Atopic dermatitis (AD) is the most common, allergic skin disease in the general population (1). It often predates the onset of food allergy, asthma and allergic rhinitis (the so-called atopic march) and adversely impacts the quality of life of patients and their families. A recent study revealed a striking association between mental health disorders and AD, suggesting the need to effectively manage this disease for patient’s general well being (2). The February 2013 theme issue of The Journal of Allergy and Clinical Immunology highlights the important role of skin barrier abnormalities in the pathophysiology of AD (3,4). There are 4 critical elements of the skin barrier involved in AD: the physical barrier (including filaggrin, and tight junctions); the chemical barrier including antimicrobial peptides (AMPs), S100 family members, lipids and filaggrin breakdown products, the microbiome or microbial barrier which usually consists of commensal organisms on the normal skin but is often replaced by *Staphylococcus aureus* during flares of AD; and the immunologic barrier which is elicited with breach of the physical barrier and is characterized acutely by enhanced Th2 and Th22 responses (5).

The stratum corneum is the first line of defense between the host and its environment, and represents the culmination of a complex cell differentiation process in which keratinocytes progress from a cell proliferative state in the basal epidermal layer to form a strong but resilient physical barrier of cross-linked lipid protein matrix which minimizes water loss and protects the body from allergen or microbial penetration. Loss-of-function mutations in the filaggrin gene (FLG), which encodes a major structural protein in the stratum corneum, have been shown to be the most significant risk factor for AD (6), particularly the subset of AD prone to eczema herpeticum (7). These findings established the importance of skin barrier dysfunction in driving the inflammatory skin process in AD and potential susceptibility to infection. FLG null mutations lead to enhanced allergen penetration through the skin, systemic IgE sensitization to environmental allergens and confers risk for eczema associated asthma, food allergy and allergic rhinitis (4). Filaggrin breakdown products [e.g trans-urocanic acid (UCA) and pyrrolidone-5-carboxylic acid (PCA)] contribute to natural moisturizing factor involved in epidermal hydration, and also acidification of the skin. An acidic pH has an antimicrobial effect, and modulates proteases required for epidermal
Recent studies also indicate that a reduction in filaggrin contributes to the generation of IL-1, contributing to the inflammatory cascade leading to AD (8). The importance of filaggrin is further reinforced by the observation that intragenic copy number variation within the filaggrin gene contributes to the risk of AD with a dose-dependent effect (9). Approximately 50% of moderate to severe AD can be attributed to FLG null mutations whereas up to 15% of mild to moderate AD can be explained by FLG mutations (4, 10). Patients who are heterozygous for FLG can also outgrow AD. This suggests that, aside from FLG mutations, there are other host and environmental factors contributing to the natural history of AD.

Patients with AD are often colonized or infected with S. aureus. To assess the relationship between skin microbiota and disease progression, Kong et al (11) performed 16S ribosomal RNA bacterial gene sequencing on DNA from serial skin sampling of children with AD. In AD, the proportion of Staphylococcus sequences, particularly S. aureus, was greater during disease flares than at baseline or post-treatment, and correlated with worsened disease severity. Studies of patients with AD reveal that they are deficient in their production of keratinocyte derived antimicrobial peptides needed to control S. aureus replication (12). Recent studies have also revealed that filaggrin breakdown products can inhibit the growth of S. aureus and control the expression of molecules mediated the adhesion of S. aureus to the epidermis (13). Filaggrin has also been found to protect against staphylococcal alpha toxin mediated keratinocyte cell death (14).

Tight junctions (TJs) are a second skin barrier structure found on opposing membranes of keratinocytes in the stratum granulosum, directly below the stratum corneum. TJs consist of a complex of adhesive proteins controlling the passage of water, and solutes via the paracellular pathway in the skin. The susceptibility of human keratinocytes to HSV-1 infection is inversely related to the degree of cell-cell contact and confluency (15). The AD epidermis has bioelectric abnormalities indicative of a TJ defect thought to be the consequence of reduced levels of claudin-1 (CLDN1), a key TJ protein (16). In AD, an inverse correlation was found between CLDN1 expression and markers of TH2 polarity (total eosinophil counts and serum total IgE). Preliminary studies also suggest that genetic variations in CLDN1 contribute to risk of EH in AD subjects. Furthermore, excluding subjects with a FLG mutation strengthened the association of CLDN1 mutations with susceptibility to EH. These data suggest that both stratum corneum and TJ epidermal barrier defects participate in mechanisms that increase the susceptibility of subjects with ADEH+ to widespread cutaneous infections with HSV.

Once the physical barrier is breached, a rapid, first line innate immune response must be initiated to prevent further microbial invasion, while simultaneously activating the adaptive immune response, which is more specific and has more long lasting memory (4). Keratinocytes express a number of innate immune
receptors also referred to as pattern recognition receptors of which Toll like receptors (TLRs) are the best known. Stimulation of TLRs by microbes or tissue injury leads to release of antimicrobial peptides, cytokines and chemokines and enhanced strength of TJs to limit penetration of allergens and microbes (3). Patients with AD have been found to have reduced TLR function. This may predispose to *S. aureus* colonization and chronic skin inflammation.

The adaptive immune response in AD is associated with increased expression of Th2 and Th22 cytokines, IL-4, IL-13, and IL-22 (5). These cytokines reduce epidermal differentiation and thereby contribute to reduced filaggrin expression. Epidermal keratinocytes in AD express increased thymic stromal lymphopoietin (TSLP), a cytokine that enhances dendritic cell driven Th2 cell differentiation (17). Mechanical injury, allergen exposure and microbial infection increases TSLP, IL-25 and IL-33 and may thereby increase Th2 responses (18). The maintenance of chronic AD involves persistent production of Th2 and Th22 and a concomitant increase in interferon gamma expression leading to intensification and persistence of immune activation with epidermal proliferation (5). Gene profiling studies have also demonstrated a reduction in systemic interferon responses that limit adaptive responses to disseminated viral infections such as eczema herpeticum (19).

Overall the complex picture of a leaky epithelial skin barrier combined with disruption of the microbial barrier, a defective innate immune response and adaptive immune abnormalities provides an explanation for the different AD subsets leading to complex clinical phenotypes. Indeed the clinician has long appreciated that AD is associated with different ages of onset, varying durations of illness, differing degrees of allergen sensitization, associated allergic diseases such as asthma, rhinitis and food allergy, differences in treatment responses, and susceptibility to skin infection.

Classification of distinct AD subsets will allow targeted therapy in the future (20). As an example, patients with filaggrin mutation, particularly those who have homozygous or compound heterozygous mutations, will have early onset, persistent and severe AD often associated with the development of asthma and systemic allergen sensitization (4). These patients are also prone to recurrent *S. aureus* infection and eczema herpeticum. Filaggrin replacement or upregulation via anti-inflammatory approaches are being pursued (21-23). Patients with wild type FLG genes, will have milder AD with lower risk of asthma and less allergen sensitization. Patients with low vitamin D level may respond to prophylactic oral vitamin D known to enhance skin barrier function and innate immune responses needed to combat infection especially during the winter (24). IgE to specific allergens may also be more likely to respond to allergen immunotherapy. Importantly patients with persistent AD require maintenance anti-inflammatory therapy combined with skin barrier repair since they often have subclinical inflammation which breaks through when they completely wean off anti-inflammatory therapy.
References


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