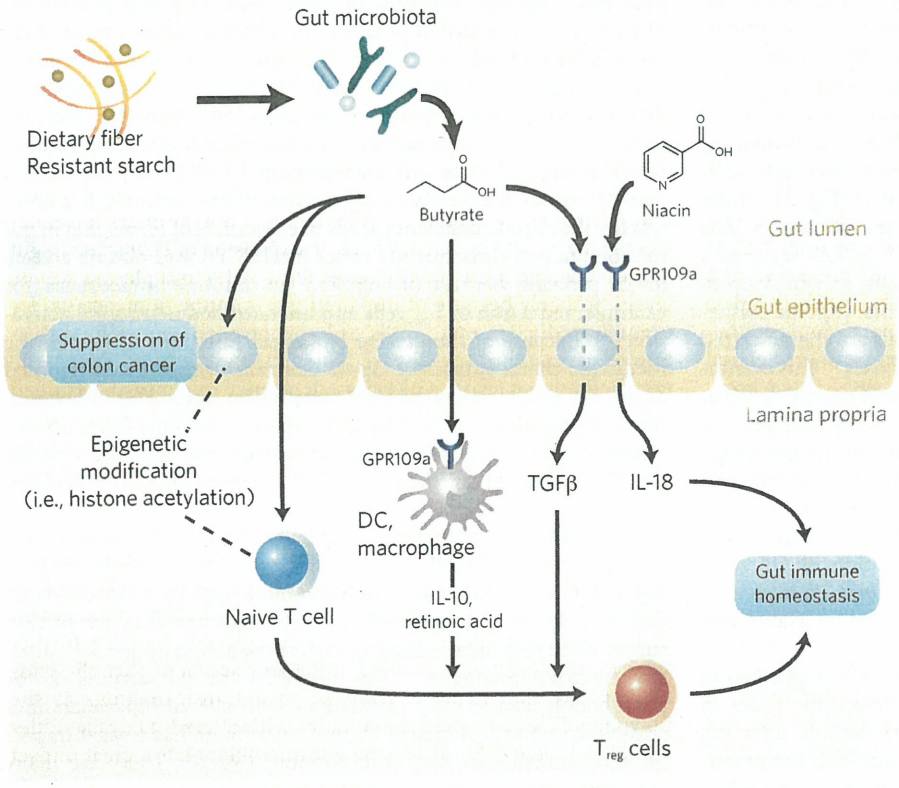

Figure 4 | Host-microbe interactions mediated by butyrate and niacin. Butyrate is mainly produced by clusters IV and XIVa of *Clostridia*. Although butyrate acts as an energy source for normal colonic epithelial cells (trophic effect), it also has the capability to suppress proliferation of cancerous epithelial cells that usually undergo the Warburg effect[99]. Butyrate upregulates histone H3 acetylation at regulatory regions of the *Foxp3* gene and facilitates differentiation of naive CD4$^+$ T cells into T_{reg} cells. In contrast, butyrate together with other SCFAs induce TGF-β secretion by epithelial cells through an unknown mechanism[71]. Gpr109a was originally described as the receptor for niacin. Butyrate and niacin bind Gpr109a on epithelial cells to trigger production of a cytoprotective cytokine IL-18. These microbial metabolites also stimulate dendritic cells and macrophages to produce IL-10 and retinoic acids, both of which are important for the development of IL-10–producing T_{reg}s in the colon. Therefore, butyrate and niacin contribute to the maintenance of intestinal homeostasis through multiple mechanisms.

hepaticus[75,76]. Furthermore, sphingolipids of *B. fragilis* reduce cell numbers of invariant NKT (iNKT) cells in the colon. Reduction of iNKT cells in response to colonization with *B. fragilis* results in alleviation of oxazolan-induced experimental colitis[77,78] because iNKT cells are responsible for the colitis development by producing large amounts of cytokines upon stimulation with glycosphingolipids presented by CD1d[79]. All of these observations indicate that different diet-independent metabolites have distinct roles in the maintenance of gut immune homeostasis.

So far, a variety of diet-dependent metabolites have been linked to the epithelial barrier, immune regulation and inflammation. These products include bile acids, short and long chain fatty acids and vitamins[66,80]. Certain *Bifidobacterium* spp. actively produce folate (vitamin B_9)[81], and its derivative, 6-formyl pterin (6-FP), is one of ligands of the MHC class I-like molecule MR1, which presents an antigen to mucosal-associated invariant T (MAIT) cells[82]. Notably, several riboflavin (vitamin B_2)-based metabolites, whose structures are closely related to 6-FP with an extra ribityl moiety, activate Jurkat T-cell lines (expressing invariant MAIT TCR α and β chains) to produce TNF and IFN-γ in an MR1-restricted manner. Given that B-group vitamins including rivoflavin are known to be synthesized *de novo* by certain commensal bacteria, it is possible that MAIT cells may sense the growth of riboflavin-producing bacteria on the mucosa.

Indole is a quorum-sensing molecule produced from tryptophan by the tryptophanase of a variety of Gram-positive and Gram-negative intestinal bacteria. Indole enhances epithelial barrier functions *in vitro* and *in vivo* through upregulation of components of tight junction complexes[83,84]. Acetate is another metabolite that enhances gut epithelial barrier functions (**Fig. 3**). GF mice succumb to *Escherichia coli* O157:H7 lethal infection; however, inoculation of mice with certain *Bifidobacteria* strains prevents *E. coil* O157–induced death[85]. *Bifidobacteria*-derived acetate inhibits translocation of luminal Shiga toxin from the gut lumen to the blood by improving epithelial defense functions and suppressing colonic inflammation. These findings provide insight into the mode of action through which probiotic bacteria exert a protective effect against pathological infections and open up a new question on how bacterial metabolites regulates epithelial barrier functions.

The anti-inflammatory effect of SCFAs, including acetate, has been well characterized on both epithelial and immune cell levels[62,86] (**Fig. 4**). Oral administration of acetate in drinking water suppresses not only DSS-induced experimental colitis but also inflammatory arthritis and ovalbumin-induced allergic airway inflammation. The therapeutic effect of acetate is canceled in Gpr43-deficient mice, implying a major role for the acetate-Gpr43 axis in containment of inflammation. Acetate-dependent Gpr43 activation on neutrophils results in upregulation of apoptosis-related gene clusters and thus provokes apoptosis.

SCFAs also have an impact on the terminal differentiation of CD4$^+$ helper T cells[62]. Administration of an individual or a cocktail of SCFAs to GF or SPF mice increased the frequency of colonic Foxp3$^+$ regulatory T_{reg} cells[87,88], which have a central role in the suppression of the inflammatory and allergic immune responses[89]. After oral administration, butyrate *per se* is less effective on the accumulation of colonic T_{reg}s as compared with that of the other two SCFAs[87]. However, this observation may reflect enhanced migration from lymphoid tissues into the colon rather than an increase in T_{reg} development in the colon, given that a large part of the orally administered SCFAs are absorbed into the portal vein and/or used by epithelial cells (butyrate is a particularly good energy source) in the upper part of the intestine before reaching the colon. The *in vitro* T_{reg} induction assay indicated that, among SCFAs, butyrate most effectively induces the differentiation of naive T cells into T_{reg} cells[88,90]. Propionate also shows the T_{reg}-inducing effect to a lesser extent, whereas acetate dose not have any impact on T_{reg} induction. Consistent with *in vitro* observations, colonic T_{reg} cells are significantly augmented in SPF mice with a diet containing butyrylate-resistant starch and slightly augmented with propionylated resistant starch but are hardly induced with acetylated resistant starch[90]. These observations show that locally produced butyrate is responsible for T_{reg} differentiation and that orally administered acetate and propionate may be important for the migration of T_{reg}s into the colon. Indeed, oral administration of propionate upregulates Gpr15 (ref. 91), a T_{reg}-specific gut-homing molecule, in a Gpr43-dependent

manner[87]. Butyrate is well known to regulate gene expression epigenetically by inhibiting histone deacetylases (HDACs). Chromatin immunoprecipitation sequencing (ChIP-seq) analysis demonstrated that butyrate upregulates histone H3 acetylation at regulatory regions of the *Foxp3* gene locus and therefore facilitates *Foxp3* expression (**Fig. 4**). In addition to such a direct effect on $CD4^+$ T cells, butyrate indirectly induces IL-10–producing T_{reg} cells by imparting anti-inflammatory properties on dendritic cells (DCs) and macrophages in the colonic lamina propria in a Gpr109a-dependent manner[56] (**Fig. 4**). Niacin, a pharmacological agonist for Gpr109a, also exhibits a similar anti-inflammatory activity (**Fig. 4**). Collectively, these findings demonstrate that microbe-derived SCFAs and niacin contribute to the maintenance of gut immune homeostasis by promoting T_{reg} accumulation in the colon through multiple mechanisms. In support of this idea, butyrate-producing bacteria decreased in the microbial community of IBD patients compared with that of healthy subjects[92]. It has also been reported that gut microbiota–derived SCFAs, particularly propionate, alleviate an allergic airway response induced by house dust mite extract in mice[93]. The feeding of a diet rich in fermentable carbohydrates promotes the outgrowth of bacteria that belong to the *Bacteroidetes* phylum, leading to increased serum levels of acetate and propionate, which in turn increase the hematopoiesis of DC precursors[93]. These DCs exhibit an impaired capacity to elicit allergy-prone T_H2 responses in the lung. This process requires the receptor Gpr41 but not Gpr43. This study provides key evidence that bacteria-derived metabolites may affect not only the local but the systemic immune system. Collectively, the recent data support the idea that diet-dependent metabolites shape host immunity by activating different mechanisms, including Gprs-dependent intracellular signaling activation and epigenetic modifications. Although further investigations will be required to clarify the precise molecular mechanism, the interactions between gut metabolites and host immunocompetent cells are essential for the successful establishment and maintenance of the host immune system.

Gut metabolites and disease development. Disturbance of the microbiota has been implicated in the pathogenesis of several human disorders, including IBD, obesity and cardiovascular disease[94]. For example, gut microbial metabolism of dietary food–derived phosphatidylcholine and L-carnitine generates trimethylamine (**Fig. 3**), which is further metabolized to trimethylamine-*N*-oxide (TMAO), a proatherogenic agent, in mice and humans[12,13]. A HFD alters gut microbial composition in mice, leading to expansion of deoxycholic acid–producing bacteria, namely cluster XI of the genus *Clostridium*[14]. This secondary bile acid induces a phenotypic change in hepatic stellate cells to secrete proinflammatory cytokines and eventually facilitates hepatocellular carcinoma (**Fig. 3**).

Accumulating reports have linked gut microbiota to emotional behavior. Alteration of the gut microbial community owing to TLR5 deficiency increases appetite (about 10% increase in food intake) and induces metabolic syndrome (for example, hyperlipidemia, insulin resistance, obesity and hepatic steatosis) in mice without affecting the efficiency of dietary energy harvest[95]. In addition, chronic ingestion of fermented milk with probiotics can modulate the responsiveness of an extensive brain network in healthy subjects[96]. Although the exact mechanism remains to be elucidated, these observations suggest that metabolites produced by microbial fermentation have a key role in brain activity.

A current study revealed that a mouse model of autism spectrum disorder (ASD) can be triggered by the gut microbial metabolites 4-ethylphenylsulfate (4EPS) and indolepyruvate[97] (**Fig. 3**). Maternal immune activation induced by the administration of an immunostimulant polyinosinic-polycytidylic acid (poly I:C) during pregnancy causes ASD-like behavior in offspring, which is associated with gut barrier dysfunction and systemic leakage of luminal metabolites. In line with these experiential observations, several metabolites (for example, *p*-cresol and indolyl-3-acryloylglycine), which are structurally similar to 4EPS and indole pyruvate, are detected as human autism biomarkers in urine[98]. On the basis of these observations, the brain-microbiota-metabolite axis can be considered a potential therapeutic target for ASD and other neurodevelopmental illnesses[97]. Future studies will provide mechanistic insights into how these gut microbiota–derived metabolites contribute to the pathophysiology of neurodevelopmental disorders.

Conclusions and perspectives

It is now becoming clear that the gut microbiota and its metabolites have an important role in host physiology. Of note, recent investigations indicate that different environmental factors, such as nutrition and drugs, can profoundly affect the gut bacterial community, thereby changing the gut microbiome activity, which may result in generations of bioactive metabolites (for example, health-promoting or disease-causing metabolites). These observations will have ramifications on what we eat and as such would influence food, pharmaceutical and medical sciences by providing new concepts. For example, the use of prebiotics and probiotics or folk medicines often rely on traditional beliefs rather than solid scientific evidence and still suffer because of the lack of more precise knowledge concerning their modes of action. Further investigations of the molecular mechanisms by which prebiotics and probiotics exert their effects on animal physiology will provide new opportunities for improving human health. Furthermore, many important immune and metabolic disorders, including diabetes, obesity, behavioral disorders and chronic inflammation, are now known to be in part due to the imbalance of interactions between the host and microbiota or metabolites. Accordingly, we expect that further investigation on the molecular relationship between microbiota and metabolites and host physiology will provide new concepts and strategies for the development of 'gut metabolite concept'–driven therapeutic agents. Considering the very high diversity of gut bacterial species in different metazoans, it is likely that yet-unexpected microbiota-metabolite-metazoa relationships and the molecular dynamics of these relationships remain to be explored. The use of powerful invertebrate and vertebrate genetic animal model system together with multi-omics approaches would allow us to discover and decipher the secrets of evolutionarily conserved molecular dialogs among gut microbiota, metabolites and metazoans, which will certainly open new avenues to prevent and/or treat a number of disorders associated with gut microbiota and metabolites.

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Competing financial interests

The authors declare no competing financial interests.

Additional information

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REVIEW

Commensal microbiota regulates T cell fate decision in the gut

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Abstract Commensal microbiota shapes the intestinal immune system by regulating T helper (T_H) cell lineage differentiation. For example, *Bacteroides fragilis* colonization not only optimizes the systemic T_H1/T_H2 balance, but also can induce regulatory T (Treg) cell differentiation in the gut. In addition, segmented filamentous bacteria (SFB) facilitate the development of T_H17 cells in the small intestine. The 17 strains within clusters IV, XIVa, and XVIII of *Clostridiales* found in human feces can also induce the differentiation and expansion of Treg cells in the colon. Thus, the regulation of T_H cell differentiation by commensal bacteria is evident; however, the molecular mechanisms underlying these processes remain uncertain. Recent studies have demonstrated that bacterial components, as well as their metabolites, play a central role in regulating T_H cell development. Furthermore, these metabolites can elicit changes in histone posttranslational modification to modify the expression of critical regulators of T cell fate. In this review, we discuss the mechanisms and biological significance of microbiota-dependent T_H differentiation.

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Introduction

Human beings harbor over 100 trillion bacterial species, comprising more than 1000 strains, in the distal intestine. Commensal bacteria facilitate the breakdown of food necessary for energy metabolism in their hosts [1, 2]. Compelling evidence suggests that colonization by commensal bacteria critically contributes to the development of the mammalian immune system. Given that patients with inflammatory bowel disease (IBD) often present with dysbiosis [3], or an imbalance of commensal bacteria, the interplay between commensals and host cells may play a critical role in the maintenance of gut immune homeostasis. This concept has been partly verified by recent studies using gnotobiotic mice, in which germ-free (GF) mice are colonized by specific strains of commensal bacteria. So far, a select number of these strains have been documented to induce the development of particular immune mediators, such as type 17 helper T cells (T_H17) and regulatory T (Treg) cells [4–6]. Although the mechanisms by which gut microbiota regulates host immunity have yet to be elucidated, their derived metabolites can partially mediate this immunomodulatory effect. Such bioactive materials are produced by microbiota through both diet-dependent and diet-independent means [7]. Here, we discuss the molecular interactions between commensal microbiota and T_H cell development.

Development of effector T_H cells by commensal bacteria

Systemic immune responses are biased to T_H2 under neonatal and GF conditions [4, 8, 9]. Microbial exposure early in life is