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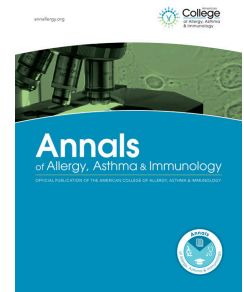
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The Microbiome and Allergic Diseases:
A struggle between good and bad microbes

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It is well established that microbial infections can influence the development and severity of allergic diseases. Examples include *S. aureus* or herpes simplex infection in atopic dermatitis (AD) and various respiratory viral infections in asthma. Adults with AD have been found to have increased cutaneous, multiorgan and system infections associated with considerable cost burden from hospitalization.¹ The strong association of *S. aureus* infection in AD has resulted in the frequent use of antibiotics for exacerbation of AD, even in the absence of overt skin infection. Antibiotic selection for AD exacerbation often involves use of anti-MRSA antibiotics due to concerns about the rising rate of MRSA.² Given concerns of increasing levels of anti-microbial resistance, there is a need for more caution in the indiscriminant use of antibiotics as they have the potential of eliminating not only bad bacteria, but also good bacteria required for the health of the epithelial surfaces of the body.³

Development of a more targeted approach, to reduce pathogenic infections in allergic disease requires a comprehensive view of why epithelial cell surfaces lose their microbial diversity and breed abundance of detrimental microbes. The microbiome is influenced by multiple immune, genetic and environmental factors across the life span. These include prior antibiotic exposure, breastfeeding, mode of birth delivery, environmental microbial influence, availability of nutrients that influence microbial growth, diet including vitamin D levels, genetic variants in epithelial barrier and immune function, local tissue pH, and factors that control inflammation. Host immune-microbial cross-talk play a key role in determining the tissue habitat.⁴ For example, in AD, it has been found that Th2 responses inhibit innate responses required to produce antimicrobial peptides needed to kill *S.aureus*. Conversely, overuse of antibiotics can select for methicillin resistant *S. aureus* which are known to enhance Th2-mediated allergic immune responses. Treatment with antibodies to IL-4 and IL13 can restore

tissue homeostasis by reducing *S. aureus* abundance and decreasing Th2 immune inflammation.

In the current issue of The Annals of Asthma, Allergy and Immunology, the emphasis is on the role of the microbiome in AD,⁵ asthma,⁶ and food allergy (FA).⁷ Each of these allergic diseases are associated with specific microbial patterns that influence epithelial function, immune responses, and inflammation. Although the focus has been on pathogenic bacteria, there is now considerable evidence that commensal bacteria have beneficial functions that include anti-inflammatory activities, stimulation of the immune response including T regulatory cell activity, production of a diverse repertoire of molecules with antimicrobial activity that play a critical role in tissue homeostasis and host defense against pathogenic microbes.⁵ Disruption of the normal homeostatic interactions of the microbiome not only leads to overabundance of a pathogenic microbes such as *S. aureus*, in AD, but also loss of the symbiotic interactions between beneficial microbes with skin and mucosal epithelial cell surfaces.

Studies by Nakatsuji and Gallo⁵ have revealed that the majority of coagulase negative (CoNS) bacterial strains that colonize non-atopic human skin in healthy subjects are capable of suppressing survival of *S. aureus*. In contrast, skin of patients with AD lacked these protective strains of CoNS. These observations suggest that the combination of impaired skin epithelial barrier function including Th2 suppression of antimicrobial peptides production and low colonization by CoNS strains with capacity to produce antimicrobials enables survival and overgrowth of *S. aureus* in AD skin. Coagulase- negative Staphylococci within the skin microbiome also exert anti-inflammatory action and influence maturation of immune responses. Recent clinical trials suggest application of these beneficial bacterial strains can inhibit *S. aureus* colonization and skin inflammation in AD.⁵

In the current issue of the Annals, Kozik and Huang review the extensive literature that

support an important role for intestinal or upper airway microbiota in determining asthma risk, pathogenesis, and clinical presentation.⁶ Interestingly, different patterns of bacterial and fungal members of the respiratory microbiota may be found in specific endotypes of asthma including those with Th2-mediated vs non-Th2-mediated asthma. Additional studies have implicated a role for lower respiratory tract microbiota in altering corticosteroid response and contribute to poor asthma control. Perinatal and early life disturbances, such as maternal antibiotic use and mode of delivery, i.e. vaginal vs C-section, have been shown to alter the microbiome. Breastfeeding has been shown to directly impact the infant gut microbiome, protecting the infant from infections. Overall there is considerable data indicating that the presence and composition of human microbiota can have long-term effects on health outcomes. □

Zhao, Ho, and Bunyavanich have reviewed the evidence that gut dysbiosis preceeds the development of FA, and the pattern of microbiota associated with individual food allergies may be distinct.⁷ Murine models support the importance of gut microbiota in shaping immunologic response to foods. Gut microbiota have been found to alter FA susceptibility via modulation of Type 2 immunity, maintenance of T regulatory cell function, regulation of basophil activation, and promotion of intestinal barrier function.

Although enormous progress has been made in the description of microbiota in various allergic diseases and their individual phenotypes, there remain many questions and challenges in this important field. Further understanding of how microbiota functionally mediate their detrimental or beneficial effects on health and disease, as well as their stability over time, will be important in designing clinical trials and development of precision medicine approaches targeting the complexity of allergic diseases. The critical timeframe for prevention remains controversial, although this window is thought to be early in life. Identification of the specific

microbes with greatest benefit in disease modification and optimal approaches to introduce them into the host microbiome is in its infancy. These efforts will likely need to be pursued with a systems-level approach to the complex interactions between human hosts and their microbiome, accounting for the impact of these interactions on changes in environmental and lifestyle factors across their lifespan amongst various organs. This will require integration of microbiome data with other investigative methods including profiling of the transcriptome, metabolome, proteome, and lipidome. These challenges will need to be addressed if new clinical strategies to manipulate microbiota, and their products, are to be successful in modifying trajectories of allergic diseases.

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