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Commentary

The increase in food allergy prevalence in recent years suggests that environmental factors, such as diet and intestinal microbiota, play contributory roles. In this issue of the *JCI*, Bao et al. compared twins that differed with respect to food allergies. The researchers analyzed sequences from microbe ribosomal RNA and profiled microbe metabolites, identifying health-associated microbes at the species level. In addition to revealing microbes from the Clostridia class enriched in healthy twins, the authors identified two commensal species (*Phascolarctobacterium faecium* and *Ruminococcus bromii*) related to the healthy fecal metabolome. This study advances the goal for next-generation probiotic therapies that effectively treat or prevent food allergy.

Dysbiosis in food allergy and implications for microbial therapeutics

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The increase in food allergy prevalence in recent years suggests that environmental factors, such as diet and intestinal microbiota, play contributory roles. In this issue of the *JCI*, Bao et al. compared twins that differed with respect to food allergies. The researchers analyzed sequences from microbe ribosomal RNA and profiled microbe metabolites, identifying health-associated microbes at the species level. In addition to revealing microbes from the Clostridia class enriched in healthy twins, the authors identified two commensal species (*Phascolarctobacterium faecium* and *Ruminococcus bromii*) related to the healthy fecal metabolome. This study advances the goal for next-generation probiotic therapies that effectively treat or prevent food allergy.

Development of food allergy

The prevalence of food allergies rose quickly at the end of the 20th century. Tree nut allergy in the United States increased from 0.2% to 1.1% between the years of 1997 and 2008, and peanut allergy increased from 0.4% to 1.4% in the same time period (1). This remarkable increase in the number of people with allergies is the focus of intense scrutiny, as such a rapid increase suggests the influence of an important environmental factor, such as diet. Until 2008, the American Academy of Pediatrics recommended delaying the introduction of allergenic foods into the infant diet in those with a family history of allergic disease. Due to poorly supporting clinical data, the recommendations for avoidance were removed in 2008. In 2015, the LEAP study found that dietary exposure to peanut beginning between 5 and 11 months of age profoundly suppressed the development of peanut allergy (2). Infant feeding guidelines were subsequently modified to encourage early introduction of peanut into the diet (3).

In addition to diet, other important parameters associate with elevated or reduced risk for development of food allergy. Interestingly, exposure to a dog in the home in the first year of life consistently associates with protection from food allergy (4) and other allergic diseases (5). Mechanistic studies of the relationship between early life dog exposure and reduced asthma risk link protection to changes in the intestinal microbiota (6). Several studies have demonstrated that individuals with established food allergy have dysbiosis (7–12), while other studies have identified infant dysbiosis preceding the development of food allergy (13, 14). A recent study associated maternal *Prevotella* colonization with protection from food allergy in offspring, independent of infant *Prevotella* colonization (15). Dysbiosis in established disease may be due to intestinal inflammation or changes in diet (i.e., a consequence of disease rather than a causative factor), while dysbiosis preceding disease is consistent with, but not proof of, a contributing role in pathogenesis. While many studies identify dysbiosis in food allergy, the specific microbial populations altered in food allergy lack clear consistency between studies. Factors such as age, diet, genetic background, and environmental exposure influence the microbiota and make it difficult to delineate patterns associated with disease between distinct and relatively small cohorts.

The most common technique to survey microbial communities relies on ribosomal gene (16S rRNA) analysis. 16S rRNA sequencing is typically limited to taxonomic classification at the family or genus level because only short 16S rRNA gene regions are sequenced. Furthermore, the overlapping effect of different organisms on host immunity (for example, the ability of different strains to generate immunomodulatory metabolites, such as short-chain fatty acids) make it difficult to identify functional differences in the microbiota using low-resolution genetic tools.

Twins discordant for food allergy

In this issue of the *JCI*, Bao et al. (16) use a powerful twin study design to examine how fecal microbiota and metabolites differ between twins discordant for food allergy. Twins share their early life environment, which is a critical window for developing microbiota, the immune system, and food allergies. Moreover, the shared genetic background of monozygotic twins eliminates many confounding factors from the study of disease-associated differences in microbiota. The researchers analyzed 18 twin pairs ranging in age from 0.5 to 58 years, including 13 disease-discordant twin pairs and 5 twin pairs who were both affected with food allergy. They analyzed 16S rRNA amplicon sequences between twin pairs and identified 64 differentially operational taxonomic units (OTUs), 62 more abundant in healthy twins and 2 more abundant in allergic twins. Most healthy-abundant OTUs were in the Clostridia class and were annotated as *Lachnospiraceae* and *Ruminococcaceae*. Interestingly, *Lachnospiraceae* associates with protection

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from milk allergy in mice colonized with healthy human microbiota (17).

Bao and colleagues also performed fecal metabolomics and identified 97 metabolites that were differentially abundant between healthy and allergic twins (16). Although short-chain fatty acids are microbial-derived metabolites that may promote tolerance, no differences were observed between the groups. In contrast, the diacylglycerol pathway was notably enriched in healthy twins. The investigators then analyzed the correlation between differentially abundant OTUs and differentially abundant metabolites. They matched two of the metabolome-correlating OTUs to the species level, *Phascolarctobacterium faecium* and *Ruminococcus bromii*, and showed an increased abundance in healthy twins. *P. faecium* was highly correlated with diacylglycerol metabolites, while *R. bromii*, which is known to play a role in starch digestion, was associated with metabolites involved in fatty acid, amino acid, and sterol metabolism. This study uses a unique twin design and strategically combines genetic and metabolomic analysis to identify microbes and their products associated with food allergy (16).

The functional consequence of food allergy–associated dysbiosis

The key next step will be to determine the functional consequences of colonization with organisms identified by Bao et al. (16) Previous studies have determined the functional consequence of food allergy–associated dysbiosis by transferring human microbiota into germ-free or antibiotic-treated mice (12, 17). When researchers transferred microbiota from healthy donors, but not allergic donors, food allergy was prevented (12, 17). Notably, healthy microbiota averted food allergy by improving intestinal barrier function (17, 18) and expanding RORγt$^+$- and Foxp3$^+$-expressing Tregs (12). Similar to Bao et al. (16), previous studies, which administered bacteria from healthy donors as an oral inoculation, also identified protective species within the Clostridia class (12, 16). Other studies have focused on the functional consequence of metabolic changes. Dysbiosis in infants with a high risk for multisensitized allergic disease was associated with elevated levels of 12,13-diHOME, a lipid fatty acid capable of driving Th2 sensitization in human immune cells in vitro (19). Furthermore, administering this lipid metabolite to mice could exacerbate experimental asthma by suppressing Tregs (20).

Clinical implications

The demonstration that microbes determine susceptibility to food allergy in experimental systems has led to a great deal of excitement about the possibility of microbial-based therapeutics. Fecal microbial transplants, involving the transplant of stool-derived microbiota from a healthy individual to an allergic recipient, are currently underway (ClinicalTrials.gov NCT02960074). However, such approaches are crude and carry risk (21). The administration of the probiotic *Lactobacillus rhamnosus* together with peanut oral immunotherapy (OIT) protected subjects from (22) peanut allergy, and another clinical trial is examining whether the combination of peanut OIT plus *L. rhamnosus* is more effective than OIT alone (ACTRN12616000322437). A clinical trial of a selected consortium (VE416) of human commensal clonal strains that suppress allergic disease is currently underway for the treatment of peanut allergy (ClinicalTrials.gov NCT03936998). However, the promise brought by human dysbiosis research is held in the identity of protective microbes or their metabolites. Rational selection of a human commensal-based therapeutic that has the capacity to colonize the human gastrointestinal tract could effectively prevent food allergy. For clinicians to move from studying human dysbiosis to providing therapy, it is necessary to identify protective organisms, ideally at the strain level; to identify metabolites associated with tolerance; and to demonstrate the corresponding regulatory functions in appropriate model systems. There is also a question of whether there is a critical window of opportunity for microbes to regulate IgE in early life, as has been suggested by mouse studies (23). Bao et al. (16) demonstrated that subjects with established food allergy also had dysbiosis; however, it is unclear if normalizing the microbiota would suppress entrenched Th2 and IgE responses. In addition, it is unknown whether treatments with commensal organisms would require cotreatment with the allergen itself in order to reestablish antigen-specific oral tolerance. Further, maintaining healthy microbiota in an allergic host may require additional factors, such as a specialized diet.

In summary, human food allergy associates with dysbiosis, which has consequences for the development of tolerance or allergy, as shown experimentally in mouse models. With the latest addition to the field by Bao et al. (16), two additional human commensal species (*P. faecium* and *R. bromii*) relate to the healthy fecal metabolome, bringing us a step closer to treating food allergies with next-generation probiotics.

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