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Invited review article

Gut microbiome, metabolome, and allergic diseases

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Abbreviations:
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