Caroline Hemphill
06/09/2022
Writ 109ST

Systematic Literature Review: The Makeup of the Gut Microbiome and Food Allergy

Introduction

In recent decades, the prevalence of food allergies has been significantly increasing (Nwaru). Some treatments, like oral tolerance, have been developed, but many still struggle with serious food allergies past childhood. The immunological mechanism of allergy is fairly well-understood. It is a misactivation of an immune response. When a person has food allergies, they have IgE antibodies that recognize antigens from foods that are foreign, but are not harmful. This then leads to inflammation, a standard part of any immune response (Haahtela). In allergic disease, however, this can lead to anaphylaxis and asphyxiation, and can be life-threatening. Even if not life-threatening, inflammation resulting from allergy is often serious and requires medical intervention.

Despite being increasingly common (Haahtela), the reason for food allergy development is still not well-understood. The rise in allergic disease seems tied to lifestyle changes, based on the fact that genetically similar populations who live in different places have different rates of allergy (Haahtela).

This has lead scientists toward the biodiversity theory of allergy, stating that a lack of species diversity in microbes leads to a high risk of inflammatory disease, including asthma and allergy (Haahtela). Another theory that ties in well with this one is the hygiene hypothesis. The hygiene hypothesis states that the lack of exposure to a diversity of microbes in early life can cause food allergies (Frei). This would be a partial explanation for where the decreased biodiversity that causes inflammatory disease comes from.

One reason the microbiome's biodiversity is being studied is because the microbiome, in both the gut and the rest of the body, has also been shown to be of immunological importance (Frei). If allergies may be caused by lack of exposure to microbes, and the biodiversity of the microbes living in the body has been shown to be related to immunity, there is a logical next step. This is to ask whether the makeup of one's own native gut microbiome could cause, or be tied to, food allergies (Haahtela).

The association between gut microbiome biodiversity and food allergy is, indeed, being studied. Some propose that the link between the two could be a big missing piece in how we understand and treat allergy. If biodiversity of the gut microbiome, or the species makeup, is related to food

allergy, this finding could go hand in hand with the hygiene and biodiversity hypotheses (Haahtela).

Additionally, learning about the link between the gut microbiome and food allergies could lead to more effective therapies. As of now, the most prominent treatment to allergy is exposure to the allergen. It is possible that exposure to particular microbes, or to a diversity of microbes, would help mitigate allergies or decrease their severity. This would be a promising and less dangerous treatment. It could also help in the creation of preventative treatments to intervene before food allergies can develop.

This systematic literature review sets out to discover the state of research on the relationship between the makeup of the gut microbiome and the presence of food allergies, as well as potential applications of that research.

Methodology

This study was conducted by establishing research questions, defining keywords, and establishing inclusion and exclusion criteria. Before any of this was done, the state of the literature was scanned to see what types of research were being conducted. Two main types of studies stood out. The first assessed whether the diversity of the gut microbiome affected food allergies. The second was whether the presence of any particular species in the gut microbiome affected allergies, or the type of allergy. Both types of studies were read and included in this review to give a more complete overview of the state of the research.

Based on preliminary research, the following three research questions were established.

RQ1: Does the diversity of the gut microbiome affect the presence or absence of food allergies?
RQ2: Does the makeup of species in the gut microbiome affect specific types of food allergies?
RQ3: Does the presence or absence of specific species in the gut microbiome cause or contribute to food allergies?

Based on these questions, inclusion and exclusion criteria were established. Some exclusion criteria were arbitrary, to reduce the volume of papers that needed to be sorted through in the time given.

Papers were included if

- They were published in the journal *Allergy*
- They discussed the link specifically between the biodiversity of the gut microbiome and food allergy

Papers were excluded if

- They addressed other diseases, such as asthma
- They were not published in the journal *Allergy*
- They were literature reviews
- They were published before 2017

The study was contained to the journal *Allergy* because it is a premiere journal in the field, as well as for limiting the amount of applicable studies due to time constraints.

Based on all of these criteria, search terms were used to optimize the variety of data found. Search terms included "gut microbiome and food allergy," "gut microbiome diversity and food allergy," and "gut microbiome and hygiene hypothesis." These search terms allowed for selection of relevant and timely papers.

Results

1. **Short Chain Fatty Acids**

The first category of studies focused on the correlation between metabolites that are produced by the gut microbiome and allergy. They sought to either see if allergic children had enriched or were lacking in these metabolites, or to see if administration of metabolites could help reduce allergic symptoms.

The first article in this category is by Roduit, et al. The study found that children with high levels of butyrate and propionate, two common short chain fatty acids, in their guts had less atopic sensitization. Atopic sensitization is similar to food allergy, but less severe, and can be a precursor to fully-developed allergy. This study aimed to look into whether children with and without allergies had different levels of short chain fatty acids in stool samples. The rationale behind this is that in the past, studies had been done to see if any foods decreased the likelihood of developing asthma or atopic dermatitis, diseases similar to allergy. It was found that foods containing a large amount of short chain fatty acids (SCFAs) did decrease the likelihood of developing these diseases. They have also, according to the article, been shown to have anti-inflammatory properties. The researchers also treated mice orally with SCFAs. They found that this treatment reduced severity of allergic reactions in mice. The study concludes by suggesting that oral administration of SCFAs could be an effective treatment in children with allergies, whose gut microbiomes may not be producing sufficient amounts of SCFAs like butyrate.

The next article in this category is by Yamagishi et al. This study found that children with egg allergies had fewer butyric acid-producing bacteria (BAPB) in their guts, as well as fewer circulating regulatory T cells (Tregs). Namely, children with allergies had higher Enterobacteriales and lower Lactobacillales. This study is similar to the first in that it also focuses on the effect of short chain fatty acids on food allergies, but has a different ratoinale.

While Roduit claimed that SCFAs have anti-inflammatory properties, Yamagishi claims that butyric acid induces the maturation of Tregs. Tregs are immune cells that are believed to suppress allergic disease and other excessive immune response. Thus, presence of Tregs could correlate with reduced allergies. This paper also takes a different approach than the first, in that it looks at microbial species in the gut microbiome that produce SCFAs, rather than looking for SCFAs themselves. This gives an idea of one of the ways the metabolic pathways of gut microbes could contribute to the presence or severity of allergy.

The final article in this category is by Paparo, et al. The study found that treatment with butyrate reduced allergic response in animal models. Butyrate also promoted precursors of several types of immune cells, including Tregs (along with M2 macrophages and dendritic cells). The article took a similar approach to Roduit. Working off of the knowledge that the gut microbiota produce butyrate, and that butyrate can assist in gut barrier integrity, they assessed whether butyrate could be a protective factor against food allergy. They specifically looked at butyrate levels in human milk (HM) to see if HM could be an effective protective factor. This study is relevant because it is showing that butyrate can protect against allergy. This suggests that the gut microbiome's lack of ability to produce butyrate could be a factor in allergy development.

All three of these studies found that there seems to be an inverse relationship between presences of SCFAs and presence of allergies. Two of the studies have found that treatment with SCFAs can reduce severity of allergies, which is a promising therapy.

2. **Gut Microbiome Diversity and Species Makeup**

The second category of studies looks more closely at the makeup of the gut microbiome. These studies analyzed differences in gut microbiota populations between children with and without allergies, or between children in populations with different frequencies of allergy.

The first study in this category is by Fazlollahi et al. Interestingly, it was found that children with egg allergies had increased diversity in their gut microbiome compared to non-allergic children. Bacteria from the genera *Ruminococcus, Lactococcus,* and *Leuconostoc* were more abundant in children with egg allergies. Additionally, it was found that subjects with the egg allergy had decreased metabolism of purine, a compound found in some foods. It was predicted that this was the functional pathway that was common between the bacterial groups that were associated with allergy. The authors acknowledge that the finding that increased diversity is associated with allergy seems counter-intuitive. They suggest that overall diversity is not what needs to be studied, but prominence of individual taxa and interactions between them, as well as more specific metabolic effects. This study analyzed fecal samples and profiled them by 16S rRNA sequencing, which allows for identification of species in a sample.

Another study in this category is by Savage et al. It found that some genera bacteria were less abundant in children with food sensitization. These were *Haemophilus, Dialister, Dorea, and Clostridium.* Genera less abundant in children with food allergies were *Citrobacter, Oscillospira, Lactococcus,* and, again, *Dorea.* Like the Fazlollahi study, this study used 16S sequencing to analyze the makeup of species in the microbiomes of subjects. Unlike Fazlollahi, however, this study found overall gut microbiome diversity to be similar between children with and without allergy. This was counter to what the authors expected, as an inverse association between diversity and risk of disease has previously been seen.

The third study in this category is by Sjodin et al.It found that children with allergies showed underrepresentation of *Ruminococcus, Bacteroides, Prevotella,* and *Coprococcus* compared to children without allergies. In allergic 8-year-olds, *Bifidobacterium* was enriched and *Lactobacillus, Enterococcus,* and *Lachnospira* were depleted. The study suggests that therapeutic treatment involving expanding gut microbiome taxa diversity could be a successful strategy. In this study stool samples from children were analyzed for their gut microbiota population by 16S rRNA sequencing, as in the Fazlollahi and Savage studies. Like the previous two studies, it was found that some specific genera of bacteria were enriched or depleted in subjects with allergies compared to those without.

The final paper in this category is by Seppo et al. This study found that in Old Order Mennonites (OOM), subjects' stool was enriched with *Bifidobacteriaceae*, *Clostridiaceae*, and *Aerococcaceae* compared to control infants from Rochester, NY. Additionally, stool with *B. infantis* had higher levels of lactate and medium/long chain Fatty Acids. This connection with the first category of studies is of note. Additionally, allergic/atopic diseases were about five times more common in Rochester infants than OOM infants. Like the Savage study, it was found that the two populations had similar levels of diversity in the gut microbiome. The rationale for studying OOM is that OOM infants have a "traditional farming lifestyle" and are likely exposed to more microbes from livestock and plants than infants in Rochester. This is, thus, a sort of offshoot of the "hygiene hypothesis" of allergy. The study analyzed both infant stool samples and human milk samples, again by 16S rRNA sequencing.

Discussion

In all three studies from Category 1, as well as the Seppo study, the presence of BAPB or SCFAs seems to indicate lower likelihood of allergy. It is interesting that this metabolite in particular has been found to be of such large importance, and surprising that this is not a more well-understood phenomenon. While researching relevant studies, no reviews were found specifically on BAPB and their relation to allergy. Two papers from this review also found that oral administration of fatty acids helped in decreasing severity of allergic reactions. Undoubtedly, this is a therapeutic

option that could prove incredibly beneficial. These findings imply one way that the makeup of the gut microbiome could be contributing to the development or severity of food allergies.

While there was not much consensus among the second category on which groups of bacteria are most linked to allergies, all seemed to agree that specific species makeup is far more important than overall biodiversity of the gut microbiome. In fact, it seems that biodiversity of the gut microbiome matters very little. Given this and the results from category one, it would be worthwhile to follow up on the results and see which genera that were found to be depleted or enriched in the subjects are fatty acid producing. Most of these papers had the goal of simply establishing whether there are bacterial families/genera differentially enriched in subjects with allergies, and determined that there are. The clear next step is to look for similarities between these species. The metabolic pathways that each of the bacteria take part in could be analyzed going forward, as well, to see if any other pathways can be linked to the presence of food allergy.

These studies largely showed that on the count of biodiversity, the hygiene hypothesis seems incorrect. Overall diversity does not seem to differ between subjects with and without allergies, but that does not mean the theory is all wrong. The Seppo study found that Old Order Mennonite communities had lower prevalence of food allergy. Seppo notes that theirs is not the only study that has found that communities with more “traditional” or less “westernized” lifestyles have lower frequency of allergy. The most notable difference between these communities and those with higher prevalence of allergy is the amount of time spent outdoors, in contact with animals and nature. It is very difficult to study whether this is the primary cause of allergy, but the correlation exists, and warrants further investigation.

Overall, these findings show that awareness of the link between the gut microbiome and food allergy is growing. It seems clear that there are differences between allergic and non-allergic subjects, but exactly what those differences are and why they matter is not determined. Looking into the metabolic pathways of differentially enriched bacterial families would be a good first step into determining how the gut microbiome affects allergy.

Bibliography

Fazlollahi, M. et al. (2018). Early-life gut microbiome and egg allergy. *Allergy, 73(7), 1515-1524*. doi: https://doi.org/10.1111/all.13389

Frei, R. et al. (2012). Microbiota and dietary interactions- an update to the hygiene hypothesis? *Allergy, 67(4), 451-461*. doi: https://doi.org/10.1111/all/j.1398-995.2011.02783.x

Haahtela, T. (2019). A biodiversity hypothesis. *Allergy, 74(8), 1445-1456.* doi: https://doi.org/10.1111/all.13763

Nwaru, BI et al. (2014). Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy, 69(8), 992-1007.* doi: https://doi.org/10.1111/all.12423

Paparo, L. et al. (2020.) Butyrate as bioactive human milk protective component against food allergy. *Allergy, 76(5), 1398-1415.* doi: https://doi.org/10.1111/all.14.625

Savage, Jessica H. et al. (2017). A prospective microbiome-wide association study of food sensitization and food allergy in early childhood. *Allergy, 73(1), 145-152.* doi: https://doi.org/10.1111/all.13232

Seppo, AE. et al. (2021). Infant gut microbiome is enriched with Bifidobacterium longum ssp. Infantis in Old Order Mennonites with traditional farming lifestyle. *Allergy, 76(11), 3489-3503.* doi: https://doi.org/10.1111/all.14877

Sjodin, KS et al. (2019). Temporal and long-term gut microbiota variation in allergic disease: A prospective study from infancy to school age. *Allergy, 74(1), 176-185.* doi: https://doi.org/10.1111/all.13485

Roduit, C. et al. (2019). High levels of butyrate and propionate in early life are associated with protection against atopy. *Allergy, 74(4), 799-809.* Doi: https://doi.org/10.1111/all.13660

Yamagishi, M. et al. (2021). Decreased butyric acid-producing bacteria in gut microbiota of children with egg allergy. *Allergy, 76(7), 2279-2282.* doi: https://doi.org/10.1111/all.14795