Gut Microbiome and the Development of Food Allergy and Allergic Disease

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KEYWORDS

• Microbiome • Gut microbiota • Commensal flora • Food allergy • Asthma • Allergic rhinitis • Eczema • Allergic disease

KEY POINTS

- Early microbial colonization plays an important role in the development of the innate and the adaptive immune systems, and there are several proposed mechanisms to explain how alterations in microbiome could lead to the development of allergic disease.
- Although some studies have identified notable relationships between the gastrointestinal microbiota and the development of asthma, allergic rhinitis, and eczema, specific studies examining the microbiome in human food allergy are lacking.
- As technology and knowledge of the microbiome advances, discoveries in food allergy and atopic disease will likely provide insight into primary prevention and treatment strategies.

INTRODUCTION

Food allergy, defined as an adverse, immune-mediated reaction to a food that is reproducible on a subsequent exposure,[1] affects nearly 5% of all adults[2] and up to 8% of children in the United States.[3] Recent data from the US Centers for Disease Control and Prevention have found that the prevalence among children 0 to 17 years increased by 50% from 1999 to 2011.[4] Even before this increase in prevalence, food

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allergies were the leading cause of anaphylaxis in patients presenting to the emergency department in the United States.[5] Studies have also shown that a diagnosis of food allergy results in a significantly lower quality of life.[6–8] Despite the increase in prevalence, the life-threatening potential, and the disease burden of food allergies, the cause of this epidemic remains elusive.

One of the leading theories to explain this modern day allergy epidemic was introduced by Strachan[9] in 1989 as the hygiene hypothesis. In his hypothesis, Strachan proposed that a larger family size was protective against allergic disease because of early life exposure to sibling infections.[9] However, since its introduction, others have revisited this idea, suggesting that changes in early life viral and bacterial exposures and intestinal colonization patterns in western countries have contributed to the failure to induce and maintain tolerance, a state of unresponsiveness to harmless antigens.[10,11]

THE HUMAN MICROBIOME

It has been estimated that the human gut is populated with up to 100 trillion microbes.[12] Rough estimates are that the microbiota (previously termed flora or microflora) contain on the order of 150-fold more genes than are encoded in the human genome.[13] The ancient symbiotic relationship between multicellular animals and resident microbes has shaped the evolution of the immune system into its present state.[14] Although the composition of the microbiota changes substantially from infancy to adulthood, most organisms come from the four phyla Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria.[15]

The advent of high-throughput DNA deep sequencing technologies has revolutionized the ability to characterize microbial diversity and compare this diversity across organs and individuals. Sequencing of diagnostic regions of the 16S rRNA gene sequence provides a robust method to identify the bacteria present in a sample. Because clinical samples can be sequenced directly, organisms are identified even if they cannot yet be cultured, and the resulting 16S rRNA sequence provides a reference for known bacterial taxa (ie, species) and for novel ones.[16,17] This bacterial census provides information on specific taxa that are present; loss of specific taxa and alterations in the community structure are associated with disease progression (eg, infection by *Clostridium difficile*).[18] Beyond 16S data, genome sequencing from microbial communities (ie, metagenomics) can enable functional studies, identify gene categories that influence the host, and reveal conservation at the level of gene function even in cases where those genes are derived from unrelated organisms.[19,20] Much current work is aimed at extending these techniques to understand gene expression at the RNA (transcriptional profiling) and protein (proteomics) levels, and to understand how microbial communities affect the flux of metabolites (metabolomics) in the host.[21]

THE MICROBIOME AND IMMUNE DEVELOPMENT

Early microbial colonization plays an important role the development of the innate and the adaptive immune systems,[22] and there are several proposed mechanisms to explain how alterations in microbiome could lead to the development of allergic disease. Experimental, germ-free (gnotobiotic) mouse models have demonstrated that gut-associated lymphoid tissues fail to develop when microbial colonization is delayed, leading to a Th2 skewed immune response.[23] Secretory IgA produced by resident B cells in gut-associated lymphoid tissues may also promote oral tolerance by binding allergens in the gut and preventing their uptake.[24] Microbial colonization has been shown to be important in the development of Th1[25,26] and regulatory