: 27078067]
10. Feng Q, Liang S, Jia H, et al. Gut microbiome development along the colorectal adenoma-carcinoma sequence. *Nat Commun*. 2015; 6:6528. [PubMed: 25758642]
- 11**. Okumura R, Kurakawa T, Nakano T, et al. Lypd8 promotes the segregation of flagellated microbiota and colonic epithelia. *Nature*. 2016; 532(7597):117–21. This study demonstrates that LYPD8 secreted by colonic epithelial cells binds to flagella to inhibit bacterial motility and invasion to mucosa. [PubMed: 27027293]
12. Wang Y, Huang D, Chen KY, et al. Fucosylation Deficiency in Mice Leads to Colitis and Adenocarcinoma. *Gastroenterology*. 2017; 152(1):193–205 e10. [PubMed: 27639802]
13. Coulombe G, Langlois A, De Palma G, et al. SHP-2 Phosphatase Prevents Colonic Inflammation by Controlling Secretory Cell Differentiation and Maintaining Host-Microbiota Homeostasis. *J Cell Physiol*. 2016; 231(11):2529–40. [PubMed: 27100271]
14. De Arcangelis A, Hamade H, Alpy F, et al. Hemidesmosome integrity protects the colon against colitis and colorectal cancer. *Gut*. 2016
15. Liu C, Liu ED, Meng YX, et al. Keratin 8 reduces colonic permeability and maintains gut microbiota homeostasis, protecting against colitis and colitis-associated tumorigenesis. *Oncotarget*. 2017
- 16*. Peuker K, Muff S, Wang J, et al. Epithelial calcineurin controls microbiota-dependent intestinal tumor development. *Nat Med*. 2016; 22(5):506–15. This study demonstrates that bacteria activate TLR-dependent calcineurin/NFAT signaling to enhance tumor cell stemness. [PubMed: 27043494]
17. Dheer R, Santaolalla R, Davies JM, et al. Intestinal Epithelial Toll-Like Receptor 4 Signaling Affects Epithelial Function and Colonic Microbiota and Promotes a Risk for Transmissible Colitis. *Infect Immun*. 2016; 84(3):798–810. [PubMed: 26755160]
- 18*. Udden SMN, Peng L, Gan JL, et al. NOD2 Suppresses Colorectal Tumorigenesis via Downregulation of the TLR Pathways. *Cell Rep*. 2017; 19(13):2756–70. This study demonstrates that NOD2 induces IRF4 to suppress TLR/NF- κ B signaling, thereby preventing tumorigenesis. [PubMed: 28658623]
19. Karki R, Man SM, Malireddi RK, et al. NLRC3 is an inhibitory sensor of PI3K-mTOR pathways in cancer. *Nature*. 2016
20. Karki R, Malireddi RKS, Zhu Q, Kanneganti TD. NLRC3 regulates cellular proliferation and apoptosis to attenuate the development of colorectal cancer. *Cell Cycle*. 2017:1–9.
21. Levy M, Thaïss CA, Zeevi D, et al. Microbiota-Modulated Metabolites Shape the Intestinal Microenvironment by Regulating NLRP6 Inflammasome Signaling. *Cell*. 2015; 163(6):1428–43. [PubMed: 26638072]
- 22**. Seregin SS, Golovchenko N, Schaf B, et al. NLRP6 Protects *Il10^{-/-}* Mice from Colitis by Limiting Colonization of *Akkermansia muciniphila*. *Cell Rep*. 2017; 19(10):2174. This study demonstrates that NLRP6-induced IL-18 inhibits *A. muciniphila* colonization to prevent spontaneous colitis in *Il-10^{-/-}* mice.
- 23*. Chen L, Wilson JE, Koenigsnecht MJ, et al. NLRP12 attenuates colon inflammation by maintaining colonic microbial diversity and promoting protective commensal bacterial growth. *Nat Immunol*. 2017; 18(5):541–51. This study demonstrates that NLRP12 deficiency leads to dysbiosis and enhanced susceptibility to DSS colitis which can be prevented by oral supplementation of Lachnospiraceae. [PubMed: 28288099]
24. Zhu H, Xu WY, Hu Z, et al. RNA virus receptor Rig-I monitors gut microbiota and inhibits colitis-associated colorectal cancer. *J Exp Clin Cancer Res*. 2017; 36(1):2. [PubMed: 28057020]
25. Kesselring R, Glaesner J, Hiergeist A, et al. IRAK-M Expression in Tumor Cells Supports Colorectal Cancer Progression through Reduction of Antimicrobial Defense and Stabilization of STAT3. *Cancer Cell*. 2016; 29(5):684–96. [PubMed: 27150039]

26. Rothschild DE, Zhang Y, Diao N, et al. Enhanced Mucosal Defense and Reduced Tumor Burden in Mice with the Compromised Negative Regulator IRAK-M. *EBioMedicine*. 2017; 15:36–47. [PubMed: 27939424]
27. Vlantis K, Wullaert A, Polykratis A, et al. NEMO Prevents RIP Kinase 1-Mediated Epithelial Cell Death and Chronic Intestinal Inflammation by NF-kappaB-Dependent and -Independent Functions. *Immunity*. 2016; 44(3):553–67. [PubMed: 26982364]
- 28*. Lamas B, Richard ML, Leducq V, et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. *Nat Med*. 2016; 22(6):598–605. This study demonstrates that CARD9 regulates the microbiota-tryptophan-AHR-IL-22 axis to affect susceptibility to DSS colitis in mice. [PubMed: 27158904]
29. Wellman AS, Metukuri MR, Kazgan N, et al. Intestinal Epithelial Sirtuin 1 Regulates Intestinal Inflammation during Aging in Mice by Altering the Intestinal Microbiota. *Gastroenterology*. 2017
- 30*. Cao H, Xu M, Dong W, et al. Secondary bile acid-induced dysbiosis promotes intestinal carcinogenesis. *Int J Cancer*. 2017; 140(11):2545–56. This study demonstrates that DCA promotes CRC by inducing microbiota dysbiosis and inflammation in *Apc^{min/+}* mice. [PubMed: 28187526]
- 31*. Bhattacharya N, Yuan R, Prestwood TR, et al. Normalizing Microbiota-Induced Retinoic Acid Deficiency Stimulates Protective CD8(+) T Cell-Mediated Immunity in Colorectal Cancer. *Immunity*. 2016; 45(3):641–55. This study demonstrates that microbiota regulates levels of atRA which protects against tumorigenesis by enhancing anti-tumor CD8+ T cell response. [PubMed: 27590114]
32. Schilderink R, Verseijden C, Seppen J, et al. The SCFA butyrate stimulates the epithelial production of retinoic acid via inhibition of epithelial HDAC. *Am J Physiol Gastrointest Liver Physiol*. 2016; 310(11):G1138–46. [PubMed: 27151945]
- 33*. Liu S, da Cunha AP, Rezende RM, et al. The Host Shapes the Gut Microbiota via Fecal MicroRNA. *Cell Host Microbe*. 2016; 19(1):32–43. This study demonstrates that abundant miRNAs are present in the intestinal lumen which is regulated by the microbiota and plays a role in shaping the microbiota composition. [PubMed: 26764595]
- 34*. Yang Y, Weng W, Peng J, et al. *Fusobacterium nucleatum* Increases Proliferation of Colorectal Cancer Cells and Tumor Development in Mice by Activating Toll-Like Receptor 4 Signaling to Nuclear Factor-kappaB, and Up-regulating Expression of MicroRNA-21. *Gastroenterology*. 2017; 152(4):851–66 e24. This study demonstrates that *F. nucleatum* enhances cancer cell proliferation and invasion by upregulating miRNA-21. [PubMed: 27876571]
35. DeStefano Shields CE, Van Meerbeke SW, Housseau F, et al. Reduction of Murine Colon Tumorigenesis Driven by Enterotoxigenic *Bacteroides fragilis* Using Cefoxitin Treatment. *J Infect Dis*. 2016; 214(1):122–9. [PubMed: 26908749]
36. Abed J, Enggård JE, Zamir G, et al. Fap2 Mediates *Fusobacterium nucleatum* Colorectal Adenocarcinoma Enrichment by Binding to Tumor-Expressed Gal-GalNAc. *Cell Host Microbe*. 2016; 20(2):215–25. [PubMed: 27512904]
37. Tomkovich S, Yang Y, Winglee K, et al. Locoregional Effects of Microbiota in a Preclinical Model of Colon Carcinogenesis. *Cancer Res*. 2017; 77(10):2620–32. [PubMed: 28416491]
- 38*. Mottawea W, Chiang CK, Mühlbauer M, et al. Altered intestinal microbiota-host mitochondria crosstalk in new onset Crohn's disease. *Nat Commun*. 2016; 7:13419. This study demonstrates that the abundance of H₂S-producing bacteria including *A. parvulum* positively correlates with pediatric IBD severity and that *A. parvulum* induces colitis in *IL-10^{-/-}* mice which can be ameliorated by the H₂S scavenger bismuth. [PubMed: 27876802]
- 39*. Tsoi H, Chu ESH, Zhang X, et al. *Peptostreptococcus anaerobius* Induces Intracellular Cholesterol Biosynthesis in Colon Cells to Induce Proliferation and Causes Dysplasia in Mice. *Gastroenterology*. 2017; 152(6):1419–33 e5. This study demonstrates that *P. anaerobius* enhances AOM-induced tumorigenesis in mice by activating the TLR2/4- ROS-cholesterol axis. [PubMed: 28126350]
40. Sartor RB, Wu GD. Roles for Intestinal Bacteria, Viruses, and Fungi in Pathogenesis of Inflammatory Bowel Diseases and Therapeutic Approaches. *Gastroenterology*. 2017; 152(2):327–39 e4. [PubMed: 27769810]

Key points

- Proper mucosal barrier function maintained by secreted molecules (mucin, IgA, AMPs, etc) and structural components (epithelium, hemidesmosome, keratin, etc) prevents microbial invasion and CAC.
- Aberrant innate signaling and immune responses fosters development of a dysbiotic microbiota which could aggravate inflammation and tumorigenesis.
- Metabolic interactions between host and microbiota via tryptophan, bile acids and vitamin A critically impact colitis and CRC development.
- MiRNAs emerge as important mediators of host-microbiota crosstalk.
- *A. finegoldii*, *A. muciniphila*, *A. parvulum* and *P. anaerobius* are newly identified microbial drivers of colitis and/or CRC.