Theme Editorial

The Microbiome in Clinical Allergy and Immunology: Emerging Role as Friend and Foe

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The current issue of *The Journal of Allergy and Clinical Immunology: In Practice* includes a compendium of review articles examining the evolving role of the human and environmental microbiome in clinical allergy and immunology, including its function in both prevention and treatment of allergic disease and its importance as a risk factor in development or severity of atopic conditions. This emerging role of the microbiome as both friend and foe and its timing on exposure is particularly relevant to the practicing clinician. The compilation of articles covers both the environmental microbiome, which represents the entirety of microbes and their metabolites that human hosts encounter in their environments,[1] and the human microbiome, which refers to the microbiome specifically found on or in an individual host, for example, inhabiting the skin, gut, or respiratory tract. Ongoing studies are identifying the importance of the microbiome in allergic disease, and the authors throughout this issue highlight the 2-pronged function of the microbiome contributing to development and manifestation of atopic conditions, while also targeting the microbiome toward development of therapeutic approaches to mitigate allergic diseases.

The review by Huang et al[2] provides a summary of recent findings in the literature on how microbial-immune interactions promote and maintain immune dysfunction associated with allergy and asthma. The authors highlight early-life microbiome perturbation and the molecular mechanisms of immune dysfunction that are related to subsequent asthma and allergy development later in childhood, as well as discussing features of the microbiome that relate to phenotypic characteristics of asthma and allergy in older patients who have established disease. The review discusses how dermal, respiratory, and intestinal microbiomes develop over the first several years of life, with increased risk of atopy and asthma development later in childhood associated with body habitat–specific microbial colonization patterns in infancy. In particular, the review notes how during infancy, upper airway colonization by respiratory pathogens such as *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* is associated with early-life wheeze, febrile respiratory illness, and asthma later in childhood, emphasizing that early life is a critical time for the establishment and development of both the immune system and the gut microbiome.[3,4] As such, the authors review several clinical and preclinical studies that have demonstrated how early-life microbial perturbation and metabolic dysfunction is associated with increased risk of allergic and asthmatic phenotypes in later childhood. It is noted how gut microbial manipulation results in reprogramming of metabolism, which has beneficial effects on airway inflammatory responses, citing oral supplementation of the gut microbiome with *Lactobacillus johnsonii*, which has been shown to protect mice from airway allergic inflammatory response to allergen exposure or viral respiratory infection.[5] Mechanisms by which microbiota-derived metabolites shape immune function are described for some classes of molecules, with the concept of "trained immunity," by which microbial metabolites influence long-term functioning of innate immune cells. The authors conclude that the future for allergy and asthma research hinges on a deeper understanding of molecular mechanisms underlying the trajectory to disease development and endotypes once established, with this aim facilitated through

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high-resolution immune and microbial cellular and molecular profiling approaches for samples collected from diverse and well-characterized human cohorts longitudinally. In the future, the authors envision cost-effective metabolomic prenatal and/or postnatal screening used as a prognostic tool to determine disease risk and also as a means to monitor microbial-immune status throughout development, allowing the identification of those at risk and assessing the efficacy of interventions that alter the disease course.

In their nonsystematic review of the literature, Fiocchi et al[6] update readers on studies aimed to influence allergic diseases through modulation of the gut microflora, focusing on relevant trials examining the effect of probiotics, prebiotics, and symbiotics in allergic disease prevention and treatment. Although 20 years of research has transpired looking at the role of probiotics, prebiotics, and symbiotics in the prevention and treatment of allergic diseases, in their review, the authors found significant uncertainty in the efficacy of gut microflora modulation in prevention and treatment of each of the following conditions examined—allergic rhinitis, allergic asthma, atopic dermatitis, food allergy, and gastrointestinal allergies. Although the effects of probiotics/prebiotics/symbiotics in the treatment of allergic diseases remain controversial and systematic reviews indicate inconsistent results, the authors note the relatively high safety of their use, though they advocate for additional investigation needed to provide more definitive conclusions. Particularly, in future research on the role of probiotics, prebiotics, and symbiotics in the prevention and treatment of allergic diseases, the authors emphasize more focus geared in the direction of at-risk groups, use of larger-scale studies, and attention in narrowing the gap between basic research and clinical claims.

The review by Kelly et al[7] focuses on the environmental microbiome and its role in allergic disease and asthma. The authors provide a framework outlining mechanisms, such as metabolite production, antigenic stimulation, and epigenetic changes, by which the environmental microbiome affects allergic disease and asthma, namely, through exposure or infection of the host and through the establishment and maintenance of the individual microbiome. In early life, when the immune system is more plastic and less rigid and reactive than an adult immune system, exposure to a diverse environmental microbiome helps create a diverse human microbiome, gearing the maturing immune system toward tolerance and protection against development of allergic disease. Evidence supports the protective effect of growing up on a farm, for example, against the development of asthma, atopic dermatitis, allergic rhinitis, and allergic sensitization, which is associated with the farm environmental microbiome. The authors, however, note how diverse exposure does not appear to be universally beneficial, with infants raised in urban environments described to develop a more homogeneous urbanized airway and gut microbiome, with relative abundance of Haemophilus, Rothia, and Veillonella, and decreased Bacteroidetes.[8] Urban house dust samples were also found to differ from those from rural house dust, with the urban gut and nasal microbiome associated with increased asthma risk. Again, the authors suggest further research focused on the environmental microbiome and allergic disease on a representative sampling of populations from diverse settings, because research has largely focused on populations with a higher burden of allergic disease skewed toward primarily affluent White populations in industrialized nations, calling for more future studies from a more equitable distribution of microbiome research.

Lastly, the review by Kloepfe et al[9] focuses on the microbiome as a gateway to prevention of allergic disease, citing evidence of age-appropriate, nonpathogenic microbiota development in the skin, gastrointestinal tract, and airway for protection against development of allergic disease. This review discusses a range of preventive actions involving the microbiome in either the prenatal or postnatal period to prevent allergic disease. The review uses current evidence and understanding of allergy-associated human microbiota patterns, their association in allergic disease development, and how to harness these associations for the host to benefit against allergies.

With the emerging potential of the microbiome to prevent or treat allergic disease, the insights in this issue are certain to contribute to future in-office clinical decision making. As mentioned by several authors from a number of the included review articles, it is imperative that robust microbiome research continue to evaluate which potential interventions will be most efficacious and practical in leading to clear impact in those at risk for allergic disease or with established atopic conditions.

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