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Invited review article

Gut microbiome, metabolome, and allergic diseases

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GPR, G protein-coupled receptor; IL, interleukin; iNKT, invariant natural killer T; LCFA, long-chain fatty acid; MAIT, mucosa-associated invariant T; MHC, major histocompatibility complex; PPAR, peroxisome proliferator-activated receptor; SCFA, short-chain fatty acid; Th2, T helper type 2; Treg, regulatory T

ABSTRACT

The number of patients with allergic and inflammatory disorders has been increasing during the past several decades. Accumulating evidence has refined our understanding of the relationship between allergic diseases and the gut microbiome. In addition, the gut microbiome is now known to produce both useful and harmful metabolites from dietary materials. These metabolites and bacterial components help to regulate host immune responses and potentially affect the development of allergic diseases. Here, we describe recent findings regarding the immunologic crosstalk between commensal bacteria and dietary components in the regulation of host immunity and the influence of this relationship on the development of allergic diseases.

Introduction

The mammalian intestine is home to trillions of commensal bacteria, representing more than 1000 species.[1] Due to difficulties in the culture of many commensal bacteria, culture-based analysis fails to provide complete and accurate information regarding the composition of the intestinal microbiota. However, recent advances in high-throughput DNA sequencing of the bacterial 16S ribosomal RNA amplicon enable the direct identification of commensal bacteria without culturing, revealing that altered composition and, consequently, decreased diversity (known as dysbiosis) of the intestinal microflora are linked to the development of inflammatory and allergic diseases.[2] For example, patients with food allergies in the United States have low species diversity, reduced Clostridiales, and increased Bacteroidales in the gut commensal bacteria.[3] In another study, an elevated Enterobacteriaceae:Bacteroidaceae ratio in early infancy was associated with subsequent food sensitization.[4]

In addition, some intestinal bacteria supply beneficial metabolites derived from the host's diet, which contribute to the development and regulation of the host immune system through their effects on differentiation, proliferation, migration, and effector functions.[5] In this review, we describe recent findings regarding how commensal bacteria and their metabolites regulate host immune responses and their possible involvement in the development and control of allergic diseases.

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Long-chain fatty acids and allergic diseases

Long-chain fatty acids (LCFAs) are major nutrients, not only acting as energy sources but also in the regulation of immune responses. In general, LCFAs are derived from dietary components and metabolized into lipid metabolites after absorption into the body. Among LCFAs, the ω3 and ω6 FAs are essential FAs that mammals cannot produce. It has long been known that ω3 FAs have anti-allergic and anti-inflammatory properties.[6] Indeed, we previously reported that allergic diarrhea was ameliorated through the consumption of ω3-enriched linseed oil.[7] An additional analysis using lipidomics technology allowed us to identify 17,18-epoxy-eicosatetraenoic acid as an anti-allergic lipid metabolite derived from eicosapentaenoic acid.[7]

Although 17,18-epoxy-eicosatetraenoic acid likely is generated in the colon through the action of cytochrome P450,[6] several lines of evidence indicate that commensal bacteria participate in LCFA metabolism. Indeed, germ-free animals exhibit alterations in lipid metabolites, some of which are derived from ω3-FA.[8–13] For example, colonic levels of the ω3 FA metabolites 14-hydroxy docosahexaenoic acid, 17-hydroxy docosahexaenoic acid, resolvin D1, and protectin D1 are greater in germ-free mice than conventional mice.[13] In addition, resolvin D1 down-regulates the gene expression of interleukin (IL) 1β during pathogenic infection,[13] and IL-1β exacerbates allergic disorders such as atopic eczema, asthma, and contact dermatitis.[14] Together, these findings imply that microbe-dependent suppression of resolvin D1 production may be associated with allergic inflammation.

We also found that ω6 FA-derived lipid metabolites are generated by commensal bacteria, especially lactic acid bacteria.[15] For example, *Lactobacillus plantarum* generates conjugated linoleic acids, oxo FAs, and hydroxy FAs from ω6 FAs (Table 1). Consistent with the fact that *Lactobacillus* spp. are predominant in the proximal small intestine,[16,17] hydroxy FAs such as 10-hydroxy-cis-12-octadecenoic acid and 10-hydroxy-cis-9-octadecenoic acid are abundant in the small intestine of specific pathogen-free mice but are decreased in the small intestine of germ-free mice. A subsequent study revealed that the administration of synthetic 10-hydroxy-cis-12-octadecenoic acid ameliorated experimental colitis by enhancing tight junctions via G protein-coupled receptor (GPR) 40 on epithelial cells (Table 1, Fig. 1).[18] Because intestinal epithelial barrier function is important for control of food allergy,[19] it is plausible that *Lactobacillus*-derived 10-hydroxy-cis-12-octadecenoic acid might protect against the development of food allergy by maintaining intestinal epithelial barrier function.

Regarding the relationship among lipids, the gut microbiome, and allergy in humans, a recent cohort study demonstrated that variations in the composition of the gut microbiota during the neonatal stage were differentially related to the relative risk of developing atopy and asthma in childhood.[20] 16S rRNA sequencing analysis revealed that neonates with decreased relative abundance of various bacterial species (e.g., *Bifidobacterium*, *Akkermansia*, and *Faecalibacterium*) and increased relative abundance of particular fungi (*Candida* and *Rhodotorula*) were at high risk for the development of allergy (Table 1). Intriguingly, whereas anti-inflammatory lipid metabolites including docosapentaenoate and dihomo-γ-linolenate were increased in the low-risk group,[20] pro-inflammatory metabolites such as 12,13-dihydroxy-9Z-octadecenoic acid, stigma- and sitosterols, and 8-hydoxyoctanoate were enriched in high-risk subjects.[20] These metabolites increased the induction of IL-4–producing T helper type 2 (Th2) cells and reduced regulatory T (Treg) cell counts, thus creating an environment highly conducive to allergic disease (Fig. 1).

Lipid-mediated anti-allergic properties involve several mechanisms, including signal transduction, transcription, and gene expression via receptors (e.g., GPR40, GPR120, and the peroxisome proliferator-activated receptor [PPAR] family). GPR40 and GPR120 are well known as LCFA receptors.[21] As mentioned earlier, 10-hydroxy-cis-12-octadecenoic acid is recognized by GPR40 and consequently suppresses *TNFR2* gene expression and nuclear factor κB (NF-κB) via the MEK-ERK pathway.[18] In addition, docosahexaenoic acid, an ω3 FA, ameliorates inflammation by binding GPR40

Table 1
Immunomodulable metabolites derived from commensal microorganisms.

Category	Metabolite	Related microorganism	Function	Reference
LCFA	10-hydroxy-cis-12-octadecenoic acid	*Lactobacillus plantarum*	GPR40 ligand	15,18
	12,13-dihydroxy-9Z-octadecenoic acid	*Candida* and *Rhodotorula* (possibly)	Unknown	20
	Unknown	*Bacteroides thetaiotaomicron*	PPARγ ligand	26
	Unknown	*Enterococcus fecalis*		29
	Conjugated linoleic acids	VSL#3 (probiotic mixture)		30
Glycolipid	Glycosphingolipids	*Sphingomonas* spp.	CD1d-dependent antigen to iNKT cells	32
	Glycodiacylglycerols	*Sphingomonas* spp., *Ehrlicha*, and *Borrelia burgdorferi*		
	Diacylglycerol-containing glycolipids	*Streptococcus pneumoniae*		
	Tetra-mannosylated form of phosphatidylinositol	*Mycobacterium bovis*		
	Cholesteryl-α-glucoside	*Helicobacter pylori*		
SCFA	Acetate	*Bifidobacterium* spp.	Acetylation of Foxp3 promoter likely through HDAC9 inhibition	50,57
	Butyrate	*Clostridium* clusters XIVa and Iva and *Bacteroides thetaiotaomicron*	Histone H3 acetylation in the Foxp3 locus	49,55
	Propionate	*Bacteroidetes*, *Phascolarctobacterium succinatutens*, *Veillonella* spp., and *Clostridium* clusters XIVa and Iva	GPR41 and GPR43 ligand	48,51,56
Vitamin	Reduced 6-hydroxymethyl-8-d-ribityllumazine	*Salmonella typhimurium*	MR1-dependent antigen to MAIT cells	70
	7-hydroxy-6-methyl-8-d-ribityllumazine			
	6,7-dimethyl-8-D-ribityllumazine (vitamin B2 metabolites)			
	6-formyl pterin (vitamin B9 metabolite)	Unknown		
Amino acid	D-tryptophan	*Lactobacillus rhamnosus* GG and *Lactobacillus casei* W56	Unknown	92

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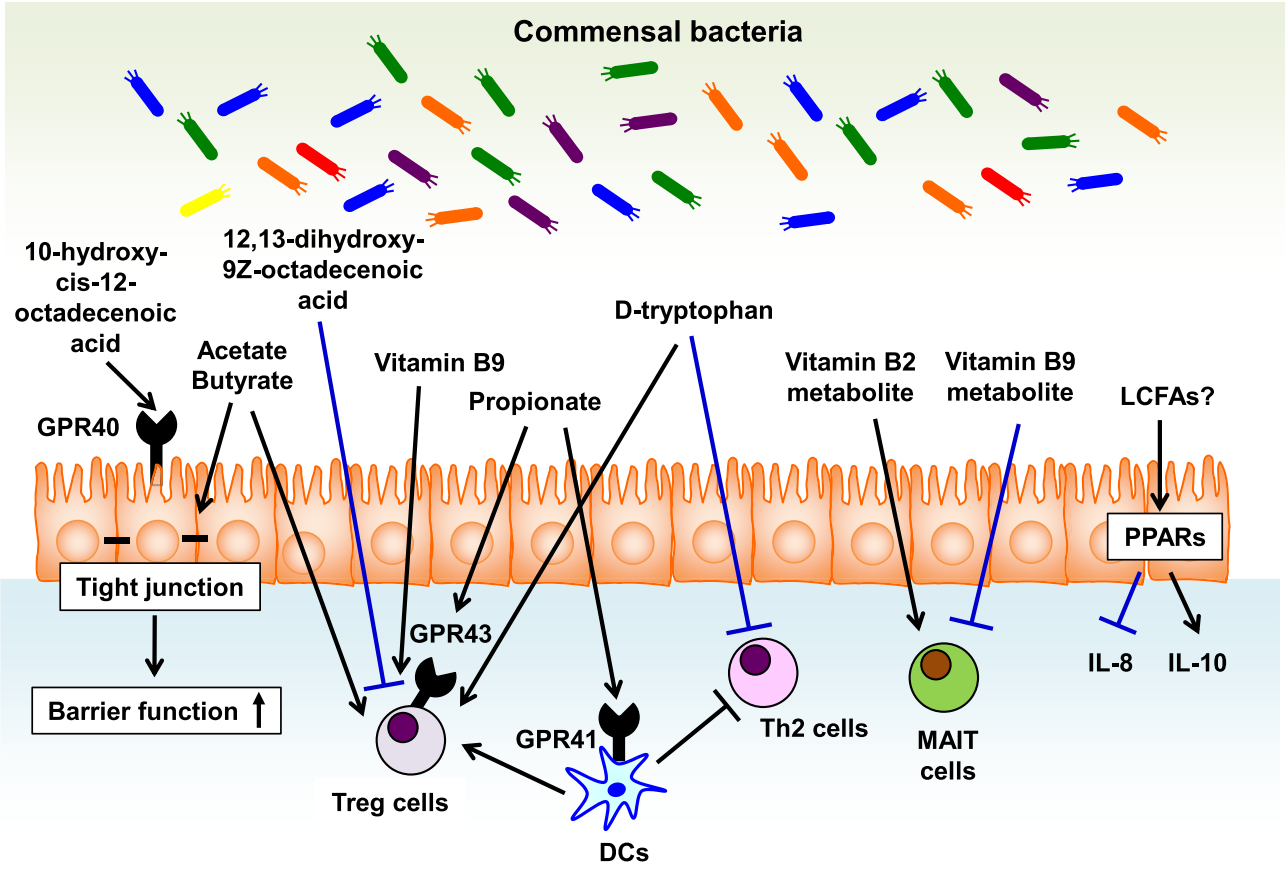

Fig. 1. Bacterial metabolites in the gut regulate immune responses for the allergic diseases. Bacterial metabolites regulate versatile biologic and immunologic functions related to allergic diseases. Epithelial barrier function is enhanced by 10-hydroxy-cis-12-octadecenoic acid, a linoleic acid-derived metabolite, and SCFAs such acetate and butylate, fermentation products by some bacteria. In addition, SCFAs (e.g., acetate, butyrate, and propionate) as well as D-type tryptophan have a potential to enhance the induction of Treg cells. Vitamin B9 plays a key role in the maintenance of Treg cells and its metabolite prevents the activation of MAIT cells by competing with vitamin B2 metabolite, MAIT cell activating ligand, in their binding to MR1. PPAR ligands such as LCFAs decrease the inflammatory cytokines such as IL-8 and induce the production of anti-inflammatory cytokines such as IL-10.

and GPR120 on macrophages, thus preventing the activation of the NLRP3 inflammasome.[22] Given that activation of the NLRP3 inflammasome on macrophages contributes to asthma exacerbation,[23] it may offer a promising approach for the regulation of other allergic diseases.

LCFAs have been proposed to modulate immune reactions via PPAR family receptors, which generally are negative regulators for allergic diseases.[24,25] As an example of the crosstalk between commensal bacteria and the PPAR family, *Bacteroides thetaiotaomicron* promoted PPAR-γ–dependent export of NF-κB from the nucleus and consequently decreased NF-κB–dependent IL-8 production (Table 1, Fig. 1),[26] thus perhaps curbing the IL-8–mediated infiltration of granulocytes in bronchial allergy.[27,28] Moreover, treatment with *Enterococcus fecalis* led to the activation of PPAR-γ1 in human intestinal epithelial cells and increased the production of IL-10 (Table 1, Fig. 1),[29] potentially suppressing allergic inflammation. Another study showed that probiotic bacteria in the intestine produce conjugated linoleic acids that target PPAR-γ in macrophages to suppress the inflammatory response (Table 1).[30]

In addition, lipids directly act as antigens to activate immune cells, especially invariant natural killer T (iNKT) cells. iNKT cells recognize glycolipid antigens presented on the MHC class I-related molecule CD1d.[31] Glycolipid antigens include α-galactosylceramide (derived from a sample of marine sponge) and microbial glycolipids (e.g., glycosphingolipids from *Sphingomonas* spp. bacteria; glycodiacylglycerols from *Sphingomonas* spp., *Ehrlicha*, and *Borrelia burgdorferi*; diacylglycerol-containing glycolipids from *Streptococcus pneumoniae*; a tetra-mannosylated form of phosphatidylinositol from *Mycobacterium bovis*; and cholesteryl-α-glucoside from *Helicobacter pylori*) (Table 1).[32] Compared with conventional mice, germ-free mice have fewer iNKT cells in the spleen, liver, and thymus, suggesting that commensal bacteria are involved in the induction of iNKT cells by producing their antigen.[33] Some studies show that iNKT cells act as key pathogenic T cells and exacerbate allergic airway diseases by promoting the production of IL-4 and IL-13 (Th2 cytokines),[34–37] whereas others suggest that iNKT cells suppress IgE production and induce the production of IL-10 from B cells and Treg cells (Table 1).[38] Together, these findings indicate that the type of lipid or timing of lipid exposure may determine the immunologic phenotype of iNKT cells, which have the potential to control allergic inflammation.

Immune regulation by short-chain fatty acids

Short-chain fatty acids (SCFAs) are 1–6 carbons in length. The major SCFAs in the gut include acetate, propionate, and butyrate.[39,40] Because SCFAs are produced through the fermentation of polysaccharides, such as cellulose,[41–43] germ-free mice exhibit remarkably decreased amounts of SCFAs and increased amounts of indigestible oligosaccharide.[10,44–47] In addition, the intake of dietary fiber was shown to change the composition of the intestinal flora, in particular by decreasing Firmicutes and simultaneously increasing Bacteroidetes at the phylum level and by increasing Bifidobacteriaceae at the family level. Organisms belonging to

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Bacteroidetes and Bifidobacteriaceae preferentially metabolized the fiber, thereby increasing the concentration of SCFAs.[48] Therefore, commensal bacteria metabolize fiber to generate SCFAs, and fiber reciprocally affects the composition of commensal bacteria in the gut.

Accumulating evidence indicates that SCFAs have several anti-allergic properties. Regarding the underlying mechanisms, SCFAs (particularly propionate) educate dendritic cells to achieve high phagocytic capacity and an ability not to promote the effector function of Th2 cells,[48] which is dependent on GPR41 but not GPR43 (Table 1, Fig. 1). In addition, SCFAs enhance the induction and function of Treg cells (Fig. 1).[49–51] Among SCFAs, butyrate induced the differentiation of Treg cells *in vitro* and *in vivo* with concurrent enhancement of histone H3 acetylation in the Foxp3 locus (Table 1).[49] Acetate increased the acetylation of the Foxp3 promoter also, likely through HDAC9 inhibition (Table 1).[50] Propionate increases the number of Treg cells mediated through GPR43 on the cells (Table 1).[51] As mentioned above, intestinal epithelial barrier is also important for prevention of the food allergy.[19] Microbial butyrate and acetate enhance the epithelial barrier function via induction of physiological hypoxia in the intestinal epithelial cells (Fig. 1).[52,53] Therefore, SCFAs have beneficial effects such as Treg cells induction and enhancement of the barrier function for allergic diseases.

Among commensal bacteria in the colon, Clostridia produce SCFAs and indeed induce colonic Treg cells, leading to the suppression of inflammatory[49] and allergic[54] responses (Table 1, Fig. 1). Clostridia, especially *Clostridium* clusters XIVa and IVa, are known to produce butyrate from pyruvate via butyryl CoA:acetate CoA transferase and from acetate (Table 1, Fig. 1).[55] Propionate is primarily produced by Bacteroidetes and some Firmicutes (e.g., *Phascolarctobacterium succinatutens*, *Veillonella* spp.), mainly via the succinate metabolic pathway (Table 1, Fig. 1).[56] Acetate is generated by many genera of intestinal organisms, including *Bifidobacterium* spp (Table 1, Fig. 1).[57] Collectively, commensal bacteria have the ability to produce different SCFAs via fermentation in the gut and thus to exert diverse anti-allergic properties.

Vitamins

There are 13 essential vitamins for humans: the hydrophobic vitamins—A, D, E and K—and the hydrophilic vitamins—the B family (B1, B2, B3, B5, B6, B7, B9, and B12) and C. Like mammals, bacteria utilize vitamins for their biologic functions. However, unlike mammals, some bacteria have the capacity to synthesize essential vitamins, especially B-family members and K, and thus are an important additional source of vitamins.[58,59] Many groups (including ours) have reported immunologic functions of vitamins.[60–67] For example, Treg cells express high levels of folate (vitamin B9) receptor 4, and vitamin B9 is essential for their maintenance (Fig. 1).[66] Indeed, a deficiency of vitamin B9 leads to the development of intestinal inflammation.[68] Because the levels of vitamin B9 produced differ among commensal bacteria,[69] the amount of dietary vitamin B9 necessary to maintain Treg cells may be totally dependent on this amount.

In addition to their functions as essential nutrients, some vitamins act as ligands for immune cells, and their presentation as ligands is mediated by monomorphic MHC class I-related protein (also known as MR1).[70] Intriguingly, MR1 presents metabolites generated in the microbial riboflavin (vitamin B2) biosynthetic pathways to mucosa-associated invariant T (MAIT) cells (Table 1), a population of T cells that produces IL-17 and IFN-γ.[70–74] Of note, MR1 also binds to a microbial vitamin B9 metabolite, 6-formyl pterin, but it does not activate MAIT cells (Table 1, Fig. 1).[70] In addition to their role in the immunosurveillance system,[70] MAIT cells are likely involved in the allergic and inflammatory diseases.[75] Therefore, it is plausible that the balance between commensal bacteria and dietary conditions determines the production of microbial vitamin metabolites and subsequent regulation of immune responses and allergic conditions.

Bacterial amino acids

Humans must obtain 20 amino acids as essential nutrients, some of which (alanine, aspartate, cysteine, glutamate, glutamic acid, glycine, and tryptophan) are metabolized by commensal bacteria.[10,76–82] In addition, all amino acids except glycine have two isoforms, the L- and D-amino acids, which are enantiomers. In general, L-amino acids are incorporated into protein in mammalian cells, whereas some bacteria can produce and use D-amino acids as bacterial cell wall components.[83] Indeed, a recent study indicated that cecal quantities of some D-amino acids (including D-alanine, D-asparagine, D-glutamic acid, and D-prorine) are greater in specific pathogen-free mice compared with germ-free mice.[84]

Several lines of evidence have indicated the potential influence of amino acids on the development, homeostasis, and function of immune cells. For instance, melatonin is a metabolite of L-tryptophan that can prevent the production of inflammatory cytokines.[85,86] Dietary glutamine has the ability to reduce the expression of P-selectin glycoprotein ligand-1, leukocyte function-associated antigen-1, and C-C chemokine receptor type 9 on T cells in the blood and mesenteric lymph node of mice.[87] The intake of dietary histidine or glycine led to the inhibition of inflammatory cytokine production from macrophages *in vitro* or colonic tissue of rodent colitis models.[88,89] Glutamine reportedly is a nutrient necessary to induce IL-10-producing intraepithelial lymphocytes in the small intestine[90]; glutamate also has a potential to promote immune tolerance in gut-associated lymphoid tissue.[91] Although few data are available regarding how D-type (or bacterial) amino acids regulate allergic inflammation, dietary intake of D-tryptophan from probiotic bacteria (such as *Lactobacillus rhamnosus* GG, *Lactobacillus casei* W56) reportedly concomitantly induced increased Treg cell counts and decreased Th2 responses in the gut and lung, consequently cooperatively ameliorating allergic airway inflammation and hyperresponsiveness (Table 1, Fig. 1).[92] Therefore, D-type amino acids derived from commensal bacteria in the gut might offer a means to regulate host allergic reactions.

Conclusion

Commensal bacteria in the gut produce several beneficial metabolites that regulate allergic responses; this effect is mediated at least in part by the induction of Treg cells, suppression of the Th2-type phenotype, up-regulation of IL-10 expression, and maintenance of the gut barrier function. In contrast, intestinal commensal bacteria also are involved in the production of pro-inflammatory metabolites. The balance between these functions might be determined by both external factors (e.g., diet) and internal factors (e.g., host genetics). Therefore, future research should focus on clarifying the versatile and complex system established in the gut, where a triangular network among diet, commensal bacteria, and host exists.

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Conflict of interest

The authors have no conflict of interest to declare.

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