



Editorial

Allergic skin diseases beyond T_H2

Recent studies have highlighted the multidimensional effect of atopic dermatitis (AD) and urticaria. Patient burden for these conditions is largely driven by the intense itching, sleep disturbance, comorbidities, and mental health illness associated with these diseases.^{1–3} Immunologic, microbial, and epithelial interactions have been reported to play an important role in AD.^{4,5} Novel therapies and management approaches are targeting the mechanisms underlying AD and urticaria.^{6,7} The current issue of the *Annals* contains 3 outstanding reviews that update readers on the pathophysiology and evolving treatments for AD and chronic urticaria.^{8–10}

Major advances have been made in our understanding of mechanisms that lead to allergic skin diseases. The ready availability of skin tissue for unprecedented systematic multiomic profiling has paved the way for mechanism-based therapies and precision medicine approaches. Filaggrin, in particular, has now been demonstrated to not only be a significant genetic risk factor for AD but also an important disease modifier, leading to increased morbidity and severity of AD. Patients with filaggrin-related AD and asthma have increased hospital admissions and medication requirements. Patients with AD and filaggrin mutations have reduced health-related quality of life compared with patients with AD and wild-type filaggrin. Beyond the well-established association of AD with filaggrin gene null mutations, immune activation and various environmental factors contribute to reduced filaggrin in the skin barrier. Drislane and Irvine⁸ review the multifunctional role of filaggrin in AD and allergic disease in the current issue of the *Annals*. In this review, the authors highlight novel methods of measuring filaggrin expression and identifying filaggrin mutations, which will aid in stratifying this patient cohort as a distinct subset of AD.

In the approximately 20% of patients who fail to respond to topical medications, novel therapeutics developed in the past few years have made a tremendous difference in their quality of life and disease outcomes. Type 2 immune activation has now been established to be the key pathway leading to allergic skin diseases, such as AD. Aside from interleukin (IL) 4 receptor antagonism, other approaches to interfere with type 2 immune responses, including direct neutralization of type 2 cytokines and prevention of alarmin action and receptors (eg, use of anti-IL-33 and IL-33 receptor antagonists), involved in the Type 2 pathway have had favorable results. In-depth immune profiling has also revealed the complex heterogeneity of AD, which demonstrates involvement of immune pathways beyond type 2 responses. These immune pathways that modify type 2 responses may include IL-1, interferons, IL-6, IL-17, and IL-22, which occur beyond the origins of allergic responses and may be the result of racial and age-related effects, duration and onset of illness, and AD triggered by different environmental factors, including allergens, pathogens, and irritants. Remert-Yuval and Guttman-Yassky⁹ provide a discussion of why treatments

that antagonize IL-4/IL-13 are insufficient and review new treatments for AD-targeting pathways beyond IL-4 and IL-13 cytokines. This article reviews multiple clinical trials, including JAK inhibitors, a dual JAK/SYK inhibitor, a histamine H4R antagonist, antagonists of the TSLP/OX40L axis, an IL-22 inhibitor, and IL-33 and IL-17C antagonists. In this rapidly evolving field of AD treatments, a completely new treatment paradigm is proposed for the future.

In the final review for this month, Maurer et al¹⁰ provide a review of the new and evolving treatments for chronic urticaria. Although antihistamines and omalizumab have become the major therapies for chronic urticaria, this common disease is heterogeneous in its pathophysiologic features and treatment response. The authors review promising targets of future therapies, including chemoattractant receptor–homologous molecule expressed on T_H2 cell antagonism, monoclonal antibody to Siglec-8, Bruton tyrosine kinase inhibitors, Syk inhibitors, and dupilumab. Taken together, with the development of new technologies to evaluate the pathophysiology of chronic urticaria and AD, novel pathways that account for treatment-resistant patients will be identified. As such, new biomarkers and treatment approaches will evolve to improve our patient's quality of life and health outcomes.

Donald Y.M. Leung, MD, PhD
Department of Pediatrics
National Jewish Health
Denver, Colorado
leungd@njhealth.org

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