Dysfunctional microbiota with reduced capacity to produce butyrate as a basis for allergic diseases

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The basis of the allergy epidemic in Western countries remains unclear. A few decades ago, there were only rare cases of children with food allergy at school. Nowadays, allergies to, for example, peanut, shellfish, and dairy affect approximately 8% of schoolchildren in Australia, the United Kingdom, or the United States.

Food allergy is perhaps the most striking example of an inflammatory condition associating with Western lifestyle. The prevailing hypothesis for this has been the hygiene hypothesis.[1] This hypothesis stemmed from the observation that birth order affects allergy and asthma, and Strachan[1] suggested that exposure of children to a less hygienic environment through older sibling interactions provided them with appropriate immune exposures and protection. Recent evidence has shown that Amish children living in traditional farming environments had more than 6 times the exposure to endotoxin than those in industrial farming environments, with 4 to 6 times less allergic sensitization.[2]

A follow-on hypothesis stated that immune alteration linked to disturbances in the gut microbiota composition (dysbiosis) was the basis for allergy by disrupting immune tolerance.[3] Prodysbiotic influences, such as decreased exposure to environmental microorganisms because of excess sanitation, urbanization, and modern farming methods, as well as excessive antibiotic use, would skew immune responses toward T_H2 and thus contribute to allergy development.[2,4]

Considering recent findings on the important influence of the gut microbiota for allergy/asthma development, the hygiene hypothesis might not be sufficient to fully explain the burden of allergic disease. Controlled animal studies using prebiotic (beneficial foodstuff) interventions, which reshape the gut microbiota, have demonstrated that a healthy gut microbiota shaped by dietary fiber protects against food allergy or asthma.[5,6] Epidemiologic studies also suggest that healthy (Mediterranean) diets were protective, whereas processed and low-fiber diets (Western diet) were detrimental.[7]

In the current issue of the *Journal*, Cait et al[8] use an interesting approach to demonstrate the connection between dietary fiber, the most potent prebiotic, and protection from allergies. Using shotgun sequencing, they analyzed the fecal microbiomes of 105 children from the Canadian Healthy Infant Longitudinal Development cohort study. Based on their allergic sensitization results, as assessed by using skin prick tests at 1 and 3 years of age, as well as asthma development at age 3 years, the children were classified as atopic (if positive for all these features) or as control subjects. The authors used a battery of allergens to test for atopy-like antigens derived from cockroach, peanut, soybean, egg white, and cow's milk at 3 months, and they added cat and dog allergens, *Penicillium* species, *Aspergillus* species, and various pollens at 1 year. The gut microbiota of these children were analyzed at 3 months and 1 year of age. Interestingly, there was no change in overall gut microbiota diversity in children who went on to have atopy versus control children in both age groups. However, there were significant differences at the species level, with some bacteria being preferentially depleted in 3-month-old children who later had atopy. Cait et al[8] identified that 40% of the bacteria depleted were known for their capacity to ferment complex carbohydrates. Human milk oligosaccharides are the primary source of resistant carbohydrates during breast-feeding, whereas plant cell-wall carbohydrates from solid foods are the primary source later in life.

Importantly, thanks to their metagenomic approach, the authors looked at the gut microbiome from a functional point of view and found that genes encoding for enzymes that break down complex carbohydrates (CAZymes) were totally depleted in these children who would go on to have atopy. These CAZymes break down resistant starch into monosaccharides and disaccharides, which are then cross-fed to short-chain fatty acid (SCFA)–producing fermentative bacteria. One such SCFA is butyrate, which we identified as critical for protection against food allergy in a mouse model.[6] Butyrate is also well known for its effects in boosting anti-inflammatory regulatory T (Treg) cell numbers and functionality, as well as epithelial integrity (which might aid in prevention of sensitization).[9] The work of Cait et al[8] suggests that the microbiomes of children who became atopic were dysfunctional at early stages before atopy development. This result emphasizes that a focus on gut microbiota composition can be misleading, and the gut microbiota might seem unaffected by a given condition while its function is in fact impaired.

Another very interesting finding of this study is that atopy can be linked to the potential inability of the gut microbiota to adapt to novel nutritional environments. During the first 6 months of life,

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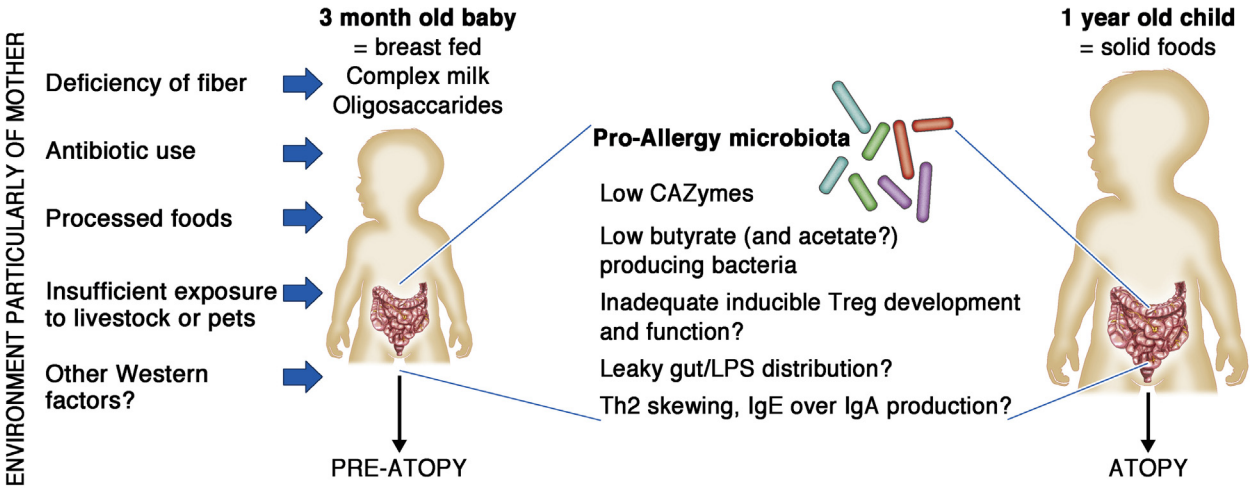

FIG 1. A new link between butyrate production, CAZymes, and atopic disease. A proallergy microbiota with reduced CAZyme levels and poor ability to produce butyrate associates with atopy. Babies (as young as 3 months of age) can contain a gut microbiota that is low in CAZyme levels and inefficient at producing butyrate (and possibly acetate and propionate). The microbiota of a 1-year-old child might also show the same features. These gut microbiota properties associate with atopy later in life. The 3-month-old baby relies on the gut microbiota and CAZymes to digest complex milk oligosaccharides from breast-feeding, whereas the 1-year-old child is usually receiving solid foods and requires other CAZymes to digest fiber from an omnivore diet. The reason the 3-month-old baby or the 1-year-old contain a proallergy microbiota is uncertain, but presumably, these subjects acquire this from their environment, including their mother, during the birthing process. Features that have been suggested are listed on the *left*. Low butyrate production by the gut microbiota could lead to poor Treg cell numbers or function, a leaky gut that would aid in antigen sensitization, or IgE over IgA production.[6] Butyrate is also anti-inflammatory through its effects on histone deacetylase inhibition.

the infant is mostly exposed to human breast milk, and as mentioned above, at 3 months of age, the microbiomes of children who will go on to have atopy are lacking the CAZymes necessary to break down complex milk oligosaccharides. At age 1 year, the baby has been exposed for 6 months to more complex types of food, with dietary fiber originating mostly from plant-based products. Cait et al[8] did a second analysis for genes encoding CAZymes with activity against resistant starch in the omnivore human diet. In the 1-year-old microbiome they found that the total number of CAZyme genes in families that degrade plant cell-wall, animal, and fungal carbohydrates were depleted in children who became atopic relative to control subjects. Thus the microbiome of children who became atopic had less capacity to degrade the resistant starch in their diet also at 1 year. Thus it is striking that children with atopy have, from early stages of life, a dysfunctional microbiome with a poor ability to efficiently degrade complex carbohydrates derived either from milk or food. This finding is aligned with prior suggestions that poor fiber-fermenting gut microbes might be a basis for disease development. How the gut microbiota becomes dysfunctional is unknown but likely relates to insufficient intake of fiber, antibiotic use, or other unknown Western lifestyle factors (Fig 1).[6] This might relate to both the mother's diet and the child's diet. The baby may inherit from the mother a dysfunctional microbiota during the birthing process.

Although not covered in the study by Cait et al,[8] it is worth considering mechanisms by which fiber breakdown and SCFA (eg, butyrate) production contribute to protection from allergy/asthma. A key immune subset responsible for immune tolerance are Treg cells. Several important articles showed that fiber/SCFAs promoted Treg cell numbers and function both in the gut[9] and in peripheral tissues. For asthma, Treg cells are an important cell type that has been implicated in disease pathogenesis as has epithelial integrity, which might limit sensitization to food antigens. Epithelial integrity is affected by metabolites, such as butyrate. A molecular mechanism by which SCFAs, such as butyrate, modulate the immune system is through binding to specific G protein–coupled receptors, such as GPR43, GPR41, and GPR109a. Butyrate and acetate were behind the beneficial effects of high fiber in a food allergy model in mice through their binding of GPR43 and GPR109a.[6] Propionate and GPR41 are protective in mice with asthma-like allergic airway inflammation.[10] SCFAs might also promote Treg cells through epigenetic changes caused by inhibition of histone deacetylases, with acetate protecting from asthma-like inflammatory diseases in mice through increases in Treg cell numbers caused by histone deacetylase 9.[5] SCFAs promote Treg cells either directly by promoting peripheral Treg cell development from naive T cells or indirectly through effects on $CD103^+$ dendritic cells (the master regulators of mucosal tolerance).[6]

A summary of all the cellular and molecular mechanisms that might be leading to allergy/asthma is presented in Fig 1. Interestingly, these same mechanisms might be equally relevant for many other Western diseases, including diabetes, and even fatty liver, cardiovascular disease, and Alzheimer disease.

What might be the potential intervention strategies to rescue the microbiome at early stages to prevent atopy? Dietary intervention with prebiotics (beneficial foodstuffs, such as fiber) might be insufficient because the enzymatic machinery in the

microbiome to digest them could be missing. Administration of probiotics containing the missing enzymes (eg, CAZymes) might be the safest and most effective option if the treated child can be colonized by these bacteria effectively. The efficacy of colonization with probiotics is highly variable in adults but in early life is largely unknown. There could be safety concerns in treating babies or infants with probiotics or prebiotics, and these need to be addressed in this promising yet emerging new field. Cait et al[8] also suggest that "early life metabolite therapy may be an effective strategy to prevent the development of atopy," which might mean butyrate itself or high butyrate-releasing diets or milk plus CAZyme–containing probiotics.

The long road to understanding allergies and asthma might be inching toward clarity. SCFAs, such as butyrate, which are derived from a healthy diet, look to be very important. Acetate and propionate will likely play a role as well. A diet/SCFA explanation for food and other allergies fits with human epidemiology, animal model data, and new knowledge on how SCFAs inhibit inflammation and promote Treg cell function and gut epithelial integrity. It is time we placed less emphasis on hygiene and incorporated the complexity of nutrition and the microbiome into the possible causes of allergies and asthma.

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