REVIEW

Bugs, genes, fatty acids, and serotonin: Unraveling inflammatory bowel disease? [version 1; peer review: 3 approved]

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V1 First published: 27 Oct 2015, 4(F1000 Faculty Rev):1146
<https://doi.org/10.12688/f1000research.6456.1>

Latest published: 27 Oct 2015, 4(F1000 Faculty Rev):1146
<https://doi.org/10.12688/f1000research.6456.1>

Abstract

The annual incidence of the inflammatory bowel diseases (IBDs) ulcerative colitis and Crohn's disease has increased at an alarming rate. Although the specific pathophysiology underlying IBD continues to be elusive, it is hypothesized that IBD results from an aberrant and persistent immune response directed against microbes or their products in the gut, facilitated by the genetic susceptibility of the host and intrinsic alterations in mucosal barrier function. In this review, we will describe advances in the understanding of how the interaction of host genetics and the intestinal microbiome contribute to the pathogenesis of IBD, with a focus on bacterial metabolites such as short chain fatty acids (SCFAs) as possible key signaling molecules. In particular, we will describe alterations of the intestinal microbiota in IBD, focusing on how genetic loci affect the gut microbial phylogenetic distribution and the production of their major microbial metabolic product, SCFAs. We then describe how enteroendocrine cells and myenteric nerves express SCFA receptors that integrate networks such as the cholinergic and serotonergic neural systems and the glucagon-like peptide hormonal pathway, to modulate gut inflammation, permeability, and growth as part of an integrated model of IBD pathogenesis. Through this integrative approach, we hope that novel hypotheses will emerge that will be tested in reductionist, hypothesis-driven studies in order to examine the interrelationship of these systems in the hope of better understanding IBD pathogenesis and to inform novel therapies.

Keywords

Inflammatory bowel disease, ulcerative colitis, crohn's diseases, IBD

Open Peer Review

Approval Status

	1	2	3
version 1			
27 Oct 2015			

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Competing interests: The authors declare that they have no disclosures.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Kaunitz JD and Nayyar P. **Bugs, genes, fatty acids, and serotonin: Unraveling inflammatory bowel disease? [version 1; peer review: 3 approved]** F1000Research 2015, 4(F1000 Faculty Rev):1146 <https://doi.org/10.12688/f1000research.6456.1>

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Introduction

Inflammatory bowel disease (IBD) is a term encompassing two major types of disorders—ulcerative colitis and Crohn’s disease—that are characterized by chronic relapsing intestinal inflammation¹. The incidence and prevalence of IBD has increased globally over the past few decades: in a systematic review of population-based IBD data, the average annual incidence rate was reported as 1.2–23.3% for Crohn’s disease and 2.4–18.1% for ulcerative colitis from 1920–2010². Recent estimates of the total annual financial burden (including direct and indirect costs) of IBD in the US are \$14.6–\$31.6 billion^{3–6}. Although newer therapies that have improved quality-of-life for a subset of patients have emerged in recent years, the underlying causes of and preventative measures against IBD remain unknown.

Major scientific advances over the last decade in the fields of genetics, immunology, and microbiology have increased our understanding of the underlying pathways involved in IBD. Although the specific pathophysiology continues to be elusive, it is hypothesized that IBD results from an aberrant and persistent immune response directed against microbes or their products in the gut, facilitated by the genetic susceptibility of the host and intrinsic alterations in mucosal barrier function. **Figure 1** depicts the historical trends of increasing IBD-related research articles that focus on genetics and gut microbiome since the year 2000⁷.

We will describe advances in the understanding of how the interaction of host genetics and the intestinal microbiome contribute to the pathogenesis of IBD, with a focus on bacterial metabolites such as short chain fatty acids (SCFAs) as possible key signaling molecules.

Genetics

The argument for a genetic predisposition to IBD begins with the observation that family members of affected persons have a greatly increased risk for developing IBD, with a relative risk 8–10 times higher amongst first-degree relatives of IBD patients compared with the general population^{8,9}. Subsequent epidemiological data, which include differences in prevalence amongst different ethnic groups, familial aggregation of IBD, concordance in twins, and association with genetic syndromes, further confirmed the influence of genetics in IBD^{8–13}. These instrumental early studies preceded the era of modern IBD genetic research with the discovery of the nucleotide-binding oligomerization domain containing 2 (*NOD2*) gene in 2001, the first susceptibility gene discovered for Crohn’s disease^{14–16}. In an analysis of 75,000 IBD cases and controls, including data from 15 different genome-wide association scans (GWAS) for ulcerative colitis and Crohn’s disease, the International IBD Genetics Consortium (IIBDGC) identified 71 new causative regions, increasing the total number of independent IBD risk loci to 163: 110 associated with both diseases, 30 classified as Crohn’s disease-specific, and 23 as

Figure 1. Historical trends of IBD research since the year 2000. The graph depicts increasing IBD-related research articles that focus on genetics and gut microbiome. Adapted from 7.

ulcerative colitis-specific. The notable overlap of genetic loci suggests that Crohn's disease and ulcerative colitis share many biological mechanisms: 43 of the 53 disease specific loci have the same direction of effect in both diseases, suggesting concordance for many of the biological mechanisms implicated in both diseases. Insight into biological differences is supported by the observation that two risk loci for Crohn's disease, *NOD2* and *PTPN22*, are protective for ulcerative colitis^{17–19}. These strategies have identified several important signaling pathways that have consistently been associated with susceptibility to IBD. **Figure 2** depicts genetic loci associated with IBD, grouped by disease specificity and involved pathways¹⁹.

Some of these pathways highlight the interaction between the host, the microbiome, and their products. Genetic analysis has highlighted the importance of autophagy in immune responses in IBD. Autophagy, involved in intracellular homeostasis, facilitates the degradation and recycling of cytosolic contents and organelles, and also helps resist microbial infection by removing intracellular microbes²⁰. In Crohn's disease, several genes (*ATG16L1*, *IRGM*, and *LRRK*) regulate the autophagy pathway, including *NOD2*, further supporting the theory of defective microbial degradation in some patients with Crohn's disease^{21–26}.

Genetic loci also affect innate and adaptive immunity and epithelial function. Specifically, *NOD2* modulates innate and adaptive immune responses^{14,15}. Further, adaptive immune genes that regulate

the interleukin (IL)-17 and IL-23 receptor pathways are implicated in IBD risk, including genes associated with risk for ulcerative colitis and Crohn's disease (e.g., *IL23R*, *IL12B*, *STAT3*, *JAK2*, and *TYK2*) and those implicated in Crohn's disease only (e.g., *IL-27*, *TNFSF15*). A number of genes associated with epithelial barrier function are also specifically associated with only ulcerative colitis and not with Crohn's disease (e.g., *OCTN2*, *ECM1*, *CDH1*, *HNF4A*, *LAMB1*, and *GNA12*)^{13,27,28,30,31}. Genes that control Paneth cell biology and the endoplasmic reticulum (ER) stress/unfolded protein response are also associated with Crohn's disease (e.g., *Xbp-1*; *Nod2*)³².

Different compositions of gut microbiota affect epigenetic regulation of genes through microbial products such as SCFAs³³. Butyrate, one type of SCFA, influences epigenetic methylation of SCFA receptors, especially the promoter region of the free fatty acid receptor 3 (FFAR3) with consequent effects on gene expression and function³⁴. We will further discuss SCFAs and their specific pathways later in this review.

Despite the above-mentioned advances, no genetic associations can be confirmed in 77% of Crohn's disease patients and in up to 84% of ulcerative colitis patients³⁰. Alterations in 163 distinct single genes confer only a modest effect in and of themselves, suggesting that an aggregate effect at several loci may be responsible for the IBD phenotype³⁵. For instance, as many as 20 to 30% of patients with Crohn's disease may have a variant *NOD2*, though the

Figure 2. Genetic loci associated with IBD. IBD loci are represented by lead gene name and grouped by disease specificity and involved pathways. Loci associated with inflammatory bowel disease are shown in black, Crohn's disease (CD) in blue, ulcerative colitis (UC) in green and both UC and CD in black. Adapted from ¹⁹.

penetrance is not more than 5% of homozygous and roughly 0.5% in heterozygous persons³¹. This indicates that disease-related allelic variants of the gene may be present in a large number of persons who do not have Crohn's disease.

While the increasing number of susceptibility gene loci described in IBD reflects their importance, the loci discovered so far account for only 20–25% of IBD heritability³⁰. Further, the remarkable rise of the incidence of IBD over the past few decades cannot be sufficiently explained by only genetic risk or increased diagnosis and accessibility of care², which has opened the doors for immunological, environmental and particularly microbial-based research in this field.

Microbiome

A microbial etiology for IBD has long been hypothesized, starting with descriptions of potential infectious agents associated with ulcerative colitis in the 19th century and Crohn's disease in the early 20th century^{36,37}. In the 1920s, Rettger *et al.* studied the effects of *Bacillus acidophilus* on IBD, while in the 1940s Kirsner evaluated the possible correlation between streptococci and ulcerative colitis^{38–40}. In the late 1990s, the association between fecal microbiota and Crohn's disease was apparent when recurrent inflammation was observed after the fecal stream was reestablished in post-operative Crohn's disease patients^{41,42}. Despite these associations, no specific microbe(s) were identified to be the cause of IBD.

With recent advances in bioinformatics and culture-independent methods used for bacterial identification, there has been a resurgence of interest in the 21st century in studying the phylogeny and function of the gut microbiome in IBD. One popular proposed mechanism is the development of dysbiosis, which is defined as an imbalance between protective and harmful intestinal bacteria causing disease. Figure 3 depicts proposed microbial composition changes underlying dysbiosis and associated pathways modulating gut inflammation, including regulation by T cells, SCFAs, sphingolipids and antimicrobial factors as reviewed recently by Huttenhower *et al.*⁴³.

The diversity of the intestinal microbiome is 30–50% lower in IBD subjects than in controls. In the past year, a study investigating twin pairs discordant for IBD revealed a reduction in microbial diversity in the healthy sibling, mirroring the changes in the ulcerative colitis-affected twin⁴⁴. Furthermore, individuals who are steroid-responsive have a more diverse microbiota when compared to non-responders (Shannon index 338 ± 62 versus 142 ± 49 ; $P = 0.013$)⁴⁵.

There is also evidence that upregulation and downregulation of the abundance of certain bacterial species correlates with disease activity. Recent studies have demonstrated a significant reduction of *Faecalibacterium prausnitzii* and *Roseburia hominis* in active ulcerative colitis patients *versus* control subjects. Moreover, a significant inverse correlation between disease activity and the

Figure 3. Dysbiosis and gut inflammation. The schematic depicts consistent observations of changes in microbial composition underlying dysbiosis and associated pathways modulating gut inflammation. The lumen (yellow), mucus layer (brown), epithelium (purple brush-border-containing cells), and lamina propria (bottom purple section) are indicated. Multiple mechanisms depicted include regulation by T cells, short chain fatty acids (SCFAs), sphingolipids and antimicrobial factors. Adapted from 85.

abundance of *R. hominis* and *F. prausnitzii* is present even in quiescent ulcerative colitis^{46,47}. *F. prausnitzii* is widely regarded as one of the main fecal bacterial groups involved in colonic saccharolytic fermentation which produces SCFAs, in particular, butyrate⁴⁸.

Further validation of the protective function of some microbial genera of the microbiome in acute and chronic colitis was confirmed by the improvement of inflammatory markers after intragastric administration of *F. prausnitzii*. In their mouse studies, Sokol *et al.* reported the protective effect of *F. prausnitzii* in a trinitrobenzene sulfonic acid (TNBS)-induced acute colitis model and, more recently, in a model of dinitrobenzene sulfonic acid (DNBS)-induced chronic colitis, in which a reduction of inflammatory markers, such as myeloperoxidase (MPO) and pro-inflammatory colonic cytokines (IL-6, IL-9, TNF- α , IFN- α), was reported, indicating a decreased severity of inflammation associated with an alteration of the microbiome^{49,50}. The findings were particularly notable in that further analysis indicated that butyrate was not implicated in this protective effect, presumably due to the limitations of the TNBS colitis model employed, but nonetheless suggesting other protective mechanisms are present. Figure 4 briefly summarizes the numerous proposed anti-inflammatory mechanisms mediated by *F. prausnitzii*, either by its metabolites or by direct contact with

the mucosa⁴⁷. These pathways, ranging from production of anti-inflammatory matrix components to SCFAs to regulation of the immune system, to activation of the inflammatory cascade and the enteric nervous system, represent the complexities inherent in elucidating the biological mechanisms relating the microbiome to IBD pathogenesis^{47,51–53}.

A multicenter cohort study that enrolled treatment-naïve and newly diagnosed patients with Crohn's disease reported increased abundance of Enterobacteriaceae, Pasteurellaceae, Veillonellaceae, and Fusobacteriaceae and decreased abundance of Erysipelotrichales, Bacteroidales, and Clostridiales in ileal and rectal biopsies⁵⁴. The complexities underlying the interpretation of such simple microbial associations through their production of SCFA are evident in conflicting observations of increased Enterobacteriaceae and Fusobacteriaceae in Crohn's disease, both of which are implicated as the main SCFA-producing bacterial groups⁴⁸.

The importance of the luminal contents and the microbiome in the foregut is also illustrated in a recent study by Said *et al.* reporting that dysbiosis in the oral cavity is associated with inflammatory responses in IBD patients. The salivary microbiome of patients with IBD had higher proportions of *Prevotella*, *Bacteroidetes*, and

Figure 4. Proposed anti-inflammatory mechanisms of *F. prausnitzii*. 1. The supernatant of *F. prausnitzii* blocks NF- κ B activation induced by inflammation. 2. Butyrate produced by *F. prausnitzii* inhibits NF- κ B activation in the mucosa. 3. *F. prausnitzii* may interact with CD103+ dendritic cells (DCs) in the lamina propria and stimulate their migration to mesenteric lymph nodes (MLN) and the induction of Tregs. 4. M cell transcytosis of *F. prausnitzii* in organized lymphoid structures may induce Tregs. 5. *F. prausnitzii* may induce IL-10 in antigen-presenting cells to enhance the suppressive activity of Foxp3+ Tregs and block Th17 cells. Adapted from 93.

Veillonella and lower proportions of *Streptococcus*, *Neisseria*, *Haemophilus*, *Proteobacteria*, and *Gemella*⁵⁵. Although the study reported changes in several bacterial groups that may have obscured the effect of a single group, *Bacteroidetes* is one of the major groups producing SCFAs⁴⁸, which are thought to protect against inflammation.

Dysbiosis is also suggested by the observations of increased prevalence of bacteria that may be implicated in the pathogenesis of IBD. For instance, in ulcerative colitis patients, the population of sulfite-reducing bacteria such as *Desulfovibrio* is increased, whereas low amounts of thiosulfate sulfur transferase (TST), an enzyme responsible for hydrogen sulfide (H₂S) detoxification, are present^{56–58}. The consequent increased intestinal H₂S content can impair DNA repair and inhibit SCFA oxidation and its protective properties^{59,60}, further implicating microbial products such as SCFAs as key mediators.

Some aspects of the specific changes of microbial composition triggering IBD, however, continue to be elusive: for instance, it is yet to be established whether the gut microbiome is stable or continuously changing during the course of the disease. Furthermore, the impact of diet, standard medical therapy, and other environmental factors on the gut microbiome is not well understood. Most importantly, it is as yet undetermined if microbial imbalance is a cause or a consequence of IBD development.

Although contemporary research has focused mostly on descriptive study of the compositional changes in gut microbiota in IBD, studies of the functional impact of microbial communities in IBD will be necessary to gain further insight into disease pathogenesis. On the basis of metagenomic and metaproteomic studies, only 2% of genera changes in stool and intestinal biopsy specimens may have a much larger functional impact, affecting up to 12% of total metabolic pathways in active IBD patients compared to controls⁶¹.

Integrating the microbiome and the genome

Isolated research on the genetic and microbial factors affecting IBD manifestations and pathogenesis over the past decades has provided valuable insights and strong associative relationships between IBD, genetics, and dysbiosis, but has been unable to provide mechanistic explanations for these associations. There have been limited studies of the co-association of complex host genetic factors with microbial composition and metabolism in IBD patients or other populations. IBD-associated genetic variants associated with alterations in the intestinal microbiome, particularly in individuals carrying polymorphisms in *NOD2* and *FUT2*, have been reported^{62,63}. The mechanisms of host genome-microbiome disease pathways are largely unknown.

There is mounting evidence that genetic loci across the human genome are instrumental in shaping the gut microbiome^{64,65}. Knights *et al.*, in a systematic analysis of the effect of 154 IBD-associated polymorphisms on microbial composition in three cohorts of patients with IBD (152 to 162 patients in each cohort) using multivariate linear models, reported that 49/154 IBD-associated genes significantly and concordantly affected microbial taxa in at

least two of the cohorts, implicating the innate immune response, the inflammatory response, and the JAK-STAT cascade⁶⁴. In a separate analysis, the *NOD2* risk allele count also influenced the overall microbial composition and abundance of Enterobacteriaceae. These data not only support an intricate link between host genetics and microbial dysbiosis in IBD, but also illustrate the ability to uncover novel associations from paired genome-microbiome data, opening the possibility that an unexpected number of genetic factors act directly on microbial composition, modulating immune pathways and metabolic phenotypes in host physiology and disease. Further studies are necessary to understand if these variants contribute to disease phenotype through their direct influence on microbiome selection, which in turn can affect disease pathophysiology either through elaboration of metabolic products or through direct mucosal interaction. These studies may involve investigating whether genetic polymorphisms concordantly affect microbial composition in healthy individuals in addition to those with IBD.

Biological reductionism

The systems-based studies of genome and microbiome in the pathogenesis of IBD have only yielded associations without a causal mechanism. Traditional reductionist experimentation is necessary to validate associations in system-based approaches. With the advent of new statistical methods, computing and technological advances termed “systems biology”, this approach has become dominant. Since complex models with emergent properties are arguably difficult to explain with a reductionist approach, the systems approach looks broadly for correlations in comprehensive data sets, building models based on these correlations. The statistical approaches used to “mine” systems-based data sets are tools from which hypotheses can be developed. These hypotheses should then be tested in specific (and often reductionist) experiments. Thus, experimental verification of the systems-based approaches will be important to establish if the statistical approaches employed in data analysis are robust. It is therefore the marriage of systems-based approaches with traditional reductionist experimentation that will be needed to advance the field.

SCFAs: pathway to IBD

Few studies have addressed the gap between intestinal microbes and inflammatory biological pathways in the understanding of IBD pathogenesis in a human host. Dysbioses in IBD are not simply structural changes in the gut microbiota, but are instead associated with major impairments of many fundamental microbial metabolic functions with potential impact on the host. Profound disturbances have been reported in the metabolic pathways associated with gut microbiota in IBD, including major shifts in oxidative stress pathways, decreased amino acid biosynthesis, increased mucin degradation, and decreased SCFA production⁶¹.

A promising route to further understanding the pathogenesis of IBD involves the investigation of the interactions of gut microbiota with the host, particularly through the bacterial fermentation products *N*-butyrate and other SCFAs. Not only do SCFAs provide essential nutrition for colonocytes, but they are also sensed by enteroendocrine and enterochromaffin cells in addition to possessing anti-inflammatory activity *in vitro* and *in vivo*^{48,66}.

SCFAs have been studied for decades for their effects on IBD. Although early clinical trials reported beneficial effects of SCFA enemas in ulcerative colitis patient subpopulations (e.g., distal ulcerative colitis, mild-to-moderate distal ulcerative colitis^{67,68}), several large randomized studies reported no significant effects of exogenous SCFA treatment of ulcerative colitis patients^{69,70}. These early trials were confounded by the now known epigenetic regulation of multiple host factors by SCFAs. Other limitations include the unknown utility of a transient rise of SCFA concentration in the distal gut achievable through enemas compared to sustained foregut elevations made possible by specific microbiome compositions of specific gut segments.

SCFAs, fermented from dietary fiber resistant to mammalian digestion, are actively produced by anaerobic microbiota in the intestine and colon. The concentration of SCFA in hindgut lumen can reach 100 mM, which provides sufficient driving force for absorption by or transport into colonocytes⁷¹. SCFAs activate specific G-protein-coupled receptors (GPCRs), in particular GPR43 (FFA2), expressed by leukocytes, adipocytes and enterochromaffin (EC) cells, myenteric nerves, and GPR41 (FFA3), expressed by adipose tissue, spleen, bone marrow, lymph nodes, enteroendocrine cells, and peripheral blood mononuclear cells. GPR signaling can regulate cell activation, proliferation, and differentiation through the release of hormones or other bioactive molecules, or possibly through direct effects on enteric nerves⁴⁸.

Another mechanism of SCFA action is inhibition of histone deacetylase (HDAC) activity, with subsequent modification of gene expression in human cells^{48,50,72}. Because HDAC inhibition increases the acetylation of histone and other proteins, it can impact multiple genes and proteins. SCFAs also regulate cell metabolism through the Krebs cycle intermediates and mechanistic target of rapamycin (mTOR) activation regulating T cells⁷².

Our laboratory has pursued experimental studies aimed at decoding how chemosensing of luminal microbial products, including SCFAs, can generate host responses. We have shown that the duodenum possesses specialized chemosensing functions that alert the distal gut to proximal conditions. The presence of SCFA in the proximal gut lumen activates mucosal defense mechanisms, including increased mucosal blood flow and mucus, bicarbonate secretion, and release of gut hormones^{73–77}. One notable mechanism implicates the expression of SCFA receptors in luminal-facing projections of rat duodenal EC cells and enteroendocrine L-cells. FFA3 colocalises with glucagon-like peptide (GLP)-1 in enteroendocrine cells, whereas FFA2 colocalises with 5-hydroxytryptamine (serotonin; 5-HT) in EC cells. Activation of FFA2 receptor expressed on EC cells releases 5-HT and acetylcholine (ACh). These activate 5-HT₄ and muscarinic receptors respectively, which are expressed on enteric nerves, afferent nerves, and epithelial cells. Activation of duodenal epithelial cells by these signals increases the rate of HCO₃⁻ secretion.

The contribution of 5-HT and ACh was confirmed subsequently when a synthetic selective FFA2 agonist dose-dependently increased HCO₃⁻ secretion, but was inhibited by atropine and a 5-HT₄ antagonist. Similarly, SCFAs are thought to activate FFA2 receptors expressed on L cells, releasing GLP-2, which activates

GLP-2 receptors expressed in myenteric neurons, enhancing HCO₃⁻ secretion, inhibited by GLP-2 receptor antagonists but enhanced by dipeptidyl peptidase (DPP) IV inhibition. These novel pathways have an inherent ability to locally regulate hormone release, implying that they are important in mucosal homeostasis⁷⁴. Dysregulation of these pathways may contribute to intestinal inflammation through possible mechanisms detailed below, highlighting 5-HT and GLP-2 mediated effector pathways.

Serotonin (5-HT) mediates many GI functions, including secretion and peristalsis, presumably through its activation of the five known gut-expressed 5-HT receptors out of the seven 5-HT receptors so far described⁷⁸. Agonists and antagonists to 5-HT₃ and 5-HT₄ receptors are particularly well studied, with many drugs in clinical use, with utility in the management of diarrhea, constipation, and gut associated pain syndromes⁷⁸. The contribution of 5-HT and its most recently discovered 5-HT₇ receptors to intestinal homeostasis and inflammation is less well understood. Initial studies reported alterations in 5-HT signaling in IBD; differences in EC cell and 5-HT content have been reported with ulcerative colitis and Crohn's disease^{79–85}. 5-HT released from EC cells can act on proximal gut 5-HT₇ receptors expressed by smooth muscle cells, enteric neurons, enterocytes, and immune cells. Activation of 5-HT₇ receptors can influence muscle tone and enteric neuron excitation, inhibit serotonin transporter (SERT) activity, and modulate inflammation through dendritic cells (DCs) in the lamina propria, which are highly involved in host immune pathways.

Guseva *et al.* investigated the enhanced expression and distribution of 5-HT₇R in the intestinal tissue of IBD patients, based on an experimental model of dextran sulfate sodium (DSS)-induced colitis in which 5-HT₇R expression was upregulated on CD11c/CD86 double-positive dendritic cells obtained from cecal and rectal tissue samples. The authors reported a similarly high expression of 5-HT₇R in analogous dendritic cells obtained from large intestinal tissue samples of patients diagnosed with Crohn's disease. Pharmacological blockade or genetic ablation of 5-HT₇R increased the severity of acute and chronic DSS-induced colitis, whereas receptor stimulation was anti-inflammatory. These experiments supported the hypothesis that 5-HT₇R expressed on CD11c/CD86-positive myeloid cells is an important component of intestinal inflammatory pathways⁸⁶. Contrary to these results, Kim *et al.* in 2013 reported that pharmacologic blockade or genetic ablation of 5-HT₇R actually alleviated intestinal inflammation in two separate chemical models of colitis (DSS and DNBS), which was confirmed histopathologically and also associated with decreased concentrations of pro-inflammatory markers, including myeloperoxidase (MPO) and cytokines IL-1 β , IL-6, and TNF- α . Mice that received hematopoietic stem cells from 5-HT₇ receptor-deficient donors exhibited decreased histopathological damage and disease activity⁸⁷. These apparently discordant effects may be due to differences in dosing of the 5-HT₇R antagonist despite substantial differences in experimental design and housing condition of the animals. In separate experiments by Kim *et al.* in which a lower dose (20mg/kg) of the antagonist was used, no significant differences were detected compared to control, though a higher dose (80mg/kg) significantly decreased colitis severity and inflammatory markers. Kim further acknowledged that the antagonist dosages were higher and dosing

periods longer in his studies than those used by Guseva *et al.*⁸⁵. Thus, 5-HT₇R expressed on CD11c/CD86-positive myeloid cells, which modulate the severity of intestinal inflammation in experimental models of acute and chronic colitis, may serve as a potential therapeutic target for the treatment of inflammatory disorders such as Crohn's disease.

The other hormone released through the action of SCFA, GLP-2, promotes mucosal growth, decreases barrier permeability and reduces inflammation in the intestine⁸⁸. After recently being approved for treatment of short bowel syndrome, there has been a surge in interest in the non-metabolizable GLP-2R agonist teduglutide due to its multiple beneficial effects, including effects on glucose homeostasis⁸⁸, and on intestinal inflammation in Crohn's disease. Pediatric patients with acute ileal Crohn's disease have lower postprandial GLP-2 release and higher intestinal permeability, which both reverse as the disease improves, suggesting a crucial link between the inflammatory state and GLP-2 meal-stimulated release⁸⁹. In another study, GLP-2 treatment was associated with a significantly reduced neutrophil infiltration and microscopic colitis scores in the TNBS model of colitis in mice. They also reported that GLP-2 contributed to protecting the enteric nervous system under basal conditions or inflamed states⁹⁰. GLP-2 is not only trophic for the intestine but also has other salutatory effects. The GLP-2R, expressed by pericryptal myofibroblasts, releases growth factors in response to GLP-2R activation⁹¹. GLP-2 decreases gut inflammation by downregulation of Th1 cytokines cells *via* an IL10-independent pathway, altering the mucosal response of inflamed intestinal epithelial cells and macrophages⁹². GLP-2 also may activate enteric nerves, since the GLP-2R is localized to myenteric neurons in addition to the myofibroblasts, but not to the intestinal epithelium⁹³.

The contribution of specific gut microbiota is evident in studies that demonstrate their influence on 5-HT biosynthesis and on the increase in endogenous GLP-2 production—both of which are implicated in modulation of gut inflammation—although the signaling pathways are yet to be fully understood^{94–96}. SCFAs may represent the biological mediators of these findings as well. SCFAs that promoted Tph1 (tryptophan hydroxylase 1) transcription in BON cells (human EC cell model) were the key link between gut microbiota regulating enteric 5-HT production and homeostasis in a recent study⁹⁴. Figure 5 outlines the proposed mechanisms through which SCFAs regulate gut inflammation.

Other pathways

There are many other pathways being investigated using the reductionist approach to help integrate genetic, microbial, and biochemical pathways. In a breakthrough study of IBD- protective single nucleotide polymorphisms (SNPs) in the *MAP3K8* gene, Roulis *et al.* reported that *MAP3K8* encodes tumor progression locus-2 (Tpl2) kinase in intestinal myofibroblasts, in addition to promoting arachidonic acid metabolism and COX-2/PGE-2 activation, which are important in the compensatory proliferative response of the intestinal epithelium to injury⁹⁷.

Mice with complete knockout of Tpl2, and conditional knockout of Tpl2 targeted to intestinal myofibroblasts, were highly susceptible

Figure 5. Short chain fatty acids (SCFAs) regulate gut inflammation. SCFAs are present in the diet and actively produced by gut microbiota as fermentation products of dietary materials. SCFAs exert their effects directly on epithelial cells, antigen-presenting cells, and T cells. Multiple mechanisms depicted above include metabolic regulation, HDAC inhibition, and GPR activation by SCFAs releasing mediators including 5-HT and GLP-2 hypothesized to modulate gut inflammation.

to DSS-induced colitis, with greater tissue damage when compared to wild-type mice despite similar DSS-induced levels of inflammation. Tpl2 expression was downregulated in intestinal myofibroblasts isolated from the inflamed ileum of nine patients with IBD.

Conclusions

Currently, the data acquisition rate in traditional IBD research has been far outpaced by the massive data generated by bioinformatics. Despite the considerable ongoing efforts of investigators across the globe, reductionist studies are still needed to help explain the basic causal mechanisms that underlie the exponentially increasing number of correlations detected through systems-based approaches in IBD. Further integration of the study of host genetics and the gut microbiome in the setting of clinical metadata has already reduced the number of confounding variables and has elicited new associations. Efforts to integrate complicated genetics and the gut microbiome in further reductionist experiments to determine causal associations may be best served by an emphasis on bacterial metabolic products, such as SCFAs, as the logical mediators of the interactions between genetic variables and the microbiota as well as key molecules of the biological etiopathogenic pathway to gut

inflammation. Further reductionist studies exploring the interactions between diet, microbiome, SCFAs and serotonin can help guide our understanding of the pathogenesis of colitis.

Author contributions

Dr. Nayyar performed the initial literature search, composed Figure 4 and wrote the draft. Dr. Kaunitz originated the underlying

concept and drafted the overall organization, revised and edited the draft, prepared the final version, and submitted the manuscript.

Competing interests

The authors declare that they have no disclosures.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

- Abraham C, Cho JH: **Inflammatory bowel disease**. *N Engl J Med*. 2009; **361**(21): 2066–78.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Molodecky NA, Soon IS, Rabi DM, *et al.*: **Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review**. *Gastroenterology*. 2012; **142**(1): 46–54. e42; quiz e30.
[PubMed Abstract](#) | [Publisher Full Text](#)
- The Facts about Inflammatory Bowel Diseases**. Crohn's & Colitis Foundation of America, 2014.
[Reference Source](#)
- Kappelman MD, Rifas-Shiman SL, Porter CQ, *et al.*: **Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults**. *Gastroenterology*. 2008; **135**(6): 1907–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Gibson TB, Ng E, Ozminkowski RJ, *et al.*: **The direct and indirect cost burden of Crohn's disease and ulcerative colitis**. *J Occup Environ Med*. 2008; **50**(11): 1261–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Longobardi T, Jacobs P, Bernstein CN: **Work losses related to inflammatory bowel disease in the United States: results from the National Health Interview Survey**. *Am J Gastroenterol*. 2003; **98**(5): 1064–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Huang H, Vangay P, McKinlay CE, *et al.*: **Multi-omics analysis of inflammatory bowel disease**. *Immunol Lett*. 2014; **162**(2 Pt A): 62–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Liu JZ, Anderson CA: **Genetic studies of Crohn's disease: past, present and future**. *Best Pract Res Clin Gastroenterol*. 2014; **28**(3): 373–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Cho JH, Brant SR: **Recent insights into the genetics of inflammatory bowel disease**. *Gastroenterology*. 2011; **140**(6): 1704–12.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Devlin SM, Yang H, Ippoliti A, *et al.*: **NOD2 variants and antibody response to microbial antigens in Crohn's disease patients and their unaffected relatives**. *Gastroenterology*. 2007; **132**(2): 576–86.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Halfvarson J: **Genetics in twins with Crohn's disease: less pronounced than previously believed?** *Inflamm Bowel Dis*. 2011; **17**(1): 6–12.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mei L, Targan SR, Landers CJ, *et al.*: **Familial expression of anti-*Escherichia coli* outer membrane porin C in relatives of patients with Crohn's disease**. *Gastroenterology*. 2006; **130**(4): 1078–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Glocker EO, Kotlarz D, Boztug K, *et al.*: **Inflammatory bowel disease and mutations affecting the interleukin-10 receptor**. *N Engl J Med*. 2009; **361**(21): 2033–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Hugot JP, Chamaillard M, Zouali H, *et al.*: **Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease**. *Nature*. 2001; **411**(6837): 599–603.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Ogura Y, Bonen DK, Inohara N, *et al.*: **A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease**. *Nature*. 2001; **411**(6837): 603–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Economou M, Trikalinos TA, Loizou KT, *et al.*: **Differential effects of NOD2 variants on Crohn's disease risk and phenotype in diverse populations: a metaanalysis**. *Am J Gastroenterol*. 2004; **99**(12): 2393–404.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Duerr RH: **Genome-wide association studies herald a new era of rapid discoveries in inflammatory bowel disease research**. *Gastroenterology*. 2007; **132**(5): 2045–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Jostins L, Ripke S, Weersma RK, *et al.*: **Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease**. *Nature*. 2012; **491**(7422): 119–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Ek WE, D'Amato M, Halfvarson J: **The history of genetics in inflammatory bowel disease**. *Ann Gastroenterol*. 2014; **27**(4): 294–303.
[PubMed Abstract](#) | [Free Full Text](#)
- Khor B, Gardet A, Xavier RJ: **Genetics and pathogenesis of inflammatory bowel disease**. *Nature*. 2011; **474**(7351): 307–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- VanDussen KL, Liu TC, Li D, *et al.*: **Genetic variants synthesize to produce paneth cell phenotypes that define subtypes of Crohn's disease**. *Gastroenterology*. 2014; **146**(1): 200–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Travassos LH, Carneiro LA, Ramjeet M, *et al.*: **Nod1 and Nod2 direct autophagy by recruiting ATG16L1 to the plasma membrane at the site of bacterial entry**. *Nat Immunol*. 2010; **11**(1): 55–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Kuballa P, Huett A, Rioux JD, *et al.*: **Impaired autophagy of an intracellular pathogen induced by a Crohn's disease associated ATG16L1 variant**. *PLoS One*. 2008; **3**(10): e3391.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Rioux JD, Xavier RJ, Taylor KD, *et al.*: **Genome-wide association study identifies new susceptibility loci for Crohn's disease and implicates autophagy in disease pathogenesis**. *Nat Genet*. 2007; **39**(5): 596–604.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Hampe J, Franke A, Rosenstiel P, *et al.*: **A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1**. *Nat Genet*. 2007; **39**(2): 207–11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Parke M, Barrett JC, Prescott NJ, *et al.*: **Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility**. *Nat Genet*. 2007; **39**(7): 830–2.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Duerr RH, Taylor KD, Brant SR, *et al.*: **A genome-wide association study identifies IL23R as an inflammatory bowel disease gene**. *Science*. 2006; **314**(5804): 1461–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Franke A, Balschun T, Sina C, *et al.*: **Genome-wide association study for ulcerative colitis identifies risk loci at 7q22 and 22q13 (IL17REL)**. *Nat Genet*. 2010; **42**(4): 292–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lees CW, Barrett JC, Parkes M, *et al.*: **New IBD genetics: common pathways with other diseases**. *Gut*. 2011; **60**(12): 1739–53.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Manichanh C, Borruel N, Casellas F, *et al.*: **The gut microbiota in IBD**. *Nat Rev Gastroenterol Hepatol*. 2012; **9**(10): 599–608.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Okazaki T, Wang MH, Rawsthorne P, *et al.*: **Contributions of IBD5, IL23R, ATG16L1, and NOD2 to Crohn's disease risk in a population-based case-control study: evidence of gene-gene interactions**. *Inflamm Bowel Dis*. 2008; **14**(11): 1528–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kaser A, Lee AH, Franke A, *et al.*: **XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease**. *Cell*. 2008; **134**(5): 743–56.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Pégorier JP, Le May C, Girard J: **Control of gene expression by fatty acids**.

- J Nutr.* 2004; **134**(9): 2444S–2449S.
[PubMed Abstract](#)
34. **F** Remely M, Aumueler E, Merold C, *et al.*: Effects of short chain fatty acid producing bacteria on epigenetic regulation of FFAR3 in type 2 diabetes and obesity. *Gene.* 2014; **537**(1): 85–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 35. **F** Zuk O, Hechter E, Sunyaev SR, *et al.*: The mystery of missing heritability: Genetic interactions create phantom heritability. *Proc Natl Acad Sci U S A.* 2012; **109**(4): 1193–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 36. Kirsner JB: Historical aspects of inflammatory bowel disease. *J Clin Gastroenterol.* 1988; **10**(3): 286–97.
[PubMed Abstract](#)
 37. Dalziel TK: Chronic interstitial enteritis. *BMJ.* 1913; **2**(2756): 1068–70.
[Reference Source](#)
 38. Rettger L, Cheplin H: *Bacillus acidophilus* and its therapeutic application. *Arch Intern Med.* 1922; **29**(3): 357–67.
[Publisher Full Text](#)
 39. Rettger L, Cheplin H: A Treatise on the transformation of the intestinal flora with special reference to the implantation of *Bacillus acidophilus*. Yale University Press, 1921.
[Publisher Full Text](#)
 40. Rodaniche E, Palmer W, Kirsner J: The streptococci present in the feces of patients with non-specific ulcerative colitis, and the effect of oral administration of sulfonamide compounds upon them. *J Infect Dis.* 1943; **72**(3): 222–7.
[Publisher Full Text](#)
 41. Rutgeerts P, Geboes K, Peeters M, *et al.*: Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. *Lancet.* 1991; **338**(8770): 771–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 42. D'Haens GR, Geboes K, Peeters M, *et al.*: Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology.* 1998; **114**(2): 262–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 43. Huttenhower C, Kostic AD, Xavier RJ: Inflammatory bowel disease as a model for translating the microbiome. *Immunity.* 2014; **40**(6): 843–54.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 44. **F** Lepage P, Häslér R, Spehlmann ME, *et al.*: Twin study indicates loss of interaction between microbiota and mucosa of patients with ulcerative colitis. *Gastroenterology.* 2011; **141**(1): 227–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 45. **F** Michail S, Durbin M, Turner D, *et al.*: Alterations in the gut microbiome of children with severe ulcerative colitis. *Inflamm Bowel Dis.* 2012; **18**(10): 1799–808.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 46. **F** Machiels K, Joossens M, Sabino J, *et al.*: A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut.* 2014; **63**(8): 1275–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 47. Miquel S, Martin R, Rossi O, *et al.*: *Faecalibacterium prausnitzii* and human intestinal health. *Curr Opin Microbiol.* 2013; **16**(3): 255–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
 48. Puertollano E, Kolida S, Yaqoob P: Biological significance of short-chain fatty acid metabolism by the intestinal microbiome. *Curr Opin Clin Nutr Metab Care.* 2014; **17**(2): 139–44.
[PubMed Abstract](#) | [Publisher Full Text](#)
 49. **F** Sokol H, Pigneur B, Watterlot L, *et al.*: *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci U S A.* 2008; **105**(43): 16731–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 50. **F** Martin R, Chain F, Miquel S, *et al.*: The commensal bacterium *Faecalibacterium prausnitzii* is protective in DNBS-induced chronic moderate and severe colitis models. *Inflamm Bowel Dis.* 2014; **20**(3): 417–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 51. **F** Rossi O, Khan MT, Schwarzer M, *et al.*: *Faecalibacterium prausnitzii* Strain HTF-F and Its Extracellular Polymeric Matrix Attenuate Clinical Parameters in DSS-Induced Colitis. *PLoS One.* 2015; **10**(4): e0123013.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 52. **F** Miquel S, Leclerc M, Martin R, *et al.*: Identification of metabolic signatures linked to anti-inflammatory effects of *Faecalibacterium prausnitzii*. *MBio.* 2015; **6**(2): pii: e00300–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 53. **F** Qiu X, Zhang M, Yang X, *et al.*: *Faecalibacterium prausnitzii* upregulates regulatory T cells and anti-inflammatory cytokines in treating TNBS-induced colitis. *J Crohns Colitis.* 2013; **7**(11): e558–68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 54. **F** Gevers D, Kugathasan S, Denson LA, *et al.*: The treatment-naïve microbiome in new-onset Crohn's disease. *Cell Host Microbe.* 2014; **15**(3): 382–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 55. **F** Said HS, Suda W, Nakagome S, *et al.*: Dysbiosis of salivary microbiota in inflammatory bowel disease and its association with oral immunological biomarkers. *DNA Res.* 2014; **21**(1): 15–25.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 56. **F** Lennon G, Balfe Á, Bambury N, *et al.*: Correlations between colonic crypt mucin chemotype, inflammatory grade and *Desulfovibrio* species in ulcerative colitis. *Colorectal Dis.* 2014; **16**(5): O161–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 57. **F** Rowan F, Docherty NG, Murphy M, *et al.*: *Desulfovibrio* bacterial species are increased in ulcerative colitis. *Dis Colon Rectum.* 2010; **53**(11): 1530–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 58. **F** De Preter V, Ajijs I, Windey K, *et al.*: Decreased mucosal sulfide detoxification is related to an impaired butyrate oxidation in ulcerative colitis. *Inflamm Bowel Dis.* 2012; **18**(12): 2371–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 59. **F** Carbonero F, Benefiel AC, Alizadeh-Ghamsari AH, *et al.*: Microbial pathways in colonic sulfur metabolism and links with health and disease. *Front Physiol.* 2012; **3**: 448.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 60. **F** Attene-Ramos MS, Nava GM, Mueller MG, *et al.*: DNA damage and toxicogenomic analyses of hydrogen sulfide in human intestinal epithelial FHs 74 Int cells. *Environ Mol Mutagen.* 2010; **51**(4): 304–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 61. **F** Morgan XC, Tickle TL, Sokol H, *et al.*: Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biol.* 2012; **13**(9): R79.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 62. **F** Li E, Hamm CM, Gulati AS, *et al.*: Inflammatory bowel diseases phenotype, *C. difficile* and NOD2 genotype are associated with shifts in human ileum associated microbial composition. *PLoS One.* 2012; **7**(6): e26284.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 63. **F** Tong M, McHardy I, Ruegger P, *et al.*: Reprogramming of gut microbiome energy metabolism by the *FUT2* Crohn's disease risk polymorphism. *ISME J.* 2014; **8**(11): 2193–206.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 64. **F** Knights D, Silverberg MS, Weersma RK, *et al.*: Complex host genetics influence the microbiome in inflammatory bowel disease. *Genome Med.* 2014; **6**(12): 107.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 65. **F** Goodrich JK, Waters JL, Poole AC, *et al.*: Human genetics shape the gut microbiome. *Cell.* 2014; **159**(4): 789–99.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 66. Soldavini J, Kaunitz JD: Pathobiology and potential therapeutic value of intestinal short-chain fatty acids in gut inflammation and obesity. *Dig Dis Sci.* 2013; **58**(10): 2756–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 67. Scheppach W, Sommer H, Kirchner T, *et al.*: Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. *Gastroenterology.* 1992; **103**(1): 51–6.
[PubMed Abstract](#)
 68. Vernia P, Marcheggiano A, Caprilli R, *et al.*: Short-chain fatty acid topical treatment in distal ulcerative colitis. *Aliment Pharmacol Ther.* 1995; **9**(3): 309–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
 69. Steinhart AH, Hiruki T, Brzezinski A, *et al.*: Treatment of left-sided ulcerative colitis with butyrate enemas: a controlled trial. *Aliment Pharmacol Ther.* 1996; **10**(5): 729–36.
[PubMed Abstract](#) | [Publisher Full Text](#)
 70. Breuer RI, Soergel KH, Lashner BA, *et al.*: Short chain fatty acid rectal irrigation for left-sided ulcerative colitis: a randomised, placebo controlled trial. *Gut.* 1997; **40**(4): 485–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 71. Rechkemmer G, Rönna K, von Engelhardt W: Fermentation of polysaccharides and absorption of short chain fatty acids in the mammalian hindgut. *Comp Biochem Physiol A Comp Physiol.* 1988; **90**(4): 563–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 72. **F** Kim CH, Park J, Kim M: Gut microbiota-derived short-chain Fatty acids, T cells, and inflammation. *Immune Netw.* 2014; **14**(6): 277–88.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 73. Akiba Y, Kaunitz JD: Duodenal luminal chemosensing; acid, ATP, and nutrients. *Curr Pharm Des.* 2014; **20**(16): 2760–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 74. Akiba Y, Inoue T, Kaji I, *et al.*: Short-chain fatty acid sensing in rat duodenum. *J Physiol.* 2015; **593**(3): 585–99.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 75. Akiba Y, Watanabe C, Mizumori M, *et al.*: Luminal L-glutamate enhances duodenal mucosal defense mechanisms via multiple glutamate receptors in rats. *Am J Physiol Gastrointest Liver Physiol.* 2009; **297**(4): G781–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 76. Inoue T, Wang JH, Higashiyama M, *et al.*: Dipeptidyl peptidase IV inhibition potentiates amino acid- and bile acid-induced bicarbonate secretion in rat duodenum. *Am J Physiol Gastrointest Liver Physiol.* 2012; **303**(7): G810–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 77. Wang JH, Inoue T, Higashiyama M, *et al.*: Umami receptor activation increases duodenal bicarbonate secretion via glucagon-like peptide-2 release in rats. *J Pharmacol Exp Ther.* 2011; **339**(2): 464–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 78. Mawe GM, Hoffman JM: Serotonin signalling in the gut—functions, dysfunctions and therapeutic targets. *Nat Rev Gastroenterol Hepatol.* 2013; **10**(8): 473–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

79. Ahonen A, Kyösola K, Penttilä O: **Enterochromaffin cells in macrophages in ulcerative colitis and irritable colon.** *Ann Clin Res.* 1976; **8**(1): 1–7.
[PubMed Abstract](#)
80. Belai A, Boulos PB, Robson T, *et al.*: **Neurochemical coding in the small intestine of patients with Crohn's disease.** *Gut.* 1997; **40**(6): 767–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
81. El-Salhy M, Danielsson A, Stenling R, *et al.*: **Colonic endocrine cells in inflammatory bowel disease.** *J Intern Med.* 1997; **242**(5): 413–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
82. Magro F, Vieira-Coelho MA, Fraga S, *et al.*: **Impaired synthesis or cellular storage of norepinephrine, dopamine, and 5-hydroxytryptamine in human inflammatory bowel disease.** *Dig Dis Sci.* 2002; **47**(1): 216–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
83. Coates MD, Mahoney CR, Linden DR, *et al.*: **Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome.** *Gastroenterology.* 2004; **126**(7): 1657–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
84. Bishop AE, Pietroletti R, Taat CW, *et al.*: **Increased populations of endocrine cells in Crohn's ileitis.** *Virchows Arch A Pathol Anat Histopathol.* 1987; **410**(5): 391–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
85. Kim JJ, Khan WL: **5-HT₇ receptor signaling: improved therapeutic strategy in gut disorders.** *Front Behav Neurosci.* 2014; **8**: 396.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
86. Guseva D, Holst K, Kaune B, *et al.*: **Serotonin 5-HT₇ receptor is critically involved in acute and chronic inflammation of the gastrointestinal tract.** *Inflamm Bowel Dis.* 2014; **20**(9): 1516–29.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
87. Kim JJ, Bridle BW, Ghia JE, *et al.*: **Targeted inhibition of serotonin type 7 (5-HT₇) receptor function modulates immune responses and reduces the severity of intestinal inflammation.** *J Immunol.* 2013; **190**(9): 4795–804.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
88. Baldassano S, Amato A: **GLP-2: what do we know? What are we going to discover?** *Regul Pept.* 2014; **194**–195: 6–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
89. Sigalet DL, Kravarusic D, Butzner D, *et al.*: **A pilot study examining the relationship among Crohn disease activity, glucagon-like peptide-2 signalling and intestinal function in pediatric patients.** *Can J Gastroenterol.* 2013; **27**(10): 587–92.
[PubMed Abstract](#) | [Free Full Text](#) | [F1000 Recommendation](#)
90. Sigalet DL, Wallace L, De Heuval E, *et al.*: **The effects of glucagon-like peptide 2 on enteric neurons in intestinal inflammation.** *Neurogastroenterol Motil.* 2010; **22**(12): 1318–e350.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
91. El-Jamal N, Erdual E, Neunlist M, *et al.*: **Glucagon-like peptide-2: broad receptor expression, limited therapeutic effect on intestinal inflammation and novel role in liver regeneration.** *Am J Physiol Gastrointest Liver Physiol.* 2014; **307**(3): G274–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
92. Ivory CP, Wallace LE, McCafferty DM, *et al.*: **Interleukin-10-independent anti-inflammatory actions of glucagon-like peptide 2.** *Am J Physiol Gastrointest Liver Physiol.* 2008; **295**(6): G1202–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
93. Pedersen J, Pedersen NB, Brix SW, *et al.*: **The glucagon-like peptide 2 receptor is expressed in enteric neurons and not in the epithelium of the intestine.** *Peptides.* 2015; **67**: 20–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
94. Reigstad CS, Salmonson CE, Rainey JF 3rd, *et al.*: **Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells.** *FASEB J.* 2015; **29**(4): 1395–403.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
95. Yano JM, Yu K, Donaldson GP, *et al.*: **Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis.** *Cell.* 2015; **161**(2): 264–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
96. Cani PD, Possemiers S, Van de Wiele T, *et al.*: **Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability.** *Gut.* 2009; **58**(8): 1091–103.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
97. Roulis M, Nikolaou C, Kotsaki E, *et al.*: **Intestinal myofibroblast-specific Tpl2-Cox-2-PGE₂ pathway links innate sensing to epithelial homeostasis.** *Proc Natl Acad Sci U S A.* 2014; **111**(43): E4658–67.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

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