New Insights into Atopic Dermatitis: Role of Skin Barrier and Immune Dysregulation

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ABSTRACT
Atopic dermatitis (AD) is a chronic inflammatory skin disease that is often associated with the development of food allergy and asthma. New insights into AD reveals an important role for structural abnormalities in the epidermis resulting in a leaky epithelial barrier as well as chronic immune activation that contribute to the pathophysiology of this common skin disease. Patients with AD have a predisposition to colonization or infection by microbial organisms, most notably Staphylococcus aureus and herpes simplex virus (HSV). Measures directed at healing and protecting the skin barrier and controlling the immune activation are needed for effective management of AD. Early intervention may improve outcomes for AD as well as reduce the systemic allergen sensitization that may lead to associated allergic diseases in other organs.

KEY WORDS
atopic dermatitis, eczema, immune, infection, skin barrier

INTRODUCTION
AD is a common chronic inflammatory skin disease that is often associated with the development of food allergy and asthma.1 Recent studies reveal strong associations between mental health disorders and AD, suggesting the need to effectively manage this disease for patient’s general well being.2,3 Lifetime prevalence of AD varies worldwide from approximately 8-18%.4 A recent report in Shanghai, China reported that the prevalence of AD was significantly higher in urban areas of Shanghai compared to rural areas of this city.5 Life style and environmental factors likely contribute to clinical expression in AD.6-9 In Japan, environmental oxidants have been implicated in the changing prevalence of AD.10 Stress, such as experienced by patients during the Great Hanshin earthquake, has also been well documented to exacerbate AD.11

The skin is an important interface between the host and its environment. A leaky skin epithelial barrier combined with abnormal immune responsiveness likely contributes to the pathophysiology of AD.12,13 The current review will highlight recent insights into the role of skin barrier, environmental factors and immune dysfunction leading to AD. The effective treatment of AD requires a multi-pronged approach involving skin barrier repair, control of skin inflammation, identification and management of allergenic triggers, as well as treatment of microbial infection.14

CLINICAL FEATURES AND PHENOTYPES OF AD
New insights into mechanisms of AD should address the key clinical features of AD as well as explain the different phenotypes associated with this skin disease.15 The cardinal feature of AD is severe pruritus that is associated with cutaneous hyperreactivity to various environmental stimuli including exposure to food and inhalant allergens, irritants, changes in physical environment (including pollution, humidity, etc), microbial infection and stress. After patients scratch their skin, an acute eczematoid eruption (with erythematous papules) appears, and lichenification with epidermal hyperplasma results from chronic eczema. This is in contrast to patients with chronic idiopathic urticaria that develop hives but not eczema after scratching, and highlights potential differences in mechanisms between chronic idiopathic urticaria (e.g. autoantigen induced mast cell degranulation...
without skin barrier dysfunction) as opposed to AD which stems from skin barrier dysfunction, and increased penetration of antigens which drive mononuclear cell infiltration and chronic skin inflammation.16

Multiple overlapping, but distinct, clinical phenotypes of AD exist (Table 1). Most infants who present with mild AD will outgrow their skin disease in later childhood. However, a group of difficult to manage patients exist who have early onset eczema, with severe life long AD. Adult onset AD also exist although it is unclear whether these may be patients that had eczema during infancy, then went into a prolonged remission only to have relapse of eczema later in life since recall history, in such cases, may not be reliable. Over 50% but certainly not all AD have associated asthma, allergic rhinitis or food allergy. Approximately 80% of AD patients have elevated serum IgE and/or immediate skin test reactivity to allergens but 20% of AD have no IgE to food or inhalant allergens. However, it is possible that such intrinsic or non-atopic patients may have IgE or autoreactive T cells to autoallergens or microbial antigens which are not routinely measured.17-20 Other AD subsets exist including those who are prone to skin infection such as Staphylococcus aureus skin infections or eczema herpeticum.21,22 Although up to 90% of AD may have problems with S. aureus skin colonization, actual overt skin infections requiring systemic antibiotic treatment affect less than 50% of AD. Less than 5% of AD are predisposed to eczema herpeticum or eczema vaccinatum.23 These different phenotypes likely arise from a complex combination of mutations and epigenetic effects on genes controlling protein expression in the skin barrier, innate and adaptive immune response with a strong environmental influence.

**EPITHELIAL SKIN BARRIER ABNORMALITIES IN AD**

**Multi-Functional Role of Filaggrin**

The skin barrier plays a critical role in host defense against microbial invasion, and allergen penetration. The stratum corneum represents the culmination of a complex epithelial cell differentiation process in which keratinocytes produce a strong but resilient physical barrier of cross-linked matrix containing lipids and proteins which minimize water loss and protects the body from allergen or microbial penetration.

Recent studies indicate that defects in epidermal barrier function contribute greatly to triggering and perpetuation of skin inflammation in AD.12,13 The skin in AD is characterized by increased transepidermal water loss, and a defect in terminal keratinocyte differentiation leading to reduced levels of ceramides, filaggrin and antimicrobial peptides.24-29 Concomitantly increased protease activity and proinflammatory cytokine release resulting from increased endogeneous keratinocyte and mast derived proteases released in atopic skin as well as exogenous proteases from environmental allergens, such as dust mites, or S. aureus results in skin barrier breakdown.30,31

In normal subjects, formation of the cornified cell envelope involves dephosphorylation and cleavage of profilaggrin by serine proteases ending in the release of filaggrin.13 Filaggrin aggregates the keratin cytoskeleton to facilitate the flattening of keratinocytes in the outermost skin layer. Additionally, other proteins encoded by genes in the epidermal differentiation complex including loricrin and involucrin are essential components of the epidermal barrier.32 As the water content of the stratum corneum drops, filaggrin is proteolyzed into pyrrolidine carboxylic acid and trans-urocanic acid which contribute to the composition of natural moisturizing factor (NMF) and accounts in part for corneocyte hydration.33 Filaggrin deficiency in AD contributes to decreased hydration of the stratum corneum and increased transepidermal water loss.34

Importantly, filaggrin breakdown products play an important role in acidifying the stratum corneum and decreased generation of filaggrin metabolites increases the pH of the stratum corneum leading to activation of a number of serine proteases and may thereby increase barrier breakdown.35 A recent in vitro study demonstrated that S. aureus growth rate and cell density were affected by the acidic filaggrin breakdown products urocanic acid and pyrrolidone carboxylic acid.36 Lower pH was associated with reduced expression of secreted and cell wall-associated proteins, including proteins involved in S. aureus adherence to the skin such as clumping factor B and fibronectin binding protein A, as well as protein A, which is involved in immune evasion.

The critical role of skin barrier dysfunction as a causative factor in AD is supported by reports demonstrating that loss-of-function mutations in the filaggrin gene (FLG) are the most significant and well replicated risk factor for development of AD.13,37 FLG mutations increase the risk for persistent dry skin,38 enhance percutaneous immune responses39 and is associated with increased expression of IL-1 in the stratum corneum of patients with AD.40 Filaggrin has also been found to protect against staphylococcal alpha toxin mediated keratinocyte cell death.41 The skin barrier abnormality caused by FLG mutations is also associated with increased serum 25-hydroxy vita-

**Table 1 Different phenotypes of atopic dermatitis**

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Fig. 1 Immunologic pathways involved in different phases of atopic dermatitis. Published with permission from: Gittler JK, Shemer A, Suárez-Fariñas M, et al. Progressive activation of TH2/TH22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol 2012; 130: 1344-54.

Min D concentrations.

Filaggrin null mutations affect a minority of subjects with AD. Reduction in filaggrin are often observed even in the skin of AD patients who have no detectable FLG null mutations. In this regard, intragenic copy number variation within the filaggrin gene has been demonstrated to contribute to the risk of AD with a dose-dependent effect. Furthermore, a variety of cytokines have been found to reduce filaggrin expression including IL-4, IL-13, TNF and IL-25. Proteomic profiling of AD skin have revealed found that multiple other proteins related to the skin barrier (filaggrin-2, corneodesmosin, desmoglein-1, desmocollin-1, and transglutaminase-3) and generation of natural moisturizing factor (arginase-1, caspase-14, and gamma-glutamyl cyclotransferase) were expressed at significantly lower levels in lesional, as compared to nonlesional, sites of patients with AD. These studies are supported by genomic and histologic profiling studies of AD skin revealing broad termination epidermal differentiation defects. Thus, a combination of genetic and acquired factors contribute to reduced epidermal differentiation, and downregulation of epidermal barrier function.

Tight Junction Abnormalities: A Second Defect in the Physical Barrier of AD

Gene expression profiling of nonlesional epithelium from patients with extrinsic AD, nonatopic subjects, and patients with psoriasis recently revealed a strikingly lower level of the tight junction proteins, claudin-1 and claudin-23, in patients with AD. Tight junctions are found on opposing membranes of stratum granulosum keratinocytes directly below the stratum corneum and thereby form a second physical barrier in the epidermis (Fig.1). They are made up of a complex of adhesive proteins that control the passage of fluids and solutes through the paracellular pathway. The nonlesional epithelium of AD subjects has been shown to have bioelectric abnormalities indicative of a tight junction defect which could be the consequence of reduced levels of claudin-1 (CLDN1), a key tight junction adhesive protein. This is consistent with earlier work in CLDN1 knockout mice that established the importance of epidermal tight junctions and claudin-1. CLDN1 knockout mice died...
within 24 hours of birth with severe dehydrated and increased epidermal permeability as measured by dye studies and transepidermal water loss. The susceptibility of human keratinocytes to HSV-1 infection is inversely related to the degree of cell-cell contact and confluency maintained by claudin-1 levels. In AD, an inverse correlation was found between CLDN1 expression and markers of Th2 polarity (total eosinophil counts and serum total IgE).

**IMMUNE RESPONSES IN AD**

Once the 2 physical barriers (filaggrin, tight junctions) are breached, a rapid, innate immune response must be initiated to prevent further microbial invasion and replication. Keratinocytes and antigen presenting cells in the skin 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. Patients with AD have been found to have reduced TLR function. Studies of patients with AD reveal that they are deficient in their production of keratinocyte derived antimicrobial peptides needed to control S. aureus and viral replication. This may predispose to microbial colonization and chronic skin inflammation.

The adaptive immune response in AD is associated with increased expression of the Th2 cytokines (IL-4, IL-13 and IL-31) and the Th22 cytokine, IL-22 during the acute phase of AD (Fig. 1). These cytokines reduce epidermal differentiation and thereby contribute to reduced filaggrin expression and anti-microbial peptide expression. IL-31 induces severe pruritus in addition to its inhibitory effects on epidermal differentiation. The complex cytokine profile that evolves after formation of acute AD lesions, includes a rise in interferon-gamma which induces apoptosis of keratinocytes. These effects, however, can be counterbalanced by IL-10 which controls dendritic cell induced T cell reactivity in the skin. Corticotropin-releasing hormone (CRH) has recently been found to downregulate IL-10 production by adaptive forkhead box protein 3-negative regulatory T cells in AD.

Although AD is known as a Th2- and Th22 mediated inflammatory skin disease whereas psoriasis is known as a Th1/Th17 mediated skin disease, there may be other AD subsets. Indeed, IL-17 expression has been reported in mouse models of eczema. Recently, a comparative transcriptomic analyses of AD and psoriasis revealed evidence for increased IL-17 gene expression and shared neutrophil inflammation in these two skin diseases.

Dendritic cells are recognized as one of the key cells involved in the initiation of T cell responses in various skin diseases. In AD, dendritic cells such as Langerhans cells and inflammatory dendritic epidermal cells express increased levels of FceRI as well as reduced interferon responses. Blocking H1 histamine receptor signaling of dendritic cells dampened allergen driven skin immune responses. Epidermal keratinocytes in AD express increased thymic stromal lymphopoietin (TSLP), a cytokine that enhances dendritic cell driven Th2 cell differentiation. IL-25 and IL-33, released from multiple cell types including keratinocytes and type 2 innate lymphoid cells, also augment Th2 responses and can activate eosinophils and mast cells. Mechanical injury, allergen exposure and microbial infection increases TSLP, IL-25 and IL-33 thus increasing Th2 responses.

A critical link between the barrier defect in AD patients with FLG mutations and Th2 polarization can explained by enhanced allergen penetration through the damaged epidermis accompanied by increased production of TSLP, IL-25 and IL-33 by keratinocytes and other skin cells leading to a Th2-type milieu. TSLP, in particular, may act as a “master switch” for allergic inflammation since it has effects on a number of key cells involved in cutaneous allergic inflammation, including mast cells, basophils and eosinophils. The clinical observation that topical calcineurin inhibitors and topical corticosteroids can partially correct the barrier defect in AD supports the concept that inflammation or immune activation can downregulate the barrier function in AD and that there is cross talk between the epidermal barrier and the immune system.

**DEFINING AD SUBSETS FOR BETTER MANAGEMENT APPROACHES**

Recent advances in the genetics and pathophysiology of AD have contributed to our understanding of endotypes in AD. Endotypes have been proposed in asthma which is recognized to be a complex disease or syndrome that can be divided into distinct disease entities based on distinct pathophysiological mechanisms, referred to as “asthma endotypes”. The importance of eventually defining endotypes in AD is that these new subtypes can be used in clinical study design and drug development to target existing and novel therapies to patients most likely to benefit from a mechanism-based treatment. In the future, AD may be characterized by genotype, biomarkers reflecting immune polarization and the clinical phenotype.

Multiple clinical phenotypes have been described in AD (Table 1). Childhood AD is common, with more than 60% of patients having onset of disease within the first 2 years of age. Complete clearance of childhood AD occurs in approximately 50% of patients. The remainder have recurrences in adolescence and adulthood. Adult onset of AD can also occur without a history of childhood AD. In all forms of AD, clinical phenotypes can be further stratified according to mild vs severe forms and their various trig-
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Fig. 2  Comparison of clinical and biophysical features of atopic dermatitis patients with (AD\textsubscript{FLG}) and without (AD\textsubscript{NON-FLG}) filaggrin mutations. Published with permission from: McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. J Allergy Clin Immunol 2013; 131: 280-91.

gers including bacterial and viral infection. There has also been considerable interest in the group who undergo the atopic march which refers to AD patients with associated food allergy who develop asthma or allergic rhinitis later in childhood as this provides an opportunity to develop preventative approaches to prevent respiratory allergy. High systemic sensitization to food and inhalant allergens may occur in AD due to penetration of these environmental allergens through the damaged skin barrier of these patients.

Genetic studies have revealed the association of mutations which are beginning to distinguish certain endotypes of AD. The strongest data involves identification of patients with filaggrin mutations.\textsuperscript{13} AD patients with homozygous filaggrin null mutations or compound heterozygotes, as compared to patients with normal filaggrin gene expression, have early onset of skin disease, more persistent, and severe eczema which can be complicated by eczema herpeticum\textsuperscript{13,73} (Fig. 2). They also often have palmar hyperlinearity, greater risk of allergen sensitization, a history of food allergy and develop asthma.\textsuperscript{74,75} These patients also have an increased pH in their stratum corneum which may predispose them to \textit{S. aureus} colonization.\textsuperscript{36} Patients who have heterozygous filaggrin mutations have an intermediate phenotype.

Although filaggrin mutations are the most significant and well replicated genetic mutation associated with AD, filaggrin mutations account for only a minority of total AD although up to 50% of severe AD can have filaggrin mutations.\textsuperscript{13} Many other genes involving skin barrier responses as well as the innate and adaptive immune response have also been implicated reinforcing the concept that AD is a complex genetic disease.\textsuperscript{15,76-78} These include various genes controlling skin barrier function such as mutations in the serine protease inhibitor Kazal-type 5 (SPINK5) gene, which encodes the protease inhibitor lymphoepithelial Kazal-type-related inhibitor (LEKTI).\textsuperscript{79} In a murine model of AD generated by epidermal LEKTI deficiency,\textsuperscript{80} severe eczema and increased TSLP production was observed mimicking some of the critical features in AD. Genetic variants in CLDN1 are also associated with risk of eczema herpeticum in AD subjects.\textsuperscript{49} 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.

Gene variants may also contribute to the abnormal
innate immune response and Th2 adaptive responses found in AD. These include the observation that certain Toll-like receptor 2 (TLR2) variants are associated with severe AD.81 A recent study found an increased association between genes encoding TSLP and its receptors, IL7R, with risk of eczema herpeticum.82 Association between gene variants encoding for the Th2 driving cytokines IL-483 and IL-13,84 and the down-stream transcription factor STAT685 support the importance of Th2 responses in AD. A common haplotype encoding IL-31, a cytokine which induces severe pruritus, has been reported to be associated with the intrinsic/non-IgE-associated form of AD.86 These findings point to the importance of both barrier and immune response genes in driving the complex phenotype of AD.

Given the complex genetic picture of AD, the development of biomarkers is important to assess the final immune polarized pathways that may exist in various AD subsets. The best biomarkers for AD currently define patients who are Th2 polarized vs those who are not. Approximately 80% of AD have elevated serum IgE levels. These patients often have increased eosinophilia and serum levels of the Th2 chemokine, thymus and activation regulated chemokine (TARC) levels. Additional markers are needed to better monitor AD patients with so-called intrinsic AD. It is noteworthy, however, that studies of so-called intrinsic AD patients who lacked IgE to conventional inhalant and food allergens did have detectable serum IgE to autoantigens in the skin and microbial antigens from bacterial and fungi that colonize the skin.19,87 Therefore a wider range of IgE screens to various exogenous and endogenous antigens is warranted to determine potential triggers of AD as it may have an important impact on pathways triggering allergic skin inflammation. Overall the various causes of a leaky epithelial skin barrier leading to disruption of the microbial flora, a defective innate immune response and enhanced Th2 adaptive immune abnormalities that influences the physical barrier provides some explanation for the different AD subsets leading to complex clinical phenotypes.

**TREATMENT AND MANAGEMENT OF AD**

The management of AD requires a systematic, multi-pronged approach. This includes skin hydration and barrier repair, topical anti-inflammatory medications, control of infection and elimination of exacerbating factors (including allergens, irritants and emotional triggers) taking into consideration that AD is a heterogeneous disease requiring an individualized approach for each patient. Treatment should utilize a stepwise approach that is dependent on the severity of skin disease (reviewed in reference 14).

The first step in AD is reduced skin barrier function resulting from lack of structural proteins and lipids in the epidermis (Fig. 3). This leads to enhanced water loss and dry skin. Except for the mildest cases, skin hydration will often require warm soaking baths...
for at least 10 minutes followed by the application of a moisturizer. Moisturizers, available in the form of creams, and ointments should be recommended as first-line therapy. When using the more occlusive ointments, consider pre-wetting the skin before its application. In patients with moderate to severe AD, ceramide rich or filaggrin containing creams may be considered.

The second step in AD is skin inflammation. This is invariably present in patients with moderate to severe AD, even involving their non-lesional skin, since a defective barrier allows allergens and microbes to penetrate the skin thereby triggering the immune and inflammatory response. In AD that is not controlled by emollients alone, a topical anti-inflammatory agent should be used. Low-potency corticosteroids are recommended for maintenance therapy, whereas medium and high-potency corticosteroids should be used for the treatment of clinical exacerbation over short periods of time. Proactive treatment with intermittent medium potency topical steroids and calcineurin inhibitors have been shown to reduce AD relapses.

Jensen et al. looked at transdermal water loss, as well as several other parameters of epidermal barrier including stratum corneum hydration and dye penetration and showed improvement in all parameters when AD patients were treated with both a topical steroid and a topical calcineurin inhibitor. Both treatments normalized markers of epidermal cell differentiation. Of note, while expression of filaggrin was reduced in untreated patients with AD, it was completely restored on treatment with either anti-inflammatory therapy. Coal tar, which has weaker anti-inflammatory effects has also been shown to improve skin barrier in AD.

Another important long-term strategy for patient management is the identification of factors that trigger AD including foods (particularly in infants and young children), aeroallergens, stress and infection. Patients with AD have a unique propensity to be colonized or infected by a number of microbial organisms. To assess the relationship between skin microbiota and disease progression, Kong et al. recently 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. Interestingly, various AD treatments were associated with increased bacterial diversity. S. aureus infection may also predispose AD patients to disseminated viral skin infections. Control of infection generally involves appropriate use of antibiotics. It is important to treat only infections that are clinically overt as most AD patients are colonized with S. aureus and overuse of antibiotics can lead to MRSA infection.

Patients with AD who are refractory to conventional treatment approaches, a number of alternative strategies have been proposed including the use of cyclosporine, methotrexate, azathioprine, immunoadsorption, IL-6 blockade, conventional immunotherapy and ultraviolet light. Vitamin D deficiency is being increasingly recognized as playing a role in allergic diseases. Vitamin D appears to also have several beneficial effects in AD including the upregulation of antimicrobial peptides involved in control of infection as well as induction of T regulatory cells which can suppress inflammation. Preliminary results of a clinical trial in children with AD treated with oral vitamin D in a randomized, controlled trial showed clinical improvement versus placebo. Since current treatment approaches are not curative, there is considerable interest in also studying approaches to prevent AD. The use of probiotic therapy or bacterial lysates early in the course of illness remains an area of active investigation.

CONCLUSIONS

Patients with AD have genetic mutations that affect their skin barrier function and immune responses triggered by unique environmental triggers. A cross-talk occurs such that the immune response can adversely impair skin barrier function in AD. Clinically, this results in intensely pruritic, inflamed skin that allows penetration of irritants and allergens and predisposes patients to colonization and infection by microbial organisms. Insights into the complex relationship between skin barrier and immune abnormalities should lead to more targeted therapy for AD and associated infectious complications. New methods to categorize distinct phenotypes and polarized immune pathways of AD may lead to novel early intervention strategies that could also interrupt the development of asthma and allergic disorders.
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