Exploration of Medicine

Open Exploration

Open Access Review

The gut microbiome and the immune system

Tenzin Choden[1], Nathaniel Aviv Cohen[1,2,3]*

[1]Section of Gastroenterology, Hepatology and Nutrition, University of Chicago Medicine, Chicago, IL 60637, USA
[2]Inflammatory Bowel Disease Center, Department of Gastroenterology and Liver Diseases, Tel Aviv Medical Center, Tel Aviv 6423906, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 6997801, Israel

***Correspondence:** Nathaniel Aviv Cohen, Section of Gastroenterology, Hepatology and Nutrition, University of Chicago Medicine, 5841 South Maryland Avenue, MC 4076 Chicago, IL 60637, USA. Nathaniel.cohen@uchospitals.edu
Academic Editor: Lee M. Wetzler, Boston University School of Medicine, USA

Received: January 31, 2022 **Accepted:** April 24, 2022 **Published:** May 31, 2022

Cite this article: Choden T, Cohen NA. The gut microbiome and the immune system. Explor Med. 2022;3:219–33. https://doi.org/10.37349/emed.2022.00087

Abstract

The human body contains trillions of microbes which generally live in symbiosis with the host. The interaction of the gut microbiome with elements of the host immune system has far-reaching effects in the development of normal gut and systemic immune responses. Disturbances to this intricate relationship may be responsible for a multitude of gastrointestinal and systemic immune mediated diseases. This review describes the development of the gut microbiome and its interaction with host immune cells in both health and disease states.

Keywords

Microbiome, immune, development

Introduction

The human microbiome is constructed of a multitude of organisms including bacteria, viruses, and fungi, which inhabit all surfaces of our bodies. Microbiomes exist on the nose, mouth, lungs, skin, stomach, sexual organs and of course the gut. The organisms comprising these microbiomes exist, largely, in symbiosis with the human host, and research over the past decade has highlighted the significant role they play in human health and disease.

The gut microbiome contains a rich and diverse microbial community consisting of over 100 trillion microorganisms [1]. In fact, the gut microbiome is considered one of the most densely populated microbial habitats and encodes for over 3 million genes as opposed to the 23,000 human genes [2, 3]. This translates to the production of thousands of metabolites which are critical to the symbiotic relationship between humans and the microbes and contribute significantly to maintaining homeostasis. The use of new technologies such as rapid throughput 16S rRNA gene sequencing and advanced analytic techniques has enabled both the identification and quantification of individual components of the gut microbiome and the dissection of their relationship to health and a multitude of human diseases [4, 5].

Indeed, these advances have revealed significant associations between perturbations in the gut microbiome and gastrointestinal diseases such as irritable bowel syndrome [6], inflammatory bowel disease (IBD) [7–9], celiac disease [10] and colorectal cancer [11] as well as a plethora of extra-intestinal diseases for example metabolic disorders such as obesity and diabetes [2, 12, 13], central nervous system diseases [14, 15] and many immune mediates diseases such as psoriasis [16], systemic lupus erythematosus [17] and rheumatoid arthritis (RA) [18] to name but a few.

The common feature of many of these diseases is that they are mediated by dysregulation of the human immune system. Recent research has shown the gut microbiome to be an important role-player in the development and modulation of host immune responses [19]. The aim of this review is to discuss the early development of the gut microbiome and how its interaction with the human immune system plays a role in both health and disease. As this topic is so vast, this review will detail some of the most important interactions and mechanisms.

Early development of the gut microbiome

Initial exposure to microbes begins in utero [20, 21] and expands dramatically following birth. There are multiple factors which influence and shape the gut microbiome in neonates and infants, and these are predominantly related to maternal-offspring exchanges of microbiota. The initial mass colonization event is childbirth. During delivery, the newborn is exposed to the vaginal, fecal and skin microbiota of the mother. As such, mode of delivery, either vaginal delivery or cesarean section, has a significant impact on the initial microbiome. Babies born by cesarean section have no vaginal microbes such as *Lactobacillus*, *Prevotella* and *Sneathia* spp. [22] and are instead colonized by skin bacteria such as *Staphyloccocus*, *Corynebacterium* and *Propionibacterium* spp. [22], in addition, there is delayed colonization by *Bacteroides* and *Bifidobacterium* spp. [23, 24] and higher levels of intestinal *Clostridioides difficile* (*C. difficile*) [25]. It is of interest that differences in composition of gut microbiome depending on mode of delivery have been seen up to 7 years after birth [26]. It is still unclear the long-term effects of mode of delivery and subsequent differences in gut microbiome have on immune development. In one study [27], the gut microbiota and T-helper (Th) cell immune responses of infants born vaginally were compared with those born by cesarean section and found that cesarean section born infants had lower microbial diversity with significantly lower abundance of the Bacteroidetes phylum and also had significantly lower type 1 T-helper (Th1) cell associated chemokines resulting in reduced Th1 cells responses which persisted during the first 2 years of life [27]. This is of interest as members of the Bacteroidetes phylum, including *Bacteroides fragilis* (*B. fragilis*), have been shown through interactions with the capsular polysaccharide, to induce the production of interleukin 10 (IL-10) and other cytokines, alter the Th cell balance and promote immunotolerance [28–30]. This alteration in Th cell balance and function may, in part, explain the association noted between cesarean section born infants and the later development of various immune mediated diseases including allergic conditions and type 1 diabetes (T1D) [31–33].

In addition to mode of delivery, factors such as antibiotic exposure and formula feeding also play an important role in shaping the gut microbiome. Formula feeding has been associated with increased prevalence of *C. difficile* [34], *B. fragilis* and *Escherichia coli* [34, 35] and decreased bifidobacterial [36]. It has been shown that even formula feeding in small quantities can influence the structure of the gut microbiome [37]. Antibiotic exposure has also been shown to interfere with the normal development of the gut microbiota with intrapartum antibiotics resulting in decreased bacterial diversity and lower abundance of lactobacilli and bifidobacterial [38, 39].

Until the age of 3, the gut microbiome shows high variability after which it reaches a more adult like composition [40, 41]. This coincides with an immature immune system highlighted by poorly regulated immune responses as seen in diseases such as necrotizing enterocolitis [42] as well as increased susceptibility to various infections [43]. It is therefore thought that early interaction with a structurally altered microbiome may lead to increased susceptibility to disease later in life such as asthma and IBD [44, 45].

Studies, primarily on germ free (GF) mice, have elucidated the role of this early host microbiome on the maturation of the immune system in greater detail. GF mice by definition have no microbiome, and compared with regular mice, show several immunological defects including a reduction in lymphoid cell numbers and function [46]. GF mice have fewer Th1 cells which promote cell-mediated immune responses and phagocyte-dependent inflammation to target intracellular pathogens [47, 48]. Interestingly, colonization of GF mice by a variety of microbes can restore Th1 responses. For example, *Listeria monocytogenes* promotes Th1 development through macrophage production of IL 12 which is a T-cell stimulating factor [49]. In addition to defective Th1 responses, GF mice also have a reduction in Th17 cells. Although generally pro-inflammatory, these cells mediate defense against extracellular pathogens and autoimmune disease [47, 48].

It must be stated that the role of the gut microbiome is not limited to the intestinal tract. The spleen and mesenteric lymph nodes of GF mice have absent lymphocyte zones [28], indicating a far-reaching and systemic influence of the gut microbiome on the host and providing insight into the possible future pathologic development of numerous diseases. Further, it appears that certain abnormalities in the immune system caused by a defective early interaction, may not be repaired by a later introduction of a normal microbiome. In GF mice, the ability to restore some of the cellular defects that occur is restricted to a short time interval in early life beyond which intestinal immune development cannot be fully achieved in an adult [50], which indicates that there may be a "window of opportunity" to influence the gut microbiome and its immune-related influences.

The microbiome and immune system interaction in health

Structural barrier

The immune system comprises a complex network of innate and adaptive components which have an extraordinary capacity to adapt and respond to a multitude of challenges. This essentially allows the host to maintain homeostasis and sustain or restore tissue function despite constant microbial and environmental exposures [51]. Indeed, a large proportion of the immune system's constitutive function is aimed at controlling this interaction. One strategy the host uses to maintain this healthy interaction is through the development of structural and immunological components which form a physical barrier and minimize the contact between the microbes and the immune cells.

This barrier includes mucus, epithelial cells, secretory immunoglobulin A (IgA), numerous antimicrobial peptides and immune cells [52] and limits contact and translocation as well as impacts commensal gene expression and prevents bacterial adhesion. The components and important interactions that comprise this structural barrier are detailed in Figure 1. The gut epithelium consists of a single layer of various epithelial cells with specialized functions. These cells have a multifaceted role in maintaining the physical barrier. Certain cells secrete antimicrobial peptides such as alpha-defensins, phospholipases, and lysozyme C which are important in warding off pathogens. The rapid turnover of these epithelial cells limits pathogen adherence and gut colonization [53] and the mucous producing goblet cells lubricate and protect the epithelial lining as well as provide a milieu for antigen presentation [54]. Another important aspect of this physical barrier is the tight junction complexes which form a dynamic seal-preventing infiltration of pathogens while allowing for the exchange of water, ions and nutrients between the gut lumen and the blood stream or lymphatics [55].

The importance of this barrier, in maintaining homeostasis and the interaction with commensal and pathogenic microbes, is most notable in certain disease states. For example, during infection with *Vibrio cholera*, bacterial toxin stimulates the adenylate cyclase enzyme in the intestinal brush border, increasing the production of cyclic adenosine monophosphate (AMP) which in turn promotes the secretion of chloride ions and fluid accumulation in the gut lumen and subsequent severe diarrhea [56]. In addition, disruptions in this physical barrier, resulting in increased gut permeability and altered bacterial sensing have been associated with the pathogenesis of Crohn's disease (CD) and could even be used as a biomarker for the risk of CD development [57].

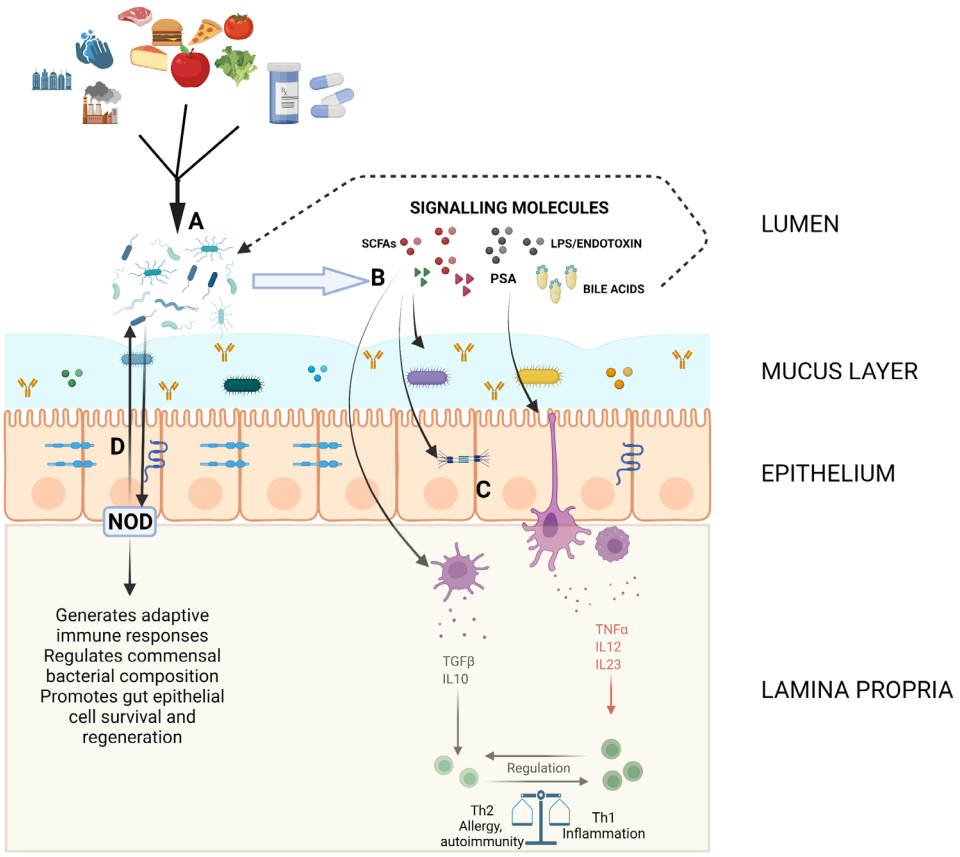

Figure 1. Diagram showing some of the important pathways and interactions in maintaining gut homeostasis. The mucous layer containing soluble IgA, antimicrobial peptides and some commensal organisms as well as the epithelial layer with proteins forming various intercellular junctions composes the structural barrier controlling the interaction between luminal contents and immune components. (A) Environmental and dietary factors influence the composition of the gut microbiome; (B and C) the microbiome produces or alters a variety of signaling molecules including SCFAs, LPS/endotoxin, PSA and bile acids which regulate intestinal barrier function and modulate innate immune responses which eventually lead to downstream shifts in adaptive immune function; (D) bacterial sensing molecules such as NOD molecules interact with and regulate commensal bacteria. Created with BioRender.com. LPS: lipopolysaccharide; NOD: nucleotide-binding oligomerization domain; PSA: polysaccharide A; SCFAs: short chain fatty acids; TGFβ: transforming growth factor β; TNFα: tumor necrosis factor α

The gut microbiota and the innate immune system

The gut microbiota is intrinsically important to the function of the host's innate immunity, both locally and systemically, by influencing the development and function of antigen presenting cells (APCs), neutrophils and other innate cell types. APCs have co-evolved with microbiota and this shapes their ability to protect the body against infection while maintaining immune tolerance to normal gut microbiota. An example of this is that dendritic cells (DCs) from Peyer's patches produce high levels of IL-10 compared with the same cells in the spleen [58]. It is well established that IL-10 has an important role in attenuating inflammatory responses and maintaining homeostasis through T-cell regulation [59]. In addition, intestinal macrophages do not produce pro-inflammatory cytokines in response to microbial stimuli such as toll-like receptor (TLR) ligands [60] further highlighting the important role of immune tolerance development over time (Figure 1).

The gut microbiota also influences APCs outside of the gut milieu. It has been shown that microbe-derived adenosine triphosphate (ATP), via stimulation of DCs leads to the differentiation of Th17 cells [61]. These cells have a role in both promoting and attenuating inflammation and the immediate microenvironment, including the interaction with an array of various cytokines, the gut microbiome and metabolites such as SCFAs, regulating the balance between Th17 cells and regulatory T cells (Tregs) [62–64]. The microbiota also has a systemic influence over the regulation of neutrophils. It has been shown that GF rats are actually neutropenic and the neutrophils that are present have impaired phagocytic and superoxide anion and nitric oxide generation [65, 66]. These features are critical to the antimicrobial function of neutrophils. Further, it has been shown that recognition of gut microbial peptidoglycan enhanced the killing activity of bone marrow neutrophils [66]. Furthermore, the gut microbiota has also been shown to be involved in the development of

other innate cell types such as natural killer (NK) cells and mast cells [67–69]. Despite these data, it is still unclear the exact influence the gut microbiome has in terms of regulating, i.e. promoting or suppressing, neutrophilic function. Future studies investigating this are required.

The gut microbiota and the adaptive immune system

The gut microbiota plays a significant role in the development of the major subtypes of $CD4^+$ T cells: Th1, Th2, Th17 and Tregs. GF mice have been shown to have a Th1/Th2 imbalance with a bias towards Th2 responses which is interesting considering the connection of gut dysbiosis to numerous atopic conditions such as asthma and eczema [44, 50, 70]. As mentioned above, specific bacterial species such as *B. fragilis* can induce the systemic development of a Th1 response through its PSA molecule [71]. Thus, it is of interest whether manipulating the gut microbiota can have an influence on Th1/Th2 balance and alter disease activity. A recent study investigated the use of fecal microbial transplantation in patients with active atopic dermatitis, a disease hallmarked by a shift to Th2 response, and found that most patients had significant improvement in disease severity scores with reduction in corticosteroid dependence [72]. This study, corroborated previous evidence from mice models which showed restoration of gut microbial diversity and Th1/Th2 immunologic balance, modulated Tregs, reduced levels of IgE, masts cells, basophils and eosinophils and resulted in suppression of atopic-dermatitis induced allergic responses [73].

As can be seen from the above, Tregs, are important in modulating inflammatory responses by suppressing other cell types and as such help prevent autoimmune disease [74]. Recent data show that the gut microbiota influences Tregs development. Clostridia can promote their induction [75], *B. fragilis* can signal Tregs to suppress pro-inflammatory Th17 responses [76] and colonic Tregs have a unique collection of T cell receptors that recognize colonic bacterial contents [77]. The gut microbiota has also been shown to be important for the presence and function of intestinal $CD8^+$ T cells including their ability to modulate other peripheral immune cells such as marginal zone B cells, plasmacytoid DCs and NK cells [78–81]. Taken together, it can be deduced that disturbed interaction between gut microbiota and T cells can lead a more pro-inflammatory milieu within the gastrointestinal tract and beyond.

In addition to T cells, the gut microbiota, also influences B cell maturation and immunoglobulin production. Gut associated B cells are mostly found in the Peyer's patches and are mostly IgA secreting plasma cells [47]. In GF mice, a reduced number of plasma cells and decreased level of IgA have been observed [82]. As mentioned above, the spleens of GF mice also contain fewer and smaller germinal centers where B cell differentiation and affinity maturation occur [83]. Accordingly, serum natural IgG levels are severely reduced in GF animals [84]. Furthermore, microbial exposures have also been shown to induce characteristic immunoglobulin heavy chain repertoires in B cells and systemic exposures to microbes induce diversified IgG production [85]. While the production of a diverse immunoglobulin profile to the gut microbiome is intuitive, the mechanism behind the apparent selectivity of immunoglobulins to tolerate beneficial commensal over potentially harmful bacteria, is unclear. Interestingly, IgE, the allergy associated Ig isotype has been found to be increased both in the gastrointestinal tract and systemically which is consistent with the Th2 response predisposition in GF animals [86]. Although it is clear the gut microbiota plays a role in B cell development and function, the exact interplay between the microbes and immunoglobulin diversity remains unknown and should be the subject of future studies.

Mechanisms of microbiome influence on immune system homeostasis

SCFAs

One of the most important aspects of gut homeostasis remains the ability to maintain a boundary between gut luminal contents and immune cells within the submucosal space and beyond. Integral to this, is the maintenance of a set luminal pH, mucosal mucous layer and tight junctions between mucosal cells. SCFAs, namely butyrate, acetate, formate amongst others, play a vital role in maintaining this barrier. They are produced by the gut bacterial fermentation process of non-digestible carbohydrates and amino acids that have escaped digestion and absorption in the small intestine [87]. These SCFAs are then absorbed by the colonocytes and used as fuel for the colonic mucosal epithelial cells or enter the portal blood stream [88].

There are specific bacteria that are responsible for SCFA production and these have been relatively well characterized, in particular, those involved in the generation of propionate, butyrate and lactate. The production of butyrate, for example, is largely dominated by the breakdown of resistant starch by organisms such as *Ruminococcus bromii*, *Faecalibacterium prausnitzii* (*F. prausnitzii*), *Eubacterium rectale*, and *Eubacterium hallii* [89, 90]. Dysbiosis, resulting in alterations to the relative proportions of these and other critical bacteria reducing SCFA production, has a direct effect on gut integrity. Mechanistically, butyrate reduces mucosal level oxidative stress by consuming local oxygen and thus stabilizes hypoxia-inducible factor which is also important for barrier protection [91]. Furthermore, a decrease in butyrate which enhances intestinal barrier function through increasing expression of proteins such as claudin-1, zonula occludens-1 (ZO-1) and occludins [92], in turn increases LPS translocation promoting pro-inflammatory cascades in immune cells that lead to the further activation of downstream signaling pathways such as a nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase, and cytokine production such as TNFα and IL-6 [93–95]. This resulting inflammatory state has been linked to both gastrointestinal [96] and systemic conditions including dermatologic, cardiovascular, renal and neurological diseases [16, 97–100]. More studies are needed at this time, particularly *in vivo* human studies, to fully elucidate the role of butyrate and other SCFAs on colonic and immune function.

Pattern recognition receptors

Another important factor in maintaining homeostasis is the pattern recognition receptors (PRRs) which sense microbial signals and are involved in defense against pathogens, regulating the composition of the commensal microbes and maintaining physical barrier integrity [101]. TLRs, a type of PRR, are highly diverse and have a significant role in immune system regulation. For example, PSA which is produced by *B. fragilis*, is recognized by the TLR1/TLR2 complex and results in the downstream expression of anti-inflammatory genes [102]. Other PRRs which play an important role in intestinal homeostasis are NOD1 and 2. NOD1 serves as an innate sensor which assists in the generation of adaptive lymphoid tissues and NOD2 is a bacterial sensor which prevents intestinal inflammation through restricting growth of certain commensal bacteria and promoting gut epithelial cell survival and regeneration (Figure 1) [103–105]. Indeed, the importance in NOD2 in intestinal homeostasis is highlighted by its role in IBD pathogenesis when mutated [106]. Other NOD like receptors (NLRs) such as NOD-, leucine-rich repeat (LRR)- and pyrin domain-containing 6 (NLRP6) form inflammasomes which are important in regulating goblet cell mucus secretion and also regulate intestinal antiviral immunity [107, 108].

Bile acid metabolism and interaction with gut microbiome

An important interaction between bile acids and the gut microbiome occurs resulting in both positive and negative effects on commensal bacteria. Bile acids, independent of the gut microbiome, can effect gut mucosal integrity as a result of direct damage to cells and alterations in oxidative stresses occurring in the immediate cellular microenvironment [109, 110]. Furthermore, certain bacteria, predominantly gram negatives, are more resistant to the actions of bile acids [111]. This implies that specific bile acid composition can either support or hamper the growth of certain bacterial colonies. For example, primary bile acids have been shown to restrict the growth of gram negative bacteria in the small intestine [112]. In addition, primary bile salts have also been shown to promote the germination of bacterial spores which helps in restoration of a diverse microbial population after a particular insult [113]. While generally beneficial this interaction can also lead to the germination of pathogens such as *C. difficile*. This complex interaction has implicated bile salts in a wide ranging spectrum of diseases including IBD [114], primary sclerosing cholangitis [115], metabolic syndrome [116], colorectal cancer [117] amongst others.

The microbiome and immune system interaction in disease

Dysbiosis and the development of immune-mediated diseases

It is apparent from myriad interactions and influences of the gut microbiome on all aspects of the hosts immune system that perturbations to this symbiotic relationship are linked to the development of

autoimmune and immune-mediated diseases. There is an ever-growing body of evidence showing how gut microbial dysbiosis is associated with both intestinal and extra-intestinal diseases. One of the more obvious immune-mediated diseases thought to develop from this disturbed interaction is IBD. Many studies have shown altered microbiota composition in IBD patients characterized as a reduction of Firmicutes and Bacteroides species and an overgrowth of proteobacteria [118, 119]. Further evidence of a possible causative role for certain bacteria in the pathogenesis of IBD comes from a study which showed that reductions of *F. prausnitzii*, increased the risk of post-operative recurrence in CD patients [9]. Further, in a mouse colitis model oral administration of *F. prausnitzii* led to a significant reduction in the severity of colitis and also tended to correct the associated dysbiosis [9]. It appears that these effects are induced via the secretion of metabolites which block NF-κβ activation and IL-8 production [9]. More evidence comes from studies which have shown that *B. fragilis*, Bacteroides thetaiotaomicron (*B. thetaiotaomicron*) and SCFAs can ameliorate colitis through diverse mechanisms including the production of the anti-inflammatory IL-10 and enhancing the nuclear export of peroxisome proliferator-activated receptor-γ (PPAR-γ) [29, 120–123]. Also as described above, *Clostridium* plays a role in the upregulation and anti-inflammatory effects of Tregs which coincided with a reduction of dextran sodium sulfate (DSS)-induced colitis in mice [75].

Beyond the gastrointestinal tract, changes in gut microbiota have been shown to be associated with many systemic autoimmune diseases. An example of this is in RA where in a spontaneous arthritis mouse model, arthritis was reduced in GF mice and introduction of a single gut microbiota species was able to trigger joint inflammation [120]. An interesting example of how gut microbiota may be protective from disease is in T1D where in a non-obese diabetic mouse model, GF mice have been found to have significantly higher rates of diabetes [121]. This is consistent with the finding that T1D is more prevalent in countries with strict hygiene practices [122]. The gut microbiota has also been shown to have distinct patterns in patients with psoriasis, with significant increases in the Firmicutes and Actinobacteria phyla compared to matched controls and increased activity in lipopolysaccharide metabolic pathways [16].

Influence of gut microbiome on cancer development and prevention

The colon harbors the highest concentration of bacteria in the gastrointestinal tract. This, together with studies showing a 12-fold increase in the risk of colorectal cancer compared with cancer in the small bowel [123], point to the important role the microbiome plays in cancer development. Certain bacteria, including *Streptococcus gallolyticus* and *Fusobacterium nucleatum*, have been directly implicated in colorectal carcinogenesis [124, 125]. These bacteria induce inflammation and alter host immune responses through various cellular adhesion molecules and suppress the function of local immune cells including macrophages and Tregs. *Fusobacterium nucleatum* in particular disrupts tight junctions and activates beta-catenin which promotes the transcription of multiple oncogenes [126, 127]. Taken together, these changes, provide a microenvironment which promotes carcinogenesis [125]. While certain bacteria are implicated in carcinogenesis, other bacteria appear to have an important role in anti-tumor activity. Both *Bifidobacterium longum* and *Bifidobacterium breve* have been shown to increase the function of DCs which subsequently recruit cytotoxic T-cells to a tumor microenvironment and suppress tumor growth [128]. Furthermore, bacterial metabolites such as the SCFAs, butyrate and propionate, have anti-cancer effects by inducing programmed cell death [129]. While complex, these interactions of various components of the microbiome with tumorgenesis, could potentially allow for the development of biomarkers for cancer diagnosis, predictors of treatment response and also development of adverse events on therapy.

Conclusions

Taken together, this review highlights the vast influence the gut microbiota has on all components of the human immune system. This influence is not limited to local gastrointestinal effects but plays a role in the development and function of systemic immune elements as well. The manipulation of the gut microbiome in the treatment of numerous diseases is the subject of intense investigation and gives hope that through the manipulation of the gut microbiome at various stages it may be possible to shape the development of the

immune system—prenatally, intrapartum, during infancy and childhood and even in adulthood—and enable the prevention of certain diseases or help treat those which have already developed.

Abbreviations

APCs: antigen presenting cells

B. fragilis: *Bacteroides fragilis*

C. difficile: *Clostridioides difficile*

CD: Crohn's disease

DCs: dendritic cells

F. prausnitzii: Faecalibacterium prausnitzii

GF: germ free

IBD: inflammatory bowel disease

IgA: immunoglobulin A

IL-10: interleukin-10

NOD: nucleotide-binding oligomerization domain

PRRs: pattern recognition receptors

PSA: polysaccharide A

SCFAs: short chain fatty acids

T1D: type 1 diabetes

Th: T-helper

Th1: type 1 T-helper

TLR: toll-like receptor

Tregs: regulatory T cells

Declarations

Author contributions

TC wrote major parts of the manuscript. NAC conceptualized this review, wrote and critically reviewed the manuscript. Both authors contributed to manuscript revision, read and approved the submitted version.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

References

1. Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J. 2017;474:1823–36.
2. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006;444:1022–3.
3. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ. 2018;361:k2179.
4. Poretsky R, Rodriguez-R LM, Luo C, Tsementzi D, Konstantinidis KT. Strengths and limitations of 16S rRNA gene amplicon sequencing in revealing temporal microbial community dynamics. PLoS One. 2014;9:e93827.
5. Mizrahi-Man O, Davenport ER, Gilad Y. Taxonomic classification of bacterial 16S rRNA genes using short sequencing reads: evaluation of effective study designs. PLoS One. 2013;8:e53608.
6. Ringel Y, Maharshak N. Intestinal microbiota and immune function in the pathogenesis of irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2013;305:G529–41.
7. Machiels K, Joossens M, Sabino J, De Preter V, Arijs I, Eeckhaut V, et al. A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. Gut. 2014;63:1275–83.
8. Hansen R, Russell RK, Reiff C, Louis P, McIntosh F, Berry SH, et al. Microbiota of *de-novo* pediatric IBD: increased *Faecalibacterium prausnitzii* and reduced bacterial diversity in Crohn's but not in ulcerative colitis. Am J Gastroenterol. 2012;107:1913–22.
9. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ, 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;105:16731–6.
10. Marasco G, Di Biase AR, Schiumerini R, Eusebi LH, Iughetti L, Ravaioli F, et al. Gut microbiota and celiac disease. Dig Dis Sci. 2016;61:1461–72.
11. Kostic AD, Gevers D, Pedamallu CS, Michaud M, Duke F, Earl AM, et al. Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma. Genome Res. 2012;22:292–8.
12. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444:1027–31.
13. Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One. 2010;5:e9085.
14. Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep. 2017;7:13537.
15. Wang L, Christophersen CT, Sorich MJ, Gerber JP, Angley MT, Conlon MA. Low relative abundances of the mucolytic bacterium *Akkermansia muciniphila* and *Bifidobacterium* spp. in feces of children with autism. Appl Environ Microbiol. 2011;77:6718–21.
16. Shapiro J, Cohen NA, Shalev V, Uzan A, Koren O, Maharshak N. Psoriatic patients have a distinct structural and functional fecal microbiota compared with controls. J Dermatol. 2019;46:595–603.
17. Silverman GJ. The microbiome in SLE pathogenesis. Nat Rev Rheumatol. 2019;15:72–4.
18. Bodkhe R, Balakrishnan B, Taneja V. The role of microbiome in rheumatoid arthritis treatment. Ther Adv Musculoskelet Dis. 2019;11:1759720X19844632.
19. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Res. 2020;30:492–506.

20. Jiménez E, Fernández L, Marín ML, Martín R, Odriozola JM, Nueno-Palop C, et al. Isolation of commensal bacteria from umbilical cord blood of healthy neonates born by cesarean section. Curr Microbiol. 2005;51:270–4.
21. Moles L, Gómez M, Heilig H, Bustos G, Fuentes S, de Vos W, et al. Bacterial diversity in meconium of preterm neonates and evolution of their fecal microbiota during the first month of life. PLoS One. 2013;8:e66986.
22. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A. 2010;107:11971–5.
23. Kabeerdoss J, Ferdous S, Balamurugan R, Mechenro J, Vidya R, Santhanam S, et al. Development of the gut microbiota in southern indian infants from birth to 6 months: a molecular analysis. J Nutr Sci. 2013;2:e18.
24. Biasucci G, Benenati B, Morelli L, Bessi E, Boehm G. Cesarean delivery may affect the early biodiversity of intestinal bacteria. J Nutr. 2008;138:1796S–800S.
25. Penders J, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, et al. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics. 2006;118:511–21.
26. Salminen S, Gibson GR, McCartney AL, Isolauri E. Influence of mode of delivery on gut microbiota composition in seven year old children. Gut. 2004;53:1388–9.
27. Jakobsson HE, Abrahamsson TR, Jenmalm MC, Harris K, Quince C, Jernberg C, et al. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by Caesarean section. Gut. 2014;63:559–66.
28. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell. 2005;122:107–18.
29. Mazmanian SK, Round JL, Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. Nature. 2008;453:620–5.
30. Round JL, Mazmanian SK. Inducible Foxp3$^+$ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc Natl Acad Sci U S A. 2010;107:12204–9.
31. Neu J, Rushing J. Cesarean *versus* vaginal delivery: long-term infant outcomes and the hygiene hypothesis. Clin Perinatol. 2011;38:321–31.
32. Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. Diabetologia. 2008;51:726–35.
33. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disesase: meta-analyses. Clin Exp Allergy. 2008;38:634–42.
34. Penders J, Vink C, Driessen C, London N, Thijs C, Stobberingh EE. Quantification of *Bifidobacterium* spp., *Escherichia coli* and *Clostridium difficile* in faecal samples of breast-fed and formula-fed infants by real-time PCR. FEMS Microbiol Lett. 2005;243:141–7.
35. Cooke G, Behan J, Clarke N, Gorman W, Costello M. Comparing the gut flora of Irish breastfed and formula-fed neonates aged between birth and 6 weeks old. Microb Ecol Health Dis. 2005;17:163–8.
36. Bezirtzoglou E, Tsiotsias A, Welling GW. Microbiota profile in feces of breast- and formula-fed newborns by using fluorescence *in situ* hybridization (FISH). Anaerobe. 2011;17:478–82.
37. Mackie RI, Sghir A, Gaskins HR. Developmental microbial ecology of the neonatal gastrointestinal tract. Am J Clin Nutr. 1999;69:1035S–45S.
38. Jauréguy F, Carton M, Panel P, Foucaud P, Butel MJ, Doucet-Populaire F. Effects of intrapartum penicillin prophylaxis on intestinal bacterial colonization in infants. J Clin Microbiol. 2004;42:5184–8.

39. Tanaka S, Kobayashi T, Songjinda P, Tateyama A, Tsubouchi M, Kiyohara C, et al. Influence of antibiotic exposure in the early postnatal period on the development of intestinal microbiota. FEMS Immunol Med Microbiol. 2009;56:80–7.
40. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe. 2015;17:852.
41. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature. 2012;486:222–7.
42. Neu J. Necrotizing enterocolitis: the mystery goes on. Neonatology. 2014;106:289–95.
43. Zhang X, Zhivaki D, Lo-Man R. Unique aspects of the perinatal immune system. Nat Rev Immunol. 2017;17:495–507.
44. Russell SL, Gold MJ, Hartmann M, Willing BP, Thorson L, Wlodarska M, et al. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. EMBO Rep. 2012;13:440–7.
45. Kronman MP, Zaoutis TE, Haynes K, Feng R, Coffin SE. Antibiotic exposure and IBD development among children: a population-based cohort study. Pediatrics. 2012;130:e794–803.
46. Fiebiger U, Bereswill S, Heimesaat MM. Dissecting the interplay between intestinal microbiota and host immunity in health and disease: lessons learned from germfree and gnotobiotic animal models. Eur J Microbiol Immunol (Bp). 2016;6:253–71.
47. Wu HJ, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes. 2012;3:4–14.
48. Damsker JM, Hansen AM, Caspi RR. Th1 and Th17 cells: adversaries and collaborators. Ann N Y Acad Sci. 2010;1183:211–21.
49. Hsieh CS, Macatonia SE, Tripp CS, Wolf SF, O'Garra A, Murphy KM. Development of TH1 $CD4^+$ T cells through IL-12 produced by Listeria-induced macrophages. Science. 1993;260:547–9.
50. El Aidy S, Hooiveld G, Tremaroli V, Bäckhed F, Kleerebezem M. The gut microbiota and mucosal homeostasis: colonized at birth or at adulthood, does it matter? Gut Microbes. 2013;4:118–24.
51. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014;157:121–41.
52. Macpherson AJ, Slack E, Geuking MB, McCoy KD. The mucosal firewalls against commensal intestinal microbes. Semin Immunopathol. 2009;31:145–9.
53. Cliffe LJ, Humphreys NE, Lane TE, Potten CS, Booth C, Grencis RK. Accelerated intestinal epithelial cell turnover: a new mechanism of parasite expulsion. Science. 2005;308:1463–5.
54. McDole JR, Wheeler LW, McDonald KG, Wang B, Konjufca V, Knoop KA, et al. Goblet cells deliver luminal antigen to $CD103^+$ dendritic cells in the small intestine. Nature. 2012;483:345–9.
55. Ramanan D, Cadwell K. Intrinsic defense mechanisms of the intestinal epithelium. Cell Host Microbe. 2016;19:434–41.
56. Van Heyningen WE, Van Heyningen S, King CA. The nature and action of cholera toxin. Ciba Found Symp. 1976;42:73–88.
57. Turpin W, Lee SH, Raygoza Garay JA, Madsen KL, Meddings JB, Bedrani L, et al.; Crohn's and Colitis Canada Genetic Environmental Microbial Project Research Consortium; CCC GEM Project recruitment site directors include Maria Abreu, Croitoru K. Increased intestinal permeability is associated with later development of Crohn's Disease. Gastroenterology. 2020;159:2092–100.e5.
58. Iwasaki A, Kelsall BL. Freshly isolated peyer's patch, but not spleen, dendritic cells produce interleukin 10 and induce the differentiation of T helper type 2 cells. J Exp Med. 1999;190:229–39.
59. Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Crit Rev Immunol. 2012;32:23–63.

60. Smythies LE, Shen R, Bimczok D, Novak L, Clements RH, Eckhoff DE, et al. Inflammation anergy in human intestinal macrophages is due to Smad-induced IκBα expression and NF-κB inactivation. J Biol Chem. 2010;285:19593–604.
61. Atarashi K, Nishimura J, Shima T, Umesaki Y, Yamamoto M, Onoue M, et al. ATP drives lamina propria T_H17 cell differentiation. Nature. 2008;455:808–12.
62. Wu X, Tian J, Wang S. Insight into non-pathogenic Th17 cells in autoimmune diseases. Front Immunol. 2018;9:1112.
63. Chen P, Tang X. Gut microbiota as regulators of Th17/Treg balance in patients with myasthenia gravis. Front Immunol. 2021;12:803101.
64. Ohkubo T, Tsuda M, Tamura M, Yamamura M. Impaired superoxide production in peripheral blood neutrophils of germ-free rats. Scand J Immunol. 1990;32:727–9.
65. Ohkubo T, Tsuda M, Suzuki S, El Borai N, Yamamura M. Peripheral blood neutrophils of germ-free rats modified by *in vivo* granulocyte-colony-stimulating factor and exposure to natural environment. Scand J Immunol. 1999;49:73–7.
66. Clarke TB, Davis KM, Lysenko ES, Zhou AY, Yu Y, Weiser JN. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. Nat Med. 2010;16:228–31.
67. Sanos SL, Bui VL, Mortha A, Oberle K, Heners C, Johner C, et al. RORγt and commensal microflora are required for the differentiation of mucosal interleukin 22-producing NKp46$^+$ cells. Nat Immunol. 2009;10:83–91.
68. Kunii J, Takahashi K, Kasakura K, Tsuda M, Nakano K, Hosono A, et al. Commensal bacteria promote migration of mast cells into the intestine. Immunobiology. 2011;216:692–7.
69. Zhang D, Frenette PS. Cross talk between neutrophils and the microbiota. Blood. 2019;133:2168–77.
70. Qian LJ, Kang SM, Xie JL, Huang L, Wen Q, Fan YY, et al. Early-life gut microbial colonization shapes Th1/Th2 balance in asthma model in BALB/c mice. BMC Microbiol. 2017;17:135.
71. Fujimura KE, Lynch SV. Microbiota in allergy and asthma and the emerging relationship with the gut microbiome. Cell Host Microbe. 2015;17:592–602.
72. Mashiah J, Karady T, Fliss-Isakov N, Sprecher E, Slodownik D, Artzi O, et al. Clinical efficacy of fecal microbial transplantation treatment in adults with moderate-to-severe atopic dermatitis. Immun Inflamm Dis. 2022;10:e570.
73. Kim JH, Kim K, Kim W. Gut microbiota restoration through fecal microbiota transplantation: a new atopic dermatitis therapy. Exp Mol Med. 2021;53:907–16.
74. Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. Nat Rev Immunol. 2008;8:523–32.
75. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, et al. Induction of colonic regulatory T cells by indigenous *Clostridium* species. Science. 2011;331:337–41.
76. Round JL, Lee SM, Li J, Tran G, Jabri B, Chatila TA, et al. The toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science. 2011;332:974–7.
77. Lathrop SK, Bloom SM, Rao SM, Nutsch K, Lio CW, Santacruz N, et al. Peripheral education of the immune system by colonic commensal microbiota. Nature. 2011;478:250–4.
78. Imaoka A, Matsumoto S, Setoyama H, Okada Y, Umesaki Y. Proliferative recruitment of intestinal intraepithelial lymphocytes after microbial colonization of germ-free mice. Eur J Immunol. 1996;26:945–8.
79. Wei B, Su TT, Dalwadi H, Stephan RP, Fujiwara D, Huang TT, et al. Resident enteric microbiota and CD8$^+$ T cells shape the abundance of marginal zone B cells. Eur J Immunol. 2008;38:3411–25.
80. Fujiwara D, Wei B, Presley LL, Brewer S, McPherson M, Lewinski MA, et al. Systemic control of plasmacytoid dendritic cells by CD8$^+$ T cells and commensal microbiota. J Immunol. 2008;180:5843–52.

81. Wei B, Wingender G, Fujiwara D, Chen DY, McPherson M, Brewer S, et al. Commensal microbiota and $CD8^+$ T cells shape the formation of invariant NKT cells. J Immunol. 2010;184:1218–26.
82. Crabbé PA, Bazin H, Eyssen H, Heremans JF. The normal microbial flora as a major stimulus for proliferation of plasma cells synthesizing IgA in the gut. The germ-free intestinal tract. Int Arch Allergy Appl Immunol. 1968;34:362–75.
83. Bauer H, Horowitz RE, Levenson SM, Popper H. The response of the lymphatic tissue to the microbial flora. Studies on germfree mice. Am J Pathol. 1963;42:471–83.
84. Hooijkaas H, Benner R, Pleasants JR, Wostmann BS. Isotypes and specificities of immunoglobulins produced by germ-free mice fed chemically defined ultrafiltered "antigen-free" diet. Eur J Immunol. 1984;14:1127–30.
85. Li H, Limenitakis JP, Greiff V, Yilmaz B, Schären O, Urbaniak C, et al. Mucosal or systemic microbiota exposures shape the B cell repertoire. Nature. 2020;584:274–8.
86. Durkin HG, Bazin H, Waksman BH. Origin and fate of IgE-bearing lymphocytes: I. Peyer's patches as differentiation site of cells. Simultaneously bearing IgA and IgE. J Exp Med. 1981;154:640–8.
87. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes. 2016;7:189–200.
88. Sanna S, van Zuydam NR, Mahajan A, Kurilshikov A, Vich Vila A, Võsa U, et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. Nat Genet. 2019;51:600–5.
89. Ze X, Duncan SH, Louis P, Flint HJ. Ruminococcus bromii is a keystone species for the degradation of resistant starch in the human colon. ISME J. 2012;6:1535–43.
90. Louis P, Young P, Holtrop G, Flint HJ. Diversity of human colonic butyrate-producing bacteria revealed by analysis of the butyryl-CoA:acetate CoA-transferase gene. Environ Microbiol. 2010;12:304–14.
91. Kelly CJ, Colgan SP. Breathless in the gut: implications of luminal O_2 for microbial pathogenicity. Cell Host Microbe. 2016;19:427–8.
92. Wang HB, Wang PY, Wang X, Wan YL, Liu YC. Butyrate enhances intestinal epithelial barrier function via up-regulation of tight junction protein claudin-1 transcription. Dig Dis Sci. 2012;57:3126–35.
93. Lewis K, Lutgendorff F, Phan V, Söderholm JD, Sherman PM, McKay DM. Enhanced translocation of bacteria across metabolically stressed epithelia is reduced by butyrate. Inflamm Bowel Dis. 2010;16:1138–48.
94. Prause M, Pedersen SS, Tsonkova V, Qiao M, Billestrup N. Butyrate protects pancreatic beta cells from cytokine-induced dysfunction. Int J Mol Sci. 2021;22:10427.
95. Schulthess J, Pandey S, Capitani M, Rue-Albrecht KC, Arnold I, Franchini F, et al. The short chain fatty acid butyrate imprints an antimicrobial program in macrophages. Immunity. 2019;50:432–45.e7.
96. Parada Venegas D, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol. 2019;10:277.
97. Anker SD, Egerer KR, Volk HD, Kox WJ, Poole-Wilson PA, Coats AJ. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. Am J Cardiol. 1997;79:1426–30.
98. Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, von Haehling S, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol. 2007;50:1561–9.
99. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. Front Endocrinol (Lausanne). 2020;11:25.
100. van de Wouw M, Boehme M, Lyte JM, Wiley N, Strain C, O'Sullivan O, et al. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. J Physiol. 2018;596:4923–44.
101. Chu H, Mazmanian SK. Innate immune recognition of the microbiota promotes host-microbial symbiosis. Nat Immunol. 2013;14:668–75.

102. Erturk-Hasdemir D, Oh SF, Okan NA, Stefanetti G, Gazzaniga FS, Seeberger PH, et al. Symbionts exploit complex signaling to educate the immune system. Proc Natl Acad Sci U S A. 2019;116:26157–66.
103. Bouskra D, Brézillon C, Bérard M, Werts C, Varona R, Boneca IG, et al. Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. Nature. 2008;456:507–10.
104. Ramanan D, Tang MS, Bowcutt R, Loke P, Cadwell K. Bacterial sensor Nod2 prevents inflammation of the small intestine by restricting the expansion of the commensal *Bacteroides* vulgatus. Immunity. 2014;41:311–24.
105. Nigro G, Rossi R, Commere PH, Jay P, Sansonetti PJ. The cytosolic bacterial peptidoglycan sensor Nod2 affords stem cell protection and links microbes to gut epithelial regeneration. Cell Host Microbe. 2014;15:792–8.
106. Yamamoto S, Ma X. Role of Nod2 in the development of Crohn's disease. Microbes Infect. 2009;11:912–8.
107. Wlodarska M, Thaiss CA, Nowarski R, Henao-Mejia J, Zhang JP, Brown EM, et al. NLRP6 inflammasome orchestrates the colonic host-microbial interface by regulating goblet cell mucus secretion. Cell. 2014;156:1045–59.
108. Wang P, Zhu S, Yang L, Cui S, Pan W, Jackson R, et al. Nlrp6 regulates intestinal antiviral innate immunity. Science. 2015;350:826–30.
109. Albalak A, Zeidel ML, Zucker SD, Jackson AA, Donovan JM. Effects of submicellar bile salt concentrations on biological membrane permeability to low molecular weight non-ionic solutes. Biochemistry. 1996;35:7936–45.
110. Bernstein C, Bernstein H, Payne CM, Beard SE, Schneider J. Bile salt activation of stress response promoters in *Escherichia coli*. Curr Microbiol. 1999;39:68–72.
111. Begley M, Gahan CG, Hill C. The interaction between bacteria and bile. FEMS Microbiol Rev. 2005;29:625–51.
112. Kakiyama G, Pandak WM, Gillevet PM, Hylemon PB, Heuman DM, Daita K, et al. Modulation of the fecal bile acid profile by gut microbiota in cirrhosis. J Hepatol. 2013;58:949–55.
113. Staley C, Weingarden AR, Khoruts A, Sadowsky MJ. Interaction of gut microbiota with bile acid metabolism and its influence on disease states. Appl Microbiol Biotechnol. 2017;101:47–64.
114. Gothe F, Beigel F, Rust C, Hajji M, Koletzko S, Freudenberg F. Bile acid malabsorption assessed by 7 alpha-hydroxy-4-cholesten-3-one in pediatric inflammatory bowel disease: correlation to clinical and laboratory findings. J Crohns Colitis. 2014;8:1072–8.
115. Hirschfield GM, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. Lancet. 2013;382:1587–99.
116. Porez G, Prawitt J, Gross B, Staels B. Bile acid receptors as targets for the treatment of dyslipidemia and cardiovascular disease. J Lipid Res. 2012;53:1723–37.
117. Kulanthaivel S, Boccuto L, Zanza C, Longhitano Y, Balasundaram K, Méndez-Sánchez N, et al. Biliary acids as promoters of colon carcinogenesis: a narrative review. Dig Med Res. 2021;4:33.
118. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci U S A. 2007;104:13780–5.
119. Sokol H, Seksik P, Rigottier-Gois L, Lay C, Lepage P, Podglajen I, et al. Specificities of the fecal microbiota in inflammatory bowel disease. Inflamm Bowel Dis. 2006;12:106–11.
120. Wu HJ, Ivanov II, Darce J, Hattori K, Shima T, Umesaki Y, et al. Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity. 2010;32:815–27.
121. Pozzilli P, Signore A, Williams AJ, Beales PE. NOD mouse colonies around the world-recent facts and figures. Immunol Today. 1993;14:193–6.

122. Wen L, Ley RE, Volchkov PY, Stranges PB, Avanesyan L, Stonebraker AC, et al. Innate immunity and intestinal microbiota in the development of type 1 diabetes. Nature. 2008;455:1109–13.
123. Barsouk A, Rawla P, Barsouk A, Thandra KC. Epidemiology of cancers of the small intestine: trends, risk factors, and prevention. Med Sci (Basel). 2019;7:46.
124. Abdulamir AS, Hafidh RR, Abu Bakar F. The association of *Streptococcus bovis/gallolyticus* with colorectal tumors: the nature and the underlying mechanisms of its etiological role. J Exp Clin Cancer Res. 2011;30:11.
125. Wu J, Li Q, Fu X. *Fusobacterium nucleatum* contributes to the carcinogenesis of colorectal cancer by inducing inflammation and suppressing host immunity. Transl Oncol. 2019;12:846–51.
126. Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, Han YW. *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. Cell Host Microbe. 2013;14:195–206.
127. Shang S, Hua F, Hu ZW. The regulation of β-catenin activity and function in cancer: therapeutic opportunities. Oncotarget. 2017;8:33972–89.
128. Cheng WY, Wu CY, Yu J. The role of gut microbiota in cancer treatment: friend or foe? Gut. 2020;69:1867–76.
129. Sánchez-Alcoholado L, Ramos-Molina B, Otero A, Laborda-Illanes A, Ordóñez R, Medina JA, et al. The role of the gut microbiome in colorectal cancer development and therapy response. Cancers (Basel). 2020;12:1406.