Gut Sphingolipid Metabolites in Infants With Atopic Dermatitis Are Associated With Food Allergy

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Food allergy (FA) can affect 20%-80% of patients with atopic dermatitis (AD) [1,2]. Sensitization to food through the skin due to damage to the skin barrier can cause FA, and failure to acquire tolerance to food allergens in the gut can also lead to FA [3]. Gut metabolites can influence the physical gut barrier and intestinal homeostasis [4]. Therefore, it is possible that gut metabolites related to gut immunity play an important role in the development of FA. Sphingolipids are key factors in cell inflammatory response and affect gut epithelial cells and skin barrier integrity and function [5]. Sphingolipid levels have been shown to be lower in FA than in controls [6]; they have also been shown to be significantly higher in patients with FA than in controls [7]. Therefore, the issue of sphingolipid levels in FA remains unresolved. The lipid messenger gut diacylglycerol (DAG), a product of the metabolic reaction between ceramides and sphingomyelins, was increased in FA [8]. In asthma, one of the main signaling pathways associated with the activation of T lymphocytes involves the generation of DAG [9]. However, targeted metabolomics has not shown FA-associated gut sphingolipid in infants. In our previous study, we showed that when FA is present in various phenotypes of AD in early life, it might be associated with subsequent development of asthma [10]. The discovery of a biomarker that can distinguish the phenotypes of AD and FA from other AD phenotypes is therefore expedient. Consequently, we used targeted metabolomics to investigate whether FA in infants with AD is associated with gut sphingolipid metabolites.

The study population consisted of 158 six-month-old infants (46 healthy infants, 30 with AD only, and 82 with combined AD and FA) from the Cohort for Childhood Origin of Asthma and Allergic Diseases (COCOA) [11], which

was a general population–based birth cohort. The baseline characteristics of the participants are presented in Table S1. Detailed methods are provided in this article's Online Supplement.

DAG, ceramide, and sphingomyelin values were higher in the AD with FA group than in the controls and AD only group (Figures S1A-C). Sphingosine values were higher in the AD with FA group than in the AD only group (Figure S1D), whereas sphingosine-1-phosphate (S1P) levels were lower in the AD with FA group than in the controls (Figure S1E). There were no significant differences in sphinganine between the 3 groups (Figure S1F). DAG and sphingomyelin values were positively correlated with total IgE and specific IgE to food allergens (Figure S2). S1P was weakly and negatively correlated with specific IgE to milk (Figure S2C).

This study showed that gut sphingolipid metabolites can distinguish cases with FA among various AD phenotypes. The metabolites were associated with total and specific IgE levels to food allergens. Our results suggest that the difference in the composition of gut sphingolipid metabolites is associated with FA and food sensitization in infants with FA and AD. Sphingomyelin, ceramide, and sphingosine can be phosphorylated to S1P. The increase observed in sphingomyelin, ceramide, and sphingosine and the decrease in S1P in infants with AD and FA suggest that the sphingolipid mechanism finds it difficult to synthesize S1P. Milk-derived sphingomyelin promotes an iNKT cell–mediated TH2-type cytokine that boosts sensitization to food allergens [12]. Sphingomyelin and ceramide values have been shown to be significantly increased in patients with inflammatory bowel disease and in an animal colitis model [13]. Accumulated ceramide in tight junctions alters lipid composition, contributing to a disturbed barrier function. Moreover, in the colitis model and IL-10 knockout mice, sphingomyelin triggers apoptosis in intestinal epithelial cells and aggravates intestinal inflammation [13]. Therefore, in AD, changes in gut sphingolipids lead to the development of FA as a result of gut barrier damage and inflammation.

In our study, gut sphingolipid levels in the AD only group tended to decrease more than those of controls (Figure S1). In a previous study, a sphingolipid module comprising several metabolites involved in de novo sphingolipid metabolism was significantly more elevated in participants with food sensitization than in those with FA [8]. The major difference was that the changes in the sphingolipid module for feces were observed based on untargeted metabolomic profiling without considering AD [8], whereas, in the present study, single sphingolipid metabolite analysis was conducted through targeted metabolomics according to the AD phenotype.

In this study, of the many sphingolipids assessed, 15 were chosen because they contain major fatty acids and are commercially available. Over time, more sphingolipids have become commercially available. However, regrettably, these newly available sphingolipids were not included in the present study. Not all gut sphingolipids, including ceramides, DAG, and sphingomyelin, could be measured in this study. However, in most of the gut sphingolipids measured, differences were only observed between the AD only and AD with FA groups. Further studies are needed to evaluate other sphingolipids such as ceramide-1-phosphate, lactosylceramide, hexosylceramide, and dihydroceramide.

Studies on sphingolipid metabolites in FA and AD to date have been limited to serum and skin samples with untargeted metabolite profiling. To our knowledge, this is the first study to explore gut sphingolipid metabolite profiles using targeted metabolomics in AD according to the presence of FA.

Restricted diets in children with FA might eventually affect metabolic profiling. The alteration of gut sphingolipids may be the result of dietary restrictions to suppress FA symptoms. Therefore, it is unclear in this study whether this result is the cause of FA or a secondary phenomenon caused by a restricted diet in patients with FA. However, since milk and eggs are sphingolipid-rich foods, sphingolipids tended to increase in patients with milk or egg allergy, probably owing to a mechanism other than the effect of dietary restrictions. Further research related to dietary restrictions is needed in this regard. In conclusion, our results indicate that gut sphingolipid metabolites may play a role in the development of FA in infants with AD.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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