



Editorial

Origins of allergy

Scratching below the surface



Despite the remarkable advances in our understanding of the phenotypes and endotypes of allergic diseases, there remains no cure for the treatment of allergic diseases, and the global burden of allergic diseases is enormous.^{1,2} The yardsticks for asthma, anaphylaxis, and atopic dermatitis (AD) published in the *Annals of Allergy, Asthma & Immunology* have offered diagnostic and treatment guidance for the management of these complex diseases.^{3–5} However, hopes to reduce the prevalence of allergic diseases lie in prevention rather than in the development of additional biologics. In the current issue of the *Annals of Allergy, Asthma & Immunology*, a series of articles review our current understanding of the origins of allergy and opportunities for prevention.^{6–9}

In a review by Sugita et al,⁶ the importance of microbial dysbiosis and epithelial barrier dysfunction in the affected tissues has been highlighted. They describe a dynamic cross talk between the environmental factors and microbial, epithelial, and immune cells in the development of allergic diseases such as AD, asthma, allergic rhinitis, and chronic rhinosinusitis. In particular, disruption of the epithelial barrier can lead to local inflammation and activation of adaptive immune responses. There is substantial evidence suggesting that environmental factors, including microbes and detergent, directly affect the epithelial barrier function. Immune responses, particularly type 2 cytokines from T-helper cells and innate lymphoid cells, can contribute to epithelial barrier dysfunction. Environmental factors may be mediated at least in part by epigenetic mechanisms. These interactions are complex, and the communication among various organs suggests that allergy can be considered as a systemic disease. Progress in this area will require noninvasive devices to monitor the epithelial function and new strategies that can protect the epithelial barrier.

Krempski et al⁷ consider a broad array of factors that predispose to allergic diseases, including the initiation and exacerbation of immune responses, epithelial barrier dysfunction, loss of immune tolerance, disturbances in the microbiome, environmental influences, diet, age, and inherent genetic predisposition using a systems approach. Damage to epithelial surfaces is considered at the origin of various manifestations of allergic diseases. As a sensor of environmental stimuli, the epithelium of the lungs, skin, and gut is affected by an altered microbiome, air pollution, food allergens, and chemicals in modern detergents. This collectively leads to alterations in the lung, skin, or gut epithelial surfaces and drives the type 2 immune responses that underlie the allergic diseases. Using a systems approach is necessary to examine the interplay of

multiple factors contributing to the complex phenotypes of allergic diseases.⁸ Treatment and prevention of allergic diseases include biologics, oral desensitization, targeted gut microbiome, and changes in behavior.

Prescott⁹ considers the possibility that the loss of biodiversity is an important driver of allergy. In particular, environmental factors, such as microbial diversity and microbial load in a child's environment, may influence the development of the immune system and protect against the allergic diseases. The exposome encompasses all environmental exposures of an individual from conception to their life span, and its impact on allergy is critical for prevention strategies. Changes in the human microbiota are occurring concomitantly with industrialization and may represent an underlying factor in driving the allergic diseases. As an example, increased abundance of *Staphylococcus aureus* with concomitant loss of beneficial bacteria has been associated with the occurrence of AD and peanut allergy.

The possibility that the origins of allergy date all the way back to conception and events in the womb and environmental factors influencing the mother has not been adequately explored. In a perspective, Hui et al¹⁰ explore the maternal and early childhood factors that may alter the course of allergy. Early life events, including viral and bacterial pathogens, environmental pollution, and allergen exposure, resulting in epithelial injury and immune activation all contribute to the origins of allergy. These are compounded by behavioral trends that have accompanied westernization, such as increased cesarean section births, increased formula feeding, refined diets, and increased antibiotic use. With the increase in the prevalence of the allergic diseases, it is important to examine the prenatal and postnatal factors contributing to atopy development. Multiple organ systems are involved in allergy development. Understanding the epithelial dysfunction leading to type 2 inflammation in the skin, lungs, and gut is critical. The continued study of genetics will further elucidate the causes of allergies. It will be important to perform prospective birth cohort studies to observe the pregnant mother and her offspring's early childhood, with close observation of the environmental exposures including pollution, detergents, hand sanitizers, soaps, diet, and medication exposures. When proposing interventions for allergy prevention, the emphasis should begin with the maternal skin barrier, limiting adverse exposures, and maintaining intact epithelial barriers of the skin, lungs, and gut in early childhood.

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References

1. Bridgman AC, Block JK, Drucker AM. The multidimensional burden of atopic dermatitis: an update. *Ann Allergy Asthma Immunol.* 2018;120(6):603–606.
2. Lieberman J, Sublett J, Haselkorn T, et al. Increased incidence and prevalence of peanut allergy in children and adolescents in the United States. *Ann Allergy Asthma Immunol.* 2018;121(5):S13.
3. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma Immunol.* 2018;120(1):10–22.e2.
4. Chipps BE, Bacharier LB, Farrar JR, et al. The pediatric asthma yardstick: practical recommendations for a sustained step-up in asthma therapy for children with inadequately controlled asthma. *Ann Allergy Asthma Immunol.* 2018;120(6):559–579.e11.
5. Carter MC, Akin C, Castells MC, Scott EP, Lieberman P. Idiopathic anaphylaxis yardstick: practical recommendations for clinical practice. *Ann Allergy Asthma Immunol.* 2020;124(1):16–27.
6. Sugita K, Soyka MB, Wawrzyniak P, et al. Outside-in hypothesis revisited: the role of microbial, epithelial, and immune interactions [e-pub ahead of print]. *Ann Allergy Asthma Immunol.* <https://doi.org/10.1016/j.anai.2020.05.016>, accessed August 18, 2020.
7. Krempski JW, Dant C, Nadeau KC. The origins of allergy from a systems approach [e-pub ahead of print]. *Ann Allergy Asthma Immunol.* <https://doi.org/10.1016/j.anai.2020.07.013>, accessed August 18, 2020.
8. Virkud YV, Kelly RS, Wood C, Lasky-Su JA. The nuts and bolts of omics for the clinical allergist. *Ann Allergy Asthma Immunol.* 2019;123(6):558–563.
9. Prescott SL. A butterfly flaps its wings: extinction of biological experience and the origins of allergy [e-pub ahead of print]. *Ann Allergy Asthma Immunol.* <https://doi.org/10.1016/j.anai.2020.05.025>, accessed August 18, 2020.
10. Hui JW, Donald YM, Leung. Origins of allergic disease: maternal and early childhood factors [e-pub ahead of print]. *Ann Allergy Asthma Immunol.* <https://doi.org/10.1016/j.anai.2020.05.013>, accessed August 18, 2020.