

Review of Critical Issues in the Pathogenesis of Atopic Dermatitis

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■ Abstract

About a decade ago, loss-of-function mutations in the filaggrin molecule were first implicated in the pathogenesis of ichthyosis vulgaris and, subsequently, of atopic dermatitis and other atopic diseases. Since then, intensive study of the role of filaggrin null mutations have led to other milestones in understanding the pathologic pathways in these diseases, including the initiation, maintenance, and promotion of the disease processes. The result has been new and emerging clinical and pharmacologic strategies for early identification of and intervention in atopic diseases.

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■ Keywords

Atopic dermatitis; eczema; filaggrin; filaggrin null mutation; ILC2s; interleukin-13; interleukin-25; nuocytes; toll-like receptors; type 2 innate lymphoid cells

Recent findings in the pathophysiologic mechanisms involved in the propensity for and clinical expression of atopic dermatitis (AD) have led to modifications of treatment strategies as well as new and emerging therapies.

Genetics and AD

In a recent paper, Paternoster and colleagues¹ described the results of the largest AD genetics study to date, a meta-analysis

of studies from European, African, Japanese, and Latino populations. More than 15 million genetic variants were involved in 21,399 patients with AD and 95,464 controls. Previously, 21 genetic susceptibility loci had been described in AD; this group identified an additional 10 AD risk loci, including genes involved in innate host defenses, T-cell function, and autoimmunity.

Although filaggrin (*FLG*) loss-of-function mutations are the strongest and best-replicated genetic links to AD worldwide (outside of Africa), the specific *FLG* mutation spectrum has been found to differ among populations. In the Han Chinese population of Singapore,² at least 25 mutations have been found. In contrast, in Europe, five mutations account for 95% of all *FLG* mutations. About 1 in 10 individuals of European ancestry carry one *FLG* null mutation, meaning that such individuals have only about half of the normal FLG protein in their skin, resulting in dry skin and/or ichthyosis vulgaris and a high risk for AD. In addition, about 1 in 400 individuals of European ancestry carry two *FLG* null mutations, meaning that such individuals have no FLG protein in the skin and have severe ichthyosis vulgaris and a very high risk for AD.³

Studies of specific populations show that genetic defects in the epidermis and the development of atopic diseases are not limited to *FLG* mutations. For example, *FLG* mutations are uncommon in African populations. A study of 100 amaXhosa children in South Africa with severe AD and ichthyosis vulgaris symptoms revealed no *FLG* mutations.⁴ A similar study in Ethiopia showed one child with an *FLG* mutation among 75 studied.⁵ African Americans are a poorly studied population with respect to AD genetics; however, *FLG* mutations that are identified in African Americans with AD are the same as those seen in European populations (about 25% of the African American genome is European).⁶

In another study, immune-mediated skin inflammation was found to be similar in severe AD in patients with and without an *FLG* mutation.⁷ Furthermore, FLG protein is secondarily downregulated in severe AD,⁸ through mechanisms that are not yet fully understood, although multiple cytokines are likely involved.⁹

Environmental Factors and Immunity

Several new, key findings in immunology research in the past 5 to 10 years hold promise for clarifying the complex mechanisms involved in AD pathophysiology.

Disruption of the skin barrier activates the adaptive immune alarm system; several cytokines have been identified in this process, including interleukin (IL)-33, thymic stromal lymphopoietin (TSLP), IL-25, toll-like receptors, and other inflammasome-activating signals. In genetically susceptible individuals, downstream activation of adaptive immunity results in expression of AD symptoms.

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Food Allergy in Patients With Atopic Dermatitis

The association between food allergy and severe atopic dermatitis (AD) has long been recognized, and the conditions coexist in approximately one-third of children.¹ In an international study of more than 2,100 children with active AD who came from families with atopic disease histories, Hill and colleagues² showed that early onset of severe AD in infancy was associated with a high risk for immunoglobulin-E (IgE) food sensitization, which is commonly associated with food allergy. As shown in the figure below, children who had severe AD in the first year of life had a high risk for food allergies, especially to cow's milk, eggs, and fish.

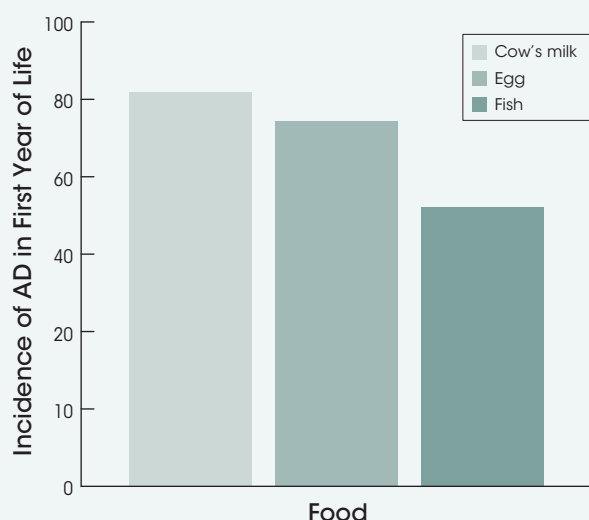


FIGURE Risk for Food Allergy Among Infants With Severe AD.

AD=atopic dermatitis.

Source: Hill et al.²

With the identification of, and increased research interest in, the presence of filaggrin (*FLG*) loss-of-function mutations in AD, a similar mechanism was hypothesized for food allergy. Brown and colleagues³ demonstrated that *FLG* loss-of-function mutations are strongly associated with IgE-mediated peanut allergy, an association that remained statistically significant in their study even after the investigators controlled for coexistent AD.

Additional research is required to further explore the association between AD and food allergy.

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Another important advance was the discovery of type 2 innate lymphoid cells (ILC2s), “first responders” in the skin. In 2010, several groups simultaneously described what were then called nuocytes, found to secrete IL-13.¹⁰ Later, ILC2s also were found to secrete IL-25, another key cytokine.¹¹

More recent data demonstrate that the populations of ILC2s expand massively in the skin of individuals with AD, as well as in those with asthma and nasal polyposis. Saunders and colleagues¹² further characterized the role of ILC2s in the diseases of the atopic march. This group found that mice deficient in *FLG* developed a skin inflammation analogous to AD (and driven by innate immunity), then later developed compromised lung function (a process resulting from adaptive immunity). These researchers demonstrated that, in the absence of the development of adaptive immunity, *FLG*-deficient mice had spontaneous, AD-like skin inflammation but did not progress to compromised lung function.

Recently published work by Jarrett and colleagues¹³ focusing on ILC2s has further elucidated the role of CD1a. CD1a-positive cells in the skin have been shown to be down-regulated by *FLG*; withdrawal of *FLG* immune suppression results in CD1a control of the inflammatory process. In addition, this article shows that the house dust mite allergens (Der p1 and Der p2) drive CD1. This work reveals both an additional pathophysiologic mechanism and another potential therapeutic target. (Currently, CD1a antibodies are available, but their use is limited to resistant Langerhans cell histiocytosis.^{14,15}) Although much remains to be understood, the importance of interactions between an “alarmed” skin barrier leading to ILC2 activation and expansion within the skin—with expression of IL-13 and subsequent recruitment of activated T cells, leading to further IL-13/IL-4 expression—is emerging as a driving pathway in this disease. Analysis of the transcriptome in AD using mRNA arrays have shown the relevance of IL-17 in chronic AD lesions, an effect seen particularly strongly among Asians with AD.¹⁶

The concept of cutaneous lymphoid stress was demonstrated by Strid and colleagues¹⁷ in a mouse model. These investigators showed that stressing the skin barrier and applying an allergen simultaneously triggers a T helper cell type 2 (T_H2) response. The imbalance in T-cell subsets in AD—predominantly T_H2 —results in expression of IL-4, IL-5, and IL-13, as well as so-called “pruritus-specific” cytokine IL-31.¹⁸ In patients with chronic AD, T_H2 activation persists, but activation of T_H1 cells also occurs. T_H2 cytokines downregulate expression of epidermal differentiation proteins (including *FLG*) as well as lipids.

New Insights and Emerging Treatments

Newer and emerging treatments are targeted toward various, specific aspects of inflammation.

In a seminal study on the topic, Hanifin and colleagues¹⁹ described increased phosphodiesterase (PDE) activity in patients with AD. Increased PDE was demonstrated in peripheral blood leukocytes of individuals with AD compared to normal controls. PDE, localized in macrophages, lymphocytes, and neutrophils, has been shown to decrease cyclic adenosine monophosphate (cAMP), causing a generalized overexpression of many proinflammatory cytokines. This led to the proposal that PDE-4 inhibition might be anti-inflammatory and to the development of the topical boron-

based small molecule PDE-4 inhibitor, crisaborole; phase III trials of this agent have been completed and publication of the results are pending.

The oral PDE-4 inhibitor apremilast was evaluated for the treatment of AD in a pilot study, with good results²⁰; it also is being evaluated in clinical trials. Apremilast currently is approved for the treatment of moderate to severe plaque psoriasis. The IL-12/IL-23p40 antagonist, ustekinumab, also currently approved for the treatment of moderate to severe plaque psoriasis as well as psoriatic arthritis, is being investigated in AD. In addition, one case report has been published on the use of this agent for severe, refractory AD in an adolescent patient.²¹

The results of phase II trials with another new agent, dupilumab, showed promising results,²² and the results of recently completed phase III trials are pending publication. Dupilumab targets the IL-4 and IL-13 receptor α chain.

With the goal of providing an improved treatment for managing AD-associated pruritus, an IL-31 receptor antagonist, nemolizumab, is being evaluated in phase II clinical trials; an IL-31 antagonist is in an earlier stage of development. Other pharmacologic targets currently being investigated include inhibitors of TSLP, chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRT_H2), IL-13 alone, IL-22, and immunoglobulin E. Further discussion of these agents and other new and emerging therapies for AD can be found in the article “Assessing the New and Emerging Treatments for Atopic Dermatitis,” on pages 92-96 of this supplement.²³

Conclusion

Numerous studies within the past decade have provided valuable insights into the pathophysiology of AD and the other diseases that comprise the triad known as the atopic march. In AD, the existence of a skin barrier abnormality has been implicated, but genetic, environmental, and immunologic factors combine to create a complex and heterogeneous clinical picture of onset of the disease, as well as its severity and course. It is clear that skin barrier events are important in AD pathogenesis; it is becoming evident that correct identification of a barrier defect early in life may alter the natural course of AD and perhaps related phenotypes as well. Once AD develops, a number of secondary immunologic events, which maintain and promote the disease, are likely targets for pharmacologic intervention.

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