Microbiome and food allergy

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Food allergy is a common disease affecting approximately 8% of children and 5% of adults. The prevalence has increased over the last two decades, suggesting an important environmental contribution to susceptibility. Studies have identified mode of birth, pet exposure, and having older siblings as being significant risk modifying factors in the development of food allergy. With the discovery that these factors significantly impact the composition of the intestinal microbiome, which is known to play a critical role in shaping the immune system, recent studies have begun to address the role of the intestinal microbiota in the development of food allergy. Studies in human cohorts support a dysbiosis in food allergy, and limited data suggest that this dysbiosis occurs early in life, preceding the onset of sensitization. Studies from animal models have clearly shown that the composition of the intestinal microbiota confers susceptibility to food allergy, and that there are organisms such as Clostridia species that are protective in the development of food allergy. Our understanding of microbial regulation of food allergy is in its nascency, but the state of the field supports an important contribution of intestinal microbes to susceptibility. Challenges going forward are to identify commensal-derived microorganisms that could be used therapeutically to prevent or perhaps treat food allergy. (Translational Research 2017;179:199–203)

Abbreviations: IgE = immunoglobulin E; IgG = immunoglobilin G; SCFAs = short-chain fatty acids; TLR = toll-like receptor; OVA = ovalbumin; Tregs = regulatory T cells; IL-4 = interleukin-4; IL-22 = interleukin-22

INTRODUCTION

Food allergy is an adverse reaction to food which can be mediated by IgE or other immune mechanisms. IgE-mediated food allergy is increasing in prevalence[1,2] for reasons that are not yet clear. Although there is a strong genetic contribution to food allergy, a number of environmental factors that influence the composition of the intestinal microbiota have also been identified as modifiers of food allergy risk. In this review, our aim is to discuss the evidence that the composition of the commensal microbiota regulates the development of food allergy.

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Submitted for publication March 26, 2016; revision submitted August 15, 2016; accepted for publication September 2, 2016.

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1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2016.09.003

EPIDEMIOLOGY OF FOOD ALLERGY

IgE-mediated food allergy affects approximately 5% of adults and 8% of children.[3] Food allergy is a disease with an onset in early life. An unselected cohort of 2848, 12-month-old infants in Australia demonstrated a prevalence of food challenge-proven peanut, sesame, and egg allergy of 3.0%, 0.8%, and 8.9%, respectively.[4] Studies to test the impact of early food introduction on the development of food allergy have found that infants have sensitization and clinical reactivity to egg or peanut as early as 4 months of age.[5,6] Therefore, environmental risk factors for food allergy are likely to play a role early in postnatal life or in utero.

Factors that have been associated with modified risk of food allergy include mode of birth, breastfeeding, having older siblings, attending daycare in early

life, and exposure to furred pets (comprehensively reviewed in the study by Marrs et al.[7]). These findings are supportive of the hygiene hypothesis, which proposes that lack of appropriate microbial exposure in early life drives allergic disease. There is evidence that each of these factors individually alters the composition of the intestinal microbiome.[8-12] Linking these 2 observations, there is great interest in determining whether an altered microbial colonization is responsible for increased susceptibility to food allergy and understanding the mechanism of that susceptibility.

EARLY LIFE BACTERIAL COLONIZATION OF THE HUMAN GUT

Yatsunenko et al. used 16S rRNA data collected from fecal specimens of geographically diverse populations to show that the greatest interindividual variability in the microbial composition occurs in the first 3 years of life.[13] Although meconium has been reported to have a detectable microbial presence, colonization of the infant starts at birth when microorganisms from the maternal body surfaces and the environment are acquired.[14] There is a preserved pattern of microbial colonization in early life from relatively aerobic to anaerobic. Newborns have a domination of proteobacteria (*Escherichia*, *Shigella*), which progresses to domination by Actinobacteria (eg, *Bifidobacterium*), followed by acquisition of an adult-like domination by Firmicutes and Bacteroidetes.[9,15,16] The maturation of the infant microbiome is driven primarily by cessation of breastfeeding. The rate of microbial maturation is influenced by environmental factors[17] and has been proposed to be a critical factor in health outcomes such as adiposity.[16] Therefore, the microbial composition of the infant gastrointestinal tract is highly dynamic, which adds to the complexity of trying to capture the impact of microbial composition on health outcomes.

INTESTINAL MICROBIAL COMPOSITION AND FOOD ALLERGY

There are a limited number of culture-independent studies that have directly looked at microbial composition associated with food allergy. Cross-sectional studies comparing food allergic to healthy subjects are confounded by differences in the diet, which is particularly problematic when studying foods that contribute significantly to the diet such as cow's milk. Ling et al. used 16S rRNA sequencing to study differences in microbial composition between children with food allergy (n = 17 with IgE-mediated food allergy and n = 17 with non–IgE-mediated food allergy) and healthy controls (n = 45).[18] Sampling was performed at the time of diagnosis, from age 2 to 11 months. There was no difference in microbial diversity, but they found increased levels of *Clostridium sensu stricto* and *Anaerobacter* and decreased levels of *Bacteroides* and *Clostridium XVIII* in infants with IgE-mediated food allergy.[18] Furthermore, levels of *Clostridium sensu stricto* correlated with levels of IgE. Strengths of the study include the use of food challenge–proven diagnosis and acquisition of samples prior to diagnosis suggesting that diet may not already have been adjusted. However, as the infants already have symptoms, dietary adjustment is likely. Furthermore, in a cross-sectional design, it is not possible to determine if changes in microbial composition preceded the development of food allergy which would support causation.

Hua et al.[19] recently reported findings from the publically available American Gut project. Of the 1879 participants (primarily adult, mean age 45 years), 2.5% self-reported allergy to peanuts, 3.2% to tree nuts, 2.6% to shellfish, and 9.1% to other foods. There was a marked reduction in microbial richness and alpha diversity in those self-reporting peanut or tree nut allergy compared to those without peanut or tree nut allergy. There were also significant differences in beta diversity in those with peanut or tree nut allergy. At the level of microbial taxa, there was an increased correlation of peanut and tree nut allergy with *Bacteroides fragilis*, which is somewhat surprising as *B. fragilis* has been shown to promote the generation of regulatory responses in the intestine.[20] There were negative correlations with *Clostridiales*, *Prevotella*, and *Ruminococcaceae*. These compositional differences were not unique to peanut and tree nut allergy and were found associated with seasonal allergies but not bee sting or shellfish allergy. Strengths of the study include the number of participants. Self-reported food allergies tend to overestimate the true prevalence of food allergy, particularly in the absence of additional questions about symptoms; however, the rate of peanut or tree nut allergy was within reported ranges and overestimation of true food allergy would likely reduce the effect observed. As with the previous study, in a cross-sectional design, it is not possible to assess probability of causation.

The only prospective study to address food allergy was recently reported by Azad et al.[21] Their findings showed that low fecal microbial richness at 3 months preceded food sensitization as measured at 12 months, whereas concurrent richness at 1 year was not associated with food sensitization.[21] Enterobacteriaceae were overrepresented while Bacteroidaceae were underrepresented in food sensitized infants at 3 months of age, suggesting a maturational difference in microbial composition. Strengths of the study were prospective