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Review

From Bacteria to Host: Deciphering the Impact of Sphingolipid Metabolism on Food Allergic Reactions

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Abstract

Purpose of Review Allergic diseases have become a burden in industrialized societies. Among children, food allergy (FA) constitutes a major impairment of quality of life. FA is partly due to a lack or loss of tolerance to food antigens at the level of the intestinal mucosa, where the microbiota plays a crucial role. Early changes in the composition of the gut microbiota may influence the development of the immune system and can be related to the risk of allergic diseases, including FA. This review will focus on the role of sphingolipids and the major bacteria involved in their metabolism, in the development of food antigen sensitization and FA.

Recent Findings Numerous studies have identified different patterns of microbial composition between individuals with and without FA, pointing to an interaction between gut microbiota, enterocytes, and immune cells. When this interaction is lost and an imbalance in the composition of the intestinal microbiota occurs, the integrity of the epithelial barrier may be altered, leading to intestinal permeability and sensitization to food antigens

and the development of FA. Gram-negative bacteria, especially those of the Proteobacteria phylum, have been associated with the development of FA. Investigating the interactions between the intestinal microbiota and the immune system, their influence on intestinal barrier function, and their production of metabolites and signaling molecules may contribute to understanding the pathogenesis of FA.

Summary Sphingolipids, a class of bioactive amphipathic lipids found in cell membranes, have emerged as critical regulators of inflammation. In this review, we will attempt to summarize the existing knowledge on the role of these molecules and the major bacteria involved in their metabolism in the mechanisms underlying sensitization to food antigens and the development of FA.

Introduction

The human body contains trillions of microorganisms, consisting of over one thousand species, which coexist with human cells. This microbial community is known as the microbiota, with most of these microorganisms residing in the gut [1]. They play an essential role in maintaining good health. The gut microbiota is a complex community primarily composed of bacteria, which dynamically interacts with the host and undergoes changes throughout life due to numerous factors. The colonization and future composition of the gut microbiota are particularly crucial during infancy, when intestine maturation and the first encounter with environmental factors occur [2]. However, certain factors such as caesarean birth, formula feeding, and antibiotic use can disrupt the transmission of microbiota from mother to child and further alter its composition, which is also influenced by other factors such as diet and the presence of siblings and pets at home, among other factors [1]. Moreover, differences in the gut microbiota have been observed among different ethnic groups, which have an impact beyond early-life exposures [3].

The gastrointestinal tract is covered by approximately 4×10^{13} microbial cells [4], with the highest concentration of bacteria found in the final part, from the appendix to the colon. The gut microbiota interacts symbiotically with intestinal epithelial cells, known as enterocytes [5]. It plays a crucial role in modulating immune responses and maintaining immune tolerance in the gut. Dysbiosis, which refers to an imbalance in gut microbiota composition and functionality, can contribute to food allergic reactions [6]. Dysbiosis may disrupt the integrity of the epithelial barrier, increasing its permeability and leading to food antigen sensitization and the development of food allergy (FA). Numerous studies have identified distinct microbial composition patterns between individuals with and without FA [7–9]. Infants with IgE-mediated FA have been observed to exhibit dysbiosis and delays in microbial maturation, suggesting that microbial composition may modify the risk of IgE-mediated FA through innate and adaptive immunity [10]. Moreover, gut microbiota from healthy infants has been shown to protect germ-free mice from anaphylactic reactions due to cow's milk allergy [11].

Identifying the specific bacterial species involved in FA and understanding their functional activities can provide valuable insights into the mechanisms underlying food allergen sensitization and progression of the disease. Gram-negative bacteria have been traditionally linked to FA, being Bacteroidetes phylum less prevalent and Proteobacteria phylum more abundant in FA patients [12••, 13]. Investigating the intricate interactions between the microbiota and the immune system, their influence on intestinal barrier function, and their production of metabolites and signaling molecules can contribute to understanding the pathogenesis of the disease, identifying diagnostic biomarkers, and developing targeted intervention strategies. However, most of the current research on the early human gut microbiome is based on cross-sectional data. More longitudinal studies exploring changes in the composition of the gut microbiota throughout childhood and their relationship to food sensitivity are needed.

On the other hand, there is a lack of biomarkers related to FA that can facilitate diagnosis or predict

the progression of the condition. In this regard, lipids, which are essential nutrients for living organisms, have been found to play a critical role as regulators of inflammation and have emerged as clinically relevant mediators in the pathophysiology of allergic diseases [14]. Lipids participate in various cellular mechanisms, including cell structure formation, energy storage, and cellular signaling. Among the diverse types of lipids, sphingolipids (SLs) and the enzymes involved in their metabolism have been recently proposed to play a role in the development of allergic diseases [15, 16].

De novo synthetized SLs are major plasma membrane components of mammalian cells and are considered potent bioactive agents involved in diverse biological functions, such as migration, apoptosis, and proliferation. The main SLs found in the human metabolism, in order of increasing complexity, include sphingosines (Sph), ceramides (Cer), and sphingomyelins (Sm). SLs are also derived from dietary sources such as meat, egg, or milk [17, 18], and several bacterial species from the gut microbiota (e.g. genus *Bacteroides* and *Prevotella*), and others such as *Sphingomonas*, which seem to be involved in their biosynthesis and metabolism [18, 19].

In this review, we pay attention to the biochemistry of SLs, the main bacteria implicated in their metabolism, and their role in the onset and progression of FA, giving the clue for identifying new biomarkers that allow for the prediction and early diagnosis of this pathology, as well as future intervention strategies.

Bacterial structure variations in gut microbiome and their implications in food allergy development

The composition of bacterial membranes, including the arrangement of their lipid components, is important when considering the complex landscape of FA. Bacteria belonging to different phyla and families exhibit diverse morphological and structural characteristics, dictated by their classification as Gram-negative or Gram-positive organisms (Fig. 1). The primary constituents of bacterial membranes are phospholipids, which are organized in a lipid bilayer, forming the fundamental framework of the bacterial membrane. In the case of Gram-negative bacteria, additional lipid components such as lipopolysaccharides (LPS) are incorporated into their membranes. These lipids play important roles in the structural integrity and protection of bacteria, as well as in interaction with the environment [20]. In addition, some bacteria possess a flagellum that can influence bacterial virulence. The bacterial flagellum is involved in bacterial locomotion, but it also assists them in colonizing specific tissues or evading the host's immune system. The presence or absence of the flagellum, and its structure and function, can vary among different bacterial species and even within the same bacterial species [21, 22].

Gram-negative bacteria have been linked to FA, with certain phyla and families standing out. FA has been related with a higher presence of Proteobacteria and a lower abundance of Bacteroidetes phyla [12••, 13]. In fact, a decrease in the Prevotellaceae family (phylum Bacteroidetes) has been widely described in allergic patients with IgE-dependent FA [23, 24••]. On the other hand, Martin et al. [25] observed in IgE-independent FA, such as food protein–induced allergic proctocolitis (FPIAP), that the composition and richness of the microbiome were similar in infants with FPIAP and controls. However, a higher abundance of Enterobacteriaceae family (phylum Proteobacteria) was observed during

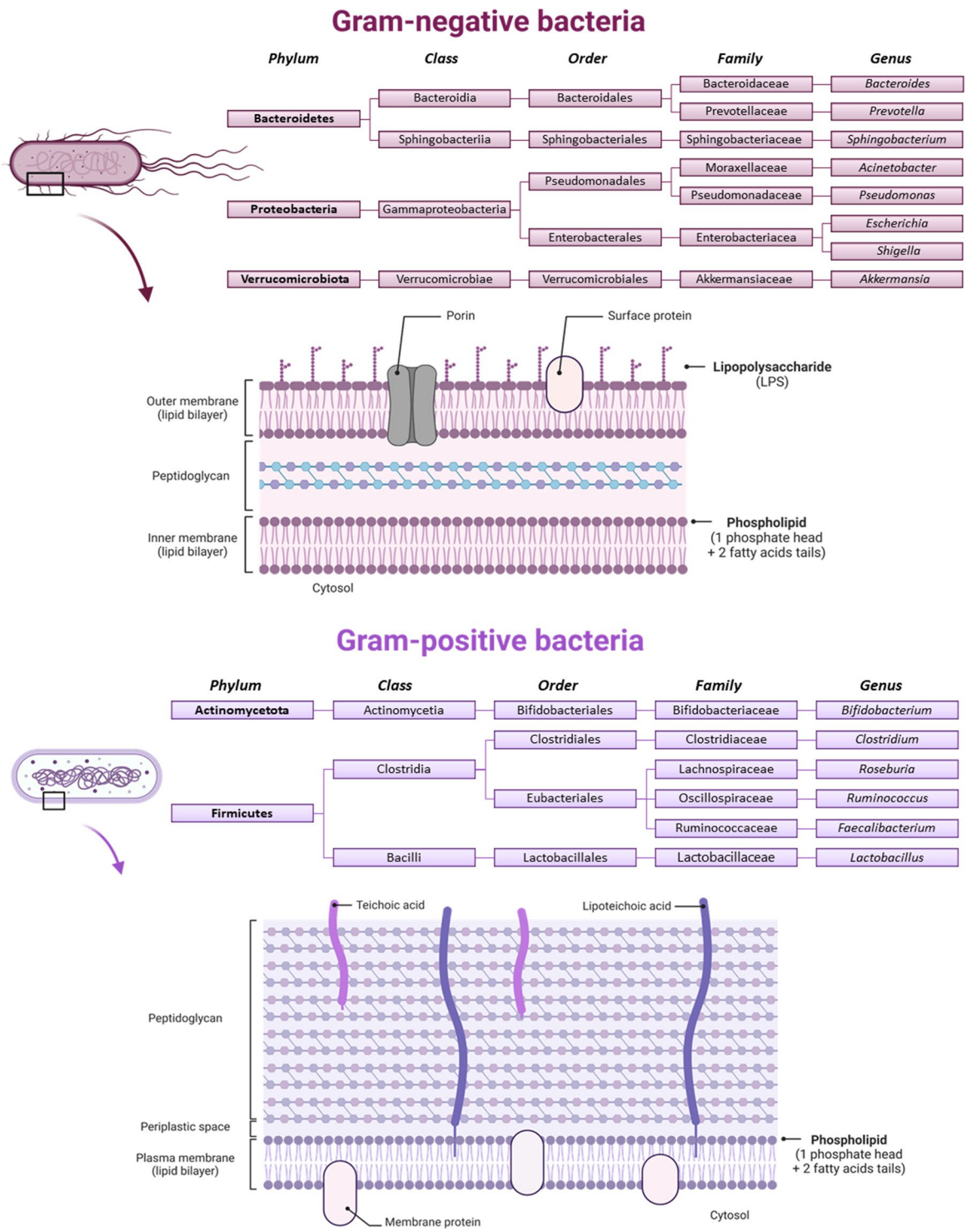

Fig. 1 Cell wall structures of Gram-negative and Gram-positive bacteria and bacterial taxonomy of the most relevant ones related to food allergy in the literature.

symptomatic periods, even preceding symptom onset [25]. In addition, the Enterobacteriaceae family, together with the Moraxellaceae (phylum Proteobacteria) and Sphingobacteriaceae (phylum Bacteroidetes) families have been observed to increase in patients with other inflammatory bowel diseases. Interestingly, recent research has shown that not only the gut microbiota, but also the microbiota of breast milk can influence the development of FA in infants. It has been shown that the composition of the breast milk microbiota of mothers of allergic infants differs from that of non-allergic infants. Specifically, the FA group showed a relatively high abundance of the genera *Acinetobacter* and *Pseudomonas* and a decrease of *Akkermansia* [24••]. Verrucomicrobiota phylum harbours the Akkermansiaceae family, including the genus *Akkermansia*. *Akkermansia muciniphila*, a commensal bacterium in the human gastrointestinal tract, has been extensively studied for its role in intestinal and metabolic health, such as mucin metabolism regulation and enhancement of intestinal barrier integrity. Indeed, it has been suggested that *Akkermansia muciniphila* could modulate immune responses and intestinal homeostasis and promising results have been even obtained in in vivo models of FA using strains of this family as probiotics [24••, 26].

Among Gram-positive bacteria, Actinomycetota and Firmicutes phyla encompass several families of interest. In the phylum Actinomycetota, the family Bifidobacteriaceae is a prominent group of bacteria, well known for its presence in the human gut microbiota and its association with intestinal health and modulation of the immune response. In this sense, a depletion of some *Bifidobacterium* species – e.g. *B. longum*, *B. breve*, and *B. infantis* – has been identified in the gut microbiome of allergic children [12••, 27, 28]. As for the phylum Firmicutes, alterations of several bacteria belonging to this phylum have been related to FA [13]. A lower abundance of the Clostridiaceae family, particularly in the genus *Clostridium*, known for its role in activating TGF-β release, has been described during the symptomatic period in IgE-independent FA [25, 29]. *Clostridium difficile*, primarily associated with intestinal infections, has been suggested to have an association with a higher risk of developing allergic diseases during early childhood [30]. In addition, increased levels of *Faecalibacterium prausnitzii* and *Ruminococcus gnavus* have also been associated with a higher risk of FA [12••]. Regarding the influence of breast milk microbiota on the development of FA, it has been described that a decrease in the relative abundance of the genera *Bifidobacterium* and *Clostridium*, and butyrate-producing bacteria such as *Faecalibacterium*, *Roseburia*, and *Ruminococcus* correlates with an increased risk of developing FA [24••, 31, 32]. Finally, Lactobacillaceae family has been extensively studied in the context of FA, with species like *Lactobacillus rhamnosus* and *Lactobacillus casei* demonstrating beneficial effects in preventing and reducing allergic responses. These species also exhibit modulatory effects on the immune response and reduce sensitization to food allergens [33–35].

Sphingolipids: structure, metabolism, and roles in bacteria

SLs are a diverse class of amphipathic lipids that are present in cell membranes and play a significant role in cellular signaling [36]. Structurally, SLs are composed of a sphingoid base linked to a fatty acid via an amide bond

and a usually hydrophilic headgroup at the primary hydroxyl. Based on these two functional groups, SLs can be divided into three structural classes of increasing complexity: sphingoid base and simple derivatives, Cer, and complex SLs [37, 38]. The first class refers to long-chain amino alcohols, such as Sph or sphinganine, that function as precursors to other SLs. Then, after acetylation, the composition of the headgroup can range from a simple hydrogen in the second class (Cer) to phospholipids (phosphosphingolipids) or sugars (glycosphingolipids), among others, in the third class [39] (Fig. 2A).

SLs were initially thought to be found only in eukaryotes, where they have been widely studied [17, 40]. In the last decade, however, the presence of these bioactive lipids has been reported in a small subset of prokaryotic cells, mainly in commensal [41••] and pathogenic bacteria [42, 43]. Within the gut microbiota, SL production is restricted to the Bacteroidetes phylum, including common genera such as *Bacteroides*, *Prevotella*, and *Porphyromonas* [44]. Additionally, certain alpha-Proteobacteria (*Acetobacter*, *Sphingomonas*), delta-Proteobacteria (*Myxococcus*, *Bdellovibrio*), and other species (*Sphingobacterium*, *Pedobacter*) have also been shown to synthesize SLs [41••, 43, 45•]. On the other hand, bacterial pathogens such as *Mycobacteria*, *Pseudomonas*, or *Neisseria*, although unable to produce them, have adapted to recognize and use host SLs to promote their survival and replication [42, 43]. Lastly, in addition to these two sources, SLs are also found in many foods that are part of our daily diet, including dairy products and eggs [46, 47], and as such they can be metabolized by the microbiota. In this regard, in a study performed both in *Bacteroides thetaomicron* strain cultures and cecal microbiota from a mouse model, Lee et al. demonstrated that several gut microbes can uptake dietary SLs [48•]. Interestingly, the authors found that dietary SLs can be assimilated and metabolized not only by known SL producers, mainly *Bacteroides* spp. and *Prevotella* spp., but also by other non-SL producer bacteria such as *Bifidobacterium* or *Lactobacillus* [48•, 49]. Subsequently, these microbiome-derived SLs have been shown to be reabsorbed by human epithelial cells and processed through mammalian SL pathways, allowing them to be incorporated into host lipid metabolism [44]. Overall, the close relationship between prokaryotic cells and SLs raises the question as to why they are important to bacteria.

Although the function of SLs in prokaryotic cells is still not fully understood, they are believed to be essential in bacterial physiology [18] and host interactions [45•]. Complex SLs or free Cer constitute up to 50% of Bacteroidetes membrane composition [41••, 50]. Furthermore, other bacterial strains including *Escherichia coli*, *Treponema denticola*, and *Porphyromonas gingivalis* have the capability to synthesize and accumulate SLs in their membranes. On the other hand, known SL producers such as *Sphingomonas* spp. naturally lack the LPS in the outer membrane and replace it with SLs [51]. Taken together, this evidence suggest that SLs may play a significant role in membrane stability and function. Regarding host interaction, certain bacteria make use of SL components to invade host cells and establish infections, potentially influencing adhesion, colonization, and virulence. Notably, within the Enterobacteriaceae family, bacteria such as *Salmonella* and *Escherichia coli*, among others, have been shown to exhibit associations with host cell SLs [52, 53]. Additionally, Cer-enriched lipid rafts and glycosphingolipids serve as binding and signaling platforms for

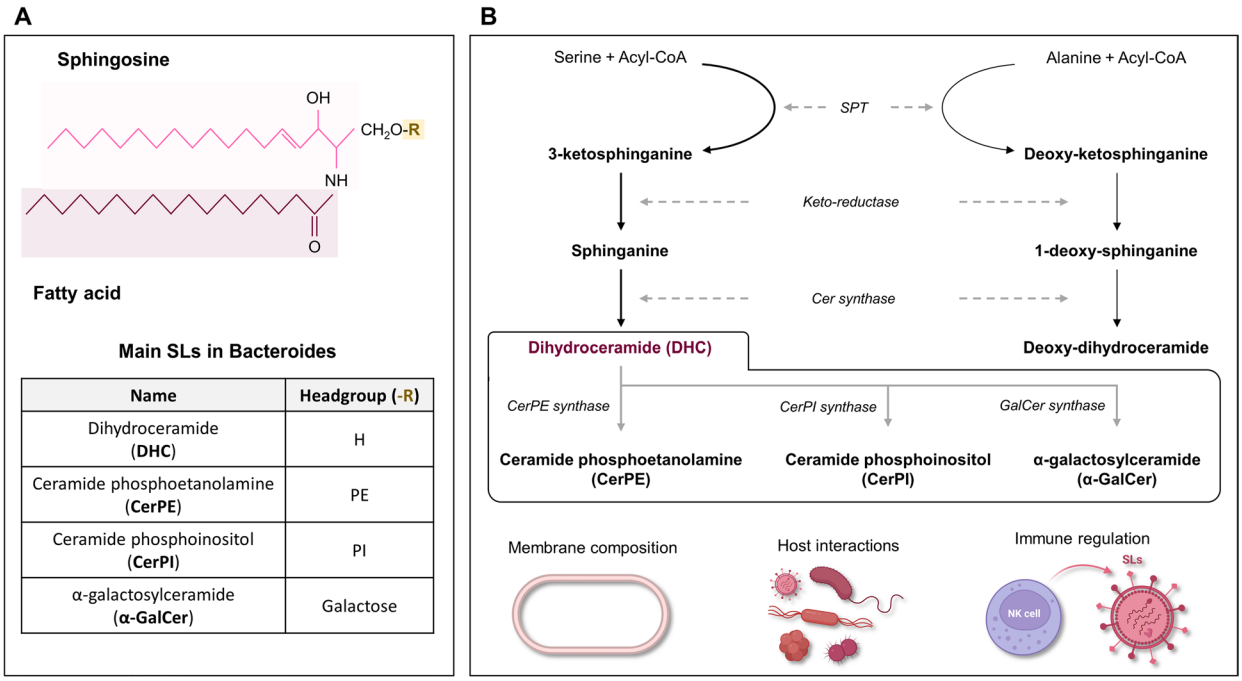

Fig. 2 Overview of the metabolism and main roles of sphingolipids (SLs) in bacteria. **A** General chemical structure of SLs (top) and the major SLs found in SL-producing bacteria classified by their head group (bottom). **B** Proposed metabolic pathway of biosynthesis for the previous SLs in Bacteroides and their potential roles within the cellular context (adapted from [41••] and [50]).

many intracellular bacterial pathogens and toxins such as choleric toxin and botulinic neurotoxin [42, 54].

In terms of metabolism, the biosynthesis of bacterial SLs appears to differ from that of eukaryotes. In eukaryotic cells, SL synthesis takes place in five stages [55]. The first and rate-limiting stage consists of the condensation of L-serine with palmitoyl coenzyme-A to form 3-ketosphinganine and is catalyzed by the enzyme serine palmitoyltransferase (SPT) [56]. Then, the three following steps involve 3-ketosphinganine reduction, acylation, and desaturation to Cer, which can then be modified with different headgroups in the final step [40, 55]. On the other hand, while the exact metabolic pathways are still under investigation, it is known that SPT is also responsible for the first step of bacterial de novo SL synthesis, making this reaction the key step in the commitment to SL biosynthesis across all organisms studied to date [41••, 44, 57]. Bacterial SPT was first reported in *Sphingomonas paucimobilis* [58] and has since then been described in other *Sphingomonas* [59] and *Sphingobacterium* [60, 61] bacterial strains, *Bbdellovibrio stolpii* [61], *B. fragilis* [62], and other *Bacteroides* or related species [18], allowing them all to produce SLs. Although conserved, these SPT orthologues are structurally and functionally distinct. While eukaryotic SPT functions as a heterodimeric membrane-bound large protein complex

that primarily utilizes L-serine as a substrate [63, 64], prokaryotes contain mainly homodimeric SPTs that are either water-soluble (*S. paucimobilis*) [65] or associated with the inner cell membrane (*Sphingobacterium multivorum*, *B. stolpii*) [61], suggesting that the latter may be more targeted to release hydrophobic SLs directly onto the membrane [57, 62].

Beyond SPT, the set of enzymes by which bacterial SLs are synthesized is still unknown. However, recent studies by Brown et al. [41••] and Ryan et al. [50] have characterized this anabolic pathway in mice models and cell cultures, respectively, of four different *Bacteroides* species, including *B. fragilis*, *B. thetaiotaomicron*, *B. ovatus*, and *B. vulgatus*, using metabolomics. As previously described, they found that bacterial de novo SL synthesis starts when the enzyme SPT uses serine or alanine as a substrate to form 3-ketosphingosine and deoxy-ketosphinganine, which would then lead to more complex SLs and deoxy-SLs, respectively. For this purpose, like eukaryotes, both precursors are reduced (3-keto sphinganine reductase) [66] and acylated (Cer synthase) to (deoxy)dihidroceramide ((deoxy)DHCer). DHCers are the central element of SL metabolism in bacteria and constitute the backbone from which most bacterial SLs are generated by adding different headgroups [41••, 50]. Notably, unlike mammalian SLs, bacterial SLs can have both odd and even numbers of carbons in their backbones and acyl chains [41••, 44, 45•]. Besides DHCers, most abundant Bacteroides-derived SLs include ceramide phosphoetanolamine (CerPE) [67], ceramide phosphoinositol (CerPI) [68], and α-galactosylceramide (α-GalCer) [69] (Fig. 2B), although their relative abundance can vary among species because of different biosynthetic pathways may be operating or because they are being metabolized [66, 70]. As an example, *B. fragilis* displays lower levels of DHCers— presumably because they are being shifted towards α-GalCer synthesis [50], which is necessary for stress resistance and prolonged survival trough their interaction with Natural Killer T cells [45•].

Association between sphingolipid metabolism in bacteria and allergic response

In the intestine, SLs are present in copious quantities. Enterocytes metabolize them from food intake into Cer and Sph. Phosphorylated SLs metabolites, such as sphingosine-1-phosphate (Sph-1-P) and ceramide 1-phosphate, generated by sphingosine kinases and ceramide kinases, respectively, showed different functions than those of their precursors [71], being considered signaling molecules playing crucial roles in cellular processes implicated in immune cell trafficking and inflammatory responses [72].

Inflammation is an important driver of Cer synthesis. In this regard, Cer production increases in response to various inflammatory stimuli, such as cytokines, oxidative stress, and bacterial LPS [73]. Inflammatory signaling pathways, as the NF-κB pathway, can activate enzymes involved in Cer synthesis, leading to increased Cer levels [74, 75]. Furthermore, Cer themselves can trigger inflammatory pathways, which can result in a positive feedback loop

that worsens inflammation. Elevated serum Cer have been suggested to be correlated with obesity-associated intestinal dysbiosis and impaired glucose metabolism in terms of decreased metagenomic richness, decreased abundance of anti-inflammatory bifidobacterial species, and increased metagenomic capacity for LPS biosynthesis and flagellar assembly, thus confirming the link between Cer and gut-derived inflammation [76•]. Indeed, Kayser et al. described that a decreased abundance of 30 metagenomic species was associated with an increase in serum concentrations of Cer (d18:1), also showing a significant association with decreased gene richness. The most abundant phylum in the human intestine, Firmicutes, comprised most associations with both gene richness and SLs. Additionally, the research notes that *Bifidobacterium bifidum* and *Bifidobacerium adolescentis* were negatively associated with Cer levels, while *Ruminococcus gnavus* was positively associated [76•]. In addition, increased Cer levels following allergen exposure in asthmatic patients have been linked to apoptosis, reactive oxygen species production, and neutrophil infiltration [77]. Furthermore, bacterial infection can worsen allergic inflammation. Although the exact mechanism of this phenomenon remains unclear, it has been described that LPS stimulates mast cells to produce pro-inflammatory (IL-6, TNF-α) and Th2-type (IL-5 and IL-13, IL-10) cytokines. It has been reported that administering Cer C8 (d18:1/8:0) reduces IL-5, IL-10, and IL-13 production in LPS-stimulated mast cells, while Fumonisin B1 (an inhibitor of de novo ceramide synthesis) increases their production. Interestingly, Cer C8 (d18:1/8:0) has opposing effects on cytokine production in LPS-stimulated macrophages, reducing IL-6 and TNF-alpha [78, 79]. On the other hand, Sph-1-P is antagonistic to Cer. Plasma levels of Sph-1-P are usually increased helping to maintain vascular endothelial integrity by promoting cell–cell interactions, whereas increased plasma levels of Cer lead to endothelial barrier dysfunction [72]. In contrast, FA has also been associated with decreased levels of plasma SLs. In a study conducted in peanut-allergic infants, a decrease in the genus *Bacteroides*, the sphingolipid metabolism and pyridoxine (vitamin B6) were observed in allergic infants compared to non-sensitized infants [80]. Decreased levels of SLs, including Sm and Cer, could point to a disruption of the process by which Cer are transformed into Sm [81], although it is still unclear how SLs interact with proteins, in particular with protein transporters. Interestingly, incubation of peripheral blood mononuclear cells with SLs has been shown to result in activation of invariant NKT cells, which can detect lipid ligands, thereby increasing Th2 cytokine production and facilitating IgE-mediated sensitization [81–83].

These contrasting effects of different SLs on endothelial integrity and immune response raise questions about the potential interplay between these SLs and the SLs produced by the family Sphingobacteriaceae (phylum Bacteroidetes) in their cell walls (sphingophospholipids and Cer, besides diacylglycerophospholipids), which are structurally similar to LPS. This family produces various metabolites, such as ribosomally synthesized and post-translationally modified peptides, terpenes, polyketides, non-ribosomal peptides, and carotenoids [84]. Furthermore, *Sphingobacterium* genus contains Cer and sphingophospholipids with isoheptadecasphinganine and 2-hydroxy or non-hydroxy isopentadecanoic acid. *S. faecale* is present in human faeces [85]. However, *S. multivorum* and *S. spiritivorum* are the most frequently found

species in clinical samples, primarily in blood and urine [86]. Indeed, it has been reported that Cer isolated from *S. spiritivorum* induced DNA cleavage in human myeloid leukaemia cells, indicating apoptosis. Cer with a 2-hydroxy fatty acid showed stronger apoptotic activity, suggesting the importance of Cer as intracellular messengers [87]. So far, no specific relationship between allergy and *Sphingobacterium* genus has been described, but there is evidence of a link between *Sphingobacterium* bacteria and inflammation and immunity. In this regard, *Sphingobacterium* genus has been positively associated with the incidence of clinical mastitis in bovines [88], and with colitis in the gut microbiota of mice [89]. In addition, a study in patients with bladder cancer showed a dysbiosis of the urinary microbiome with an enrichment of some bacterial genera (e.g. *Acinetobacter*, *Anaerococcus*, and *Sphingobacterium*) in the cancer group compared to non-cancer group [90]. Furthermore, another study in humans with urogenital schistosomiasis identified the genus *Sphingobacterium* as an immune-stimulatory taxa marker of the infection [91]. The association between the genus *Sphingobacterium* and parasitic infections is of great interest as parasitic infections are characterized by an IgE-mediated immune response, like most allergic diseases [92]. Finally, it has been reported a significant decrease of *Lactobacillus salivarius*, *Anaerobaculum hydrogeniformans*, *S. spiritivorum*, and *Pseudomonas fluorescens*, among others, in the plasma of rheumatoid arthritis patients compared with control subjects [93].

Overall, the metabolism of bacterial SLs and their role in allergic diseases remain a yet to be explored field. In this sense, the use of omics sciences could be useful to characterize and obtain a more complete picture of the implications of SLs in the prokaryotic cellular context [1]. Omics sciences are based on the use of high amounts of data and bioinformatic high-throughput techniques to study the phenotype of an organism, specific tissues or individual cells, and their main disciplines include genomics, epigenomics, transcriptomics, proteomics, and metabolomics [94–96]. These techniques study different steps of cell biology. Genomics is focused the study of genes and noncoding DNA (genome), which are transcribed into RNA (transcriptome), translated into proteins (proteome), and their end products are metabolites (metabolome) [94]. A good example of how the use of multidisciplinary approaches and multiomic analyses can help us to obtain a more complete map of the interaction between metabolites, such as SLs, and different diseases, including allergy, is a recently published study by Cui et al. [97••]. This research used animal models of FA to ovalbumin to demonstrate that treatment with the prebiotic strain *Bifidobacterium longum* alleviates the allergic phenotype of these mice by regulating sphingolipid metabolism at the transcriptomic, metagenomic, and metabolomic levels. Among these changes, it is interesting to note that the treatment induced a decrease in the levels of several sphingolipids, as well as the genus *Sphingobacterium*, with respect to the allergic group, confirming that there could indeed exist a link between microbial sphingolipid metabolism and the development of allergic diseases [97••].

Conclusions

This review underscores the role of SLs and the major bacteria involved in their metabolism in the development of food antigen sensitization and FA.

Gram-negative and Gram-positive bacteria, influenced by phospholipid structures and the incorporation of LPS in Gram-negatives, emerge as important factors in FA development. Notably, Gram-negative bacteria, especially within the Proteobacteria and Bacteroidetes phyla, are closely associated with FA, with a decrease of *Prevotellaceae* family being particularly noteworthy in IgE-dependent FA. In IgE-independent FA, the microbiome exhibits similar dynamics, with an increased prevalence of the *Enterobacteriaceae* family during symptomatic phases. Furthermore, breast milk microbiota composition influences infant FA development, with observed variations in mothers of allergic infants. Among Gram-positive bacteria, families such as *Bifidobacteriaceae* and *Clostridiaceae* within the Actinomycetota and Firmicutes phyla, respectively, are implicated in FA risk.

Furthermore, bacterial SLs, primarily synthesized by bacteria within the Bacteroidetes phylum, assume a pivotal role in immune responses and inflammation. The enzyme SPT serves as a linchpin in bacterial SL production, connecting prokaryotic and eukaryotic lipid biology. In the context of FA, SLs have a dual function: to exacerbate inflammation by increasing their levels in response to inflammatory triggers, particularly Cer; and to serve as signaling molecules in immune cell mobilization and inflammation. The potential interplay between eukaryotic SLs, and the sphingophospholipids and Cer found in the cell walls of SL-producing bacteria such as the *Sphingobacteriaceae* family, presents new research opportunities to understand their role in immunological responses. While no direct link between *Sphingobacterium* and allergies exists, its associations with inflammation and immunity warrant further exploration. These findings collectively illuminate the intricate relationship between bacterial components and FA, emphasizing the need for continued investigation into the microbiota's impact on allergic responses.

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Author contribution

The conceptualization of the paper was carried out by M.P-G. M.P-G, E.Z-V and A.M-C performed the literature search and drafted the review. E.Z-V. prepared Fig. 1 and A.M-C. prepared Fig. 2. All authors reviewed the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Conflict of Interest
E. Zubeldia-Varela declares that she has no conflict of interest. A. Macías-Camero declares that she has no conflict of interest. M. Pérez-Gordo declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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