Editorial

Genetics, epigenetics, and allergic disease: A gun loaded by genetics and a trigger pulled by epigenetics

The allergic diseases addressed in this issue comprise a group of disorders mediated by chronic allergic inflammation and frequently activated by immunoglobulin E. The prevalence and severity of many of these allergic disorders have increased dramatically over the past few decades, creating a mystery as to why. Although genetics plays an important role in the development of atopy, genetics alone cannot fully explain this rapid growth. In this issue, a review article by Bellanti[1] may help us understand the important role that epigenetics plays in the development and management of allergic disease. An evidence-based proposal is presented that posits that DNA methylation plays a major role in epigenetic mechanisms involved in both the development of allergic disease as well as in the response to immunotherapy. The article reviewed the application of DNA methylation and regulatory T cell induction not only to allergic disorders but also to cancer and autoimmune diseases. Bellanti[1] illustrated the relationship between genetics and epigenetics with the comparative analogy, "genetics loads the gun and epigenetics pulls the trigger." It is also apparent that epigenetics holds the key to unraveling the complex associations between disease phenotypes and endotypes by identifying safer and effective therapies, and by improving diagnosis and treatment of allergic diseases.

Among the chronic, inflammatory, allergic diseases, none illustrate the genetics-epigenetics paradigm better than atopic dermatitis, and, as such, it has been featured as a recurring topic in recent issues of the *Proceedings*.[2–9] Genetic predisposition, epidermal barrier disruption, and dysregulation of the immune system are some of the critical pathophysiologic components that lead to this condition. In this issue, Kim *et al.*[10] provided an updated review of the pathophysiology of atopic dermatitis, with a particular focus on the role of epidermal lipid profiles, neuroimmune interactions, and microbial dysbiosis. The role of epigenetics in the development of atopic dermatitis is comprehensively reviewed by the authors, who cite increasing evidence that demonstrates that environmental exposures of patients with atopic dermatitis induce epigenetic changes through DNA modification and micro-RNA–mediated posttranscriptional regulation. Understanding this complex pathophysiology allows for development of a contemporary precision medicine approach to the prevention and the treatment of atopic dermatitis. In this way, the insights provided by Kim *et al.*[10] directly relate to newer therapeutic strategies that are becoming available for the management of this condition.

In transitioning from the most common, chronic, inflammatory, cutaneous disease of childhood to one more rare, Ertugrul *et al.*[11] presented the results of their investigation of 32 children with cutaneous mastocytosis. These authors directed their efforts to discover prognostic factors for achieving remission and to determine the concomitant diagnostic value of DNA analysis of peripheral blood for the *c-Kit* mutation. Although the authors identified a number of useful prognostic factors, such as a triggering effect of tobacco exposure and of clarithromycin and vitamin D usage, they found that testing peripheral blood for the *c-Kit* mutation provided no diagnostic contribution in their cohort of pediatric patients with cutaneous mastocytosis.

In moving on to another rare cutaneous disease, hereditary angioedema (HAE) is an autosomal dominant, genetic disorder associated with C1-inhibitor deficiency, which has been a recurrent topic in the *Proceedings* due to the recent development of a multitude of novel treatment options.[12–24] In this issue, Arce-Ayala *et al.*[25] reported on the clinical profile and quality of life displayed by Puerto Rican patients with HAE. Compared with U.S. population norms for quality-of-life measures, in Puerto Rico, patients with HAE manifested significantly lower scores, both in the physical and mental components. Arce-Ayala *et al.*[25] have expanded the understanding of the burden of illness attributable to HAE by having demonstrated a substantial and noteworthy decrease in quality of life in patients with HAE and an increase risk for depression associated with the disorder.

The burden of illness attributable to disease in general involves the direct cost attributable to treatment, in addition to measures of human suffering. A major factor that contributes to the cost of care is hospitalization, with asthma being among the costliest of the allergic diseases. Research that can lead to reduced

hospital stays, therefore, is greatly needed. In this spirit, in Japan, Okada *et al.*[26] investigated the utility of a therapeutic strategy based on a modified pulmonary index score among a group of children hospitalized for asthma. Although the modified pulmonary index score has been proposed as a quantitative indicator of the severity of childhood asthma exacerbations, the utility of the score as a treatment decision-making tool had not previously been investigated. The case-control study by Okada *et al.*[26] of 346 pediatric patients hospitalized for asthma demonstrated a significantly shorter length of stay attributable to implementing therapeutic strategies based on the modified pulmonary index score. The results of this study, therefore, suggests that further study of this strategy should be considered in other countries, including the United States.

Just as a modified pulmonary index score has been proposed as a severity indicator for childhood asthma exacerbations, severity indicators are needed in other allergic disorders. In efforts to meet this need, scoring systems are being increasingly developed for various diseases, with the objectives of improving the classification of disease severity and of assessing therapeutic modalities. In this issue, Alvarado *et al.*[27] provided a concise summary of scoring systems used for allergic rhinitis, asthma, atopic dermatitis, urticaria, Stevens-Johnson syndrome/toxic epidermal necrolysis, eosinophilic esophagitis, and systemic allergic reactions (anaphylaxis). In addition to providing objective measurements of patients' progress in clinical practice, such assessment methods have been shown to be useful for designing clinical trials and for making comparisons with other studies.

In continuing with the theme of severity assessment, Soyyigit *et al.*[28] conducted an investigation to determine the factors associated with the severity of allergic reactions to Hymenoptera venom stings in 82 patients with a history of allergic reactions to Hymenoptera venom. They reported that a high basal serum tryptase level was a risk factor for the development of severe systemic reactions in venom allergy and that this risk increased with increasing age.

A recurring section of the *Proceedings* is dedicated to the pearls and pitfalls of disease management. In this issue, Kobrynski,[29] from Emory University School of Medicine, provided a practical review of the diagnostic and treatment parameters of common variable immune deficiency, a primary immune deficiency due to defective B-cell maturation. The article began with a clinical question regarding a case vignette and ended with the presentation of bulleted pearls and pitfalls of disease management. Kobrynski[29] emphasized that patients with common variable immune deficiency must be monitored for the classic findings of increased susceptibility to infections but also for noninfectious complications, such as inflammatory disease of the lung and gastrointestinal tract, because of the decreased survival known to be associated with these complications. Because of the importance of this article and its clinically useful implications, it was chosen for this issue's "For the Patient" section. This segment, found in the final pages of the print version of this issue and also available online, consists of a 1-page article synopsis, written in a readily comprehensible fashion to help patients better understand the content of the full article.

In summary, the collection of articles found within the pages of this issue provided further insight into the intersecting crossroads of genetics and the environment, which manifest as the allergic, cutaneous, and respiratory disorders that afflict patients whom the allergist/immunologist serves. In particular, these articles exemplify how the complexities of atopic dermatitis, mastocytosis, asthma, food allergy, Hymenoptera venom allergy, immunodeficiency, and HAE continue to challenge the allergist/immunologist. In keeping with the overall mission of the *Proceedings*, which is to distribute timely information regarding advancements in the knowledge and practice of allergy, asthma, and immunology to clinicians entrusted with the care of patients, it is our hope that the articles found within this issue will help foster enhanced patient management and outcomes. On behalf of the Editorial Board, we hope that you are able to make practical use of the diversity of literature offered in this issue of the *Proceedings.*

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