



Published in final edited form as:

J Allergy Clin Immunol. 2014 October ; 134(4): 769–779. doi:10.1016/j.jaci.2014.08.008.

Deciphering the Complexities of Atopic Dermatitis: Shifting Paradigms in Treatment Approaches

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Abstract

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease. It often precedes the development of food allergy and asthma. Recent insights into AD reveal abnormalities in terminal differentiation of the epidermal epithelium leading to a defective stratum corneum, which allows enhanced allergen penetration and systemic IgE sensitization. Atopic skin is also predisposed to colonization or infection by pathogenic microbes, most notably *Staphylococcus aureus* and herpes simplex virus (HSV). Causes of this abnormal skin barrier are complex and driven by a combination of genetic, environmental and immunologic factors. These factors likely account for the heterogeneity of AD onset, severity and natural history of this skin disease. Recent studies suggest prevention of AD can be achieved by early interventions protecting the skin barrier. Onset of lesional AD requires effective control of local and systemic immune activation for optimal management. Early intervention may improve long term outcomes for AD and reduce the systemic allergen sensitization leading to associated allergic diseases in the gastrointestinal and respiratory tract.

Keywords

atopic dermatitis; eczema; skin epithelium; immune; infection; filaggrin

Introduction

AD is the most common chronic inflammatory skin disease (1,2). 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 and their family's quality of life (3). AD is often associated with food allergy and asthma (4,5). The abnormal skin barrier in AD may allow epicutaneous absorption of environmental allergens through the

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skin and promote systemic allergen sensitization, which predisposes to the development of food allergy and asthma. In this month's journal, researchers report that AD increases the impact of environmental peanut exposure in AD children (6-8). Because there are currently no cures for food allergy and asthma, the development of effective treatments for AD may be an important strategy for prevention of the Atopic March. Elucidation of the underlying mechanisms of AD therefore provides a critical opportunity for early intervention.

AD is a complex disease with a genetic predisposition that is strongly influenced by innate and adaptive immune responses as well as environmental factors including allergen exposure, irritants, microbes, diet, stress, and air quality (9-13). Although it is commonly referred to as a single disease (14), recent studies suggest that the time has come to distinguish various AD phenotypes and endotypes (15,16) in much the same manner in which attempts have been made to categorize asthma and rhinosinusitis into different subtypes based on a constellation of the onset, biomarkers, immune polarization, gene variants and natural history of the disease (17-19). Identification of immune pathway polarity will be of particular importance as biologics become more readily available to target specific immune pathways such as Th2 and Th22 pathways as well as various inflammatory cytokines and mediators (20, 21).

This month's JACI theme focuses particularly on the importance of both genetic and acquired causes of epithelial skin barrier dysfunction in driving the natural history of AD (22-24). Two original articles this month report that early emollient use to protect the skin barrier may prevent AD (25,26). While dermatologists and allergists often debate the relative importance of genetic defects in the skin barrier giving rise to a leaky skin epithelial barrier that allows the penetration of allergens and microbes into AD skin, i.e. the so-called "outside-in hypothesis" as opposed to the "inside-out hypothesis", i.e. a polarized immune response giving rise to the defective skin barrier, this argument is moot in patients with established AD as both processes are equally important (Figure 1). The majority of AD patients constitute admixtures of genetic defects in their skin barrier and immune responses strongly influenced by environmental factors. The current review will highlight recent insights into the crosstalk between the skin barrier and immune dysfunction leading to AD. Effective prevention and treatment of AD requires a multi-pronged approach involving the maintenance of skin barrier integrity, control of skin inflammation, nutrition, identification and management of allergenic and microbial triggers (27).

Complex Causes of Epithelial Skin Barrier Dysfunction in AD

Multi-functional Role of Filaggrin—The robust association of loss of function mutations in the skin barrier gene encoding filaggrin (*FLG*) with risk of AD has focused attention on the important role of epithelial barrier dysfunction in this skin disease (28, 29). Patients with filaggrin mutations have been found to have dry skin, early onset AD that is more persistent and often associated with asthma, food allergy and microbial infection (30-32). Recent studies suggest that stratification of patients with vs without filaggrin mutations identifies patients with different mechanistic pathways of inflammation (Table 1). Patients with filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in their stratum corneum and type 1 interferon-mediated stress response

(33, 34). AD children with normal filaggrin genes have been reported to have dysregulation of lipid metabolic processes (34). Filaggrin dependent secretion of sphingomyelinase has also been found to protect against Staphylococcal alpha-toxin-induced keratinocyte death (35). This strongly suggests that patients with filaggrin mutations are a distinct endotype of AD with different mechanistic outcomes (Table 1), which could be used to identify one subset of AD, particularly for the development of new therapies targeting skin barrier function.

Clinical expression of AD is dependent on gene-environment and gene-gene interactions. Gene-environmental interactions is best illustrated in filaggrin deficient mice where exposure of the skin to allergens or microbes predictably leads to the development of eczema (36). Three recent articles in JACI demonstrate that environmental peanut may drive sensitization to peanut allergy in AD patients particularly those with filaggrin mutations is a clinically relevant example of the importance that environmental exposures in house dust may contribute to allergen sensitization in AD (6-8).

The importance of gene-gene interactions is illustrated in Flaky Tail mice, an animal model of AD that spontaneously develops eczema under pathogen-free conditions. These mice carry a double mutation involving the *matted* (*ma*) gene giving them a matted hair phenotype as well as a deletion in *FLG*. It was originally thought that the filaggrin deficiency in Flaky Tail mice explained the propensity of these mice to develop AD. Surprisingly, the derivation of genetically engineered filaggrin-deficient mice that were free of the *ma* gene mutation, were found to display impaired barrier function but to lack the propensity to spontaneously develop eczema (37, 38). The matted phenotype in flaky tail mice was found to be due to a loss-of-function mutation in the *Tmem79* gene. Unexpectedly, the *Tmem79* mutation rather than the deletion in *FLG* was found to be associated with the development of dermatitis in mice. Interestingly, *Tmem79* encodes lamellar granules that are required for processing of filaggrin, lipids, proteases and antimicrobial peptides (22). Saunders et al (37) has also found that a single nucleotide polymorphism in the human *TMEM79* gene confers a significant risk for AD in humans, even when controlling for the effect of *FLG* mutations, suggesting both genes are involved in AD and the need for gene-gene interactions.

Depending on the population, *FLG* mutations are found in up to 40% of patients with severe AD, but less than 20% of these severe patients are homozygous or compound heterozygotes for *FLG* mutations (39). Furthermore, only a minority of European American and Asian, and none of the African American patients with AD have *FLG* mutations (28,29, 40, 41). Reduction in filaggrin expression are also pronounced in the skin of AD patients who have no detectable *FLG* null mutations but are most profound when combined with *FLG* mutations (42). Thus, there are multiple causes for the low *FLG* expression in the skin. The most common reason is likely to be immune activation (42-44). Intragenic copy number variation within the filaggrin gene also contributes to the risk of AD with a dose-dependent effect (45). The expression of *FLG* gene expression can also be reduced by epigenetic modification (46).

Skin Barrier Dysfunction- beyond filaggrin—Aside from *FLG*, AD has been associated with variants in other genes that encode a cluster of proteins in the epidermal differentiation complex located on chromosome 1q21 (47). These include filaggrin-2 (48), hornerin (49) and the cornified envelope precursor, *SPRR3* (50). It is noteworthy, however, that unlike *FLG*, the biologic function of these EDC gene variants as it relates to AD are not well understood. A substantial amount of information, however, indicates that loss of function mutations in serine protease inhibitors (e.g. *SPINK5*), augments protease activated pathways that enhance Th2 responses supporting the argument that epidermal barrier dysfunction can induce allergic skin diseases (23). This complexity in epidermal gene variants is further modified by variants in genes that control innate and adaptive immune responses (reviewed in references 9 and 51).

The normal skin can be viewed as containing a series of interrelated barriers whose function is retention of moisture and to repel penetration of the skin with allergens and microbial invasion. Once the stratum corneum is breached, e.g. due to a deficiency of structural proteins such as filaggrin, involucrin, loricrin and/or lipids such as ceramides, other barrier structures are engaged (Figure 2). These includes tight junction proteins, such as the claudins, which are found on opposing membranes of stratum granulosum keratinocytes directly below the stratum corneum and thereby form a second physical barrier in the epidermis (51). Gene profiling in AD epidermis have revealed downregulation of claudin protein and function in AD. Once these 2 physical barriers (filaggrin, tight junctions) are breached, a rapid, innate immune response must be initiated to prevent further microbial invasion. Keratinocytes and antigen presenting cells in the skin express innate pattern recognition receptors such as Toll like receptors (TLRs). Stimulation of TLRs by microbes or tissue injury leads to the release of antimicrobial peptides, and enhanced strength of TJs to limit penetration of allergens and microbes (51). Patients with AD have reduced TLR function.

Loss of skin barrier function and increased severity of AD predisposes to microbial colonization and chronic skin inflammation. This is due to increased expression of tissue receptors for *Staphylococcus aureus* that leads to colonization of *S. aureus* in atopic skin (52, 53). Keratinocytes from AD skin have also been found to be deficient in their ability to produce antimicrobial peptides that are needed to control *S. aureus* and viral replication (54,55). Interestingly commensal bacteria also produce antimicrobial peptides capable of controlling *S. aureus* growth (56). *S. aureus* produce high levels of serine proteases that can degrade skin barrier (57). Therefore an overabundance of *S. aureus* in poorly controlled AD can reduce barrier function via multiple mechanistic pathways.

Immune mediated barrier dysfunction—Although there are strong arguments for the “outside-in” hypothesis suggesting that AD is fundamentally a disease of fixed (genetic) epidermal barrier defects (22, 23), there are equally compelling arguments that some forms of AD are primarily driven by polarized immune pathways that downregulate keratinocyte terminal differentiation thereby creating a secondary skin barrier defect. The arguments against a primary role of the barrier defect in triggering keratinocyte hyperplasia and secondary immune activation include: 1) The *FLG* mutation is absent in most AD patients (28, 29, 58); 2) The majority of children with AD outgrow their disease even in the presence

of a *FLG* mutation (59); 3) Unlike ichthyosis vulgaris where the entire skin is affected at birth, in the same genetic background AD patients with *FLG* mutations have both lesional and non-lesional skin, and the disease develops at some later time-point and does not start at birth; 4) Both lesional and non-lesional AD skin exhibit a broad range of differentiation abnormalities beyond filaggrin (loricrin, involucrin, corneodesmosin, claudins, etc), suggesting reactive epidermal differentiation/cornification alterations (60, 71); 5) treatment of keratinocytes with IL-4, IL-13, IL-22, IL-25 and IL-31 directly downregulate filaggrin expression and increases kallikrein function which can directly cause barrier dysfunction (21, 23, 42-44, 61, 62). IL-22 directly induces keratinocyte hyperplasia, and down-regulation of filaggrin expression (63, 79); 6) mice that are genetically engineered to overexpress Th2 cytokines in their skin spontaneously develop AD and *in vivo* skin barrier defects (64-67); 7) Filaggrin expression is restored using anti-inflammatory regimens with either topical calcineurin inhibitors or topical corticosteroids (68); 8) Finally, the strongest argument is resolution of clinical AD disease activity in moderate to severe patients with broad based immunosuppressive therapies such as cyclosporine or narrow band UV phototherapy (69, 70), and immune targeted therapeutics (dupilumab), that is coupled with resolution of the abnormal epidermal responses (20).

It is noteworthy that AD skin lesions are always associated with underlying immune activation (71-73). In chronic AD, several underlying features are invariably present: 1) increased skin infiltration by T-cells (approx. 10-fold increase over background T-cell levels in normal skin); 2) increased skin infiltration by myeloid (CD11c+) dendritic cells (DCs) (also approx. 10-fold increase over normal skin levels), with most DCs having an “inflammatory phenotype” (BDCA1-/CD11c+) (74); 3) increased production of cytokines and chemokines by activated T-cells and DCs within skin lesions, as measured by quantitative mRNA measures for individual molecules, and by immunohistochemical detection of associated protein products in skin lesions; and 4) reactive epidermal hyperplasia or “regenerative maturation,” showing an unusual hyperplasia response in which mRNAs and proteins of epidermal cornification are highly suppressed in the associated epidermis (21, 75-77).

Immune Pathways Driving AD Skin Lesions—In AD patients with elevated IgE levels, non-lesional AD is associated with a selective expansion of Th2 cells in a dermal perivascular distribution (72). The acute initiation of AD skin lesions is associated with Th2, Th22, and also Th17 cytokine activation (see Figure 3). In parallel, there are epidermal (S100) responses marked by an extremely high increase in the expression of the pro-inflammatory epidermal differentiation complex (EDC) cluster-encoded S100A (S100A7-9) genes, known to be regulated by IL-22 and IL-17 cytokines (78, 79). In chronic AD, intensification of Th2 and Th22 activation occurs with the appearance of a significant Th1 component, but not a complete switch to Th1 (21). Although Th2 cytokine effects remain during chronic AD, the rise in interferon gamma contributes to the inflammatory response and causes keratinocyte apoptosis (80).

In the last decade, Th2 and Th22 cytokines have been reported to modulate the epidermal barrier, including suppression of keratinocyte differentiation, hyperplasia, apoptosis of keratinocytes, and production of antimicrobial peptides (AMPs) (42-44, 54, 81-84). The

cytokine effects include: 1) Suppression of terminal differentiation genes such as filaggrin (FLG), loricrin (LOR) and involucrin (IVL) by Th2 cytokines (IL-4, IL-13, IL-31) and Th22/IL-22 cytokines; 2) Inhibition of AMP production by the Th2 cytokines (IL-4, IL-13); 3) Upregulation of S100As by IL-17 and IL-22 (21, 83-85); and 4) Induction of epidermal hyperplasia by the Th22 IL-22 cytokine (78).

AD disease activity (quantified by SCORAD) has also been shown to positively correlate with lesional and non-lesional skin expression of Th2 and Th22 mediators (i.e IL-13, IL-22), and negatively with expression of terminal differentiation markers (71, 81-84). Although immune activation is significantly higher in lesional than in non-lesional skin, impressive reductions in expression of a broad array of epidermal differentiation genes (i.e., loricrin, periplakin, and involucrin, in addition to filaggrin) characterize both lesional and non-lesional AD skin. Since Th2 (IL-4/IL-13) and Th22 (IL-22) cytokines have been shown to inhibit expression of terminal differentiation products in keratinocytes, increased circulating levels of these cytokines may cause this global suppression of barrier proteins as well as the increases in S100As detected in onset of acute lesions (21).

Implications of AD Pathobiology for General Management Approaches

Patients with established AD, will have a combination of skin barrier dysfunction and skin inflammation driving their skin disease. Therefore keys to successful management of AD should include skin hydration and skin barrier repair, topical anti-inflammatory medications (topical corticosteroids or calcineurin inhibitors), control of infection and elimination of exacerbating factors (including allergens, irritants and emotional triggers) that may exacerbate the scratch-itch cycle. Treatment should utilize a stepwise approach that is dependent on the severity of skin disease. The reader is referred to several recent excellent reviews on the management of AD (27, 85-87).

In managing patients with chronic AD, it is important to recognize that gene profiling and immunohistology studies reveal subclinical inflammation and downregulation of terminal epithelial differentiation with reduced skin barrier proteins and increased trans epidermal water loss (TEWL) even in non-lesional AD skin (47, 71, 73, 87, 88). Thus, it is important to maintain skin barrier therapy in the form of emollient therapy even during periods of remission. In AD patients who are prone to frequent relapses, the subclinical inflammation can be managed with intermittent (2 times per week) corticosteroids or alternate day topical calcineurin inhibitors as maintenance therapy (89). For acute AD exacerbations, medium and high-potency corticosteroids can be used short periods of time to control the disease. Oral or systemic corticosteroids should be avoided due to rebound flares when patients are being weaned for oral corticosteroids.

In AD patients who are refractory or do not clinically respond to conventional treatment approaches, a number of alternative strategies may be used including cyclosporine, methotrexate, azathioprine, IL-6 blockade, dust mite immunotherapy when indicated, Wet Wrap therapy and ultraviolet light (90-94). Recent studies with broad based targeting therapeutics (69-70) have used disease-related cellular and molecular biomarkers to: i) show that the chronic AD phenotype can be reversed to a non-lesional state, as has been shown for psoriasis patients treated with effective therapeutics and ii) map inflammatory disease-

related pathways. The narrowband (NB) UVB phototherapy and CsA trials showed elimination of the pathologic epidermal hyperplasia (suprabasal K16 expression immunohistochemically and increased K16 and Ki67 mRNA expression) after 12 wks of treatments. The improvement in disease activity as identified by Scoring of AD (SCORAD) and epidermal pathology were highly linked to clearance of excess T-cell and dendritic-cell (DC) infiltrates, as well as decreased expression of inflammatory markers (69-70, 95, 96).

Prevention of Atopic Dermatitis by Early Intervention

Since current treatment approaches are not curative, there is considerable interest in studying approaches to prevent AD (97). The use of probiotic therapy or bacterial lysates early in the course of illness to prevent AD remains an area of active investigation (98-100) but results have been inconsistent. This may be due to lack of standardization of the bacterial preparations, or lack of biomarkers to identify which AD phenotype would benefit from this approach.

The potential contribution of vitamin D deficiency to allergic inflammation, corticosteroid insensitivity and downregulation of innate immune responses has also been an active area of study (101-106). Reproducible well controlled studies of oral vitamin D supplementation are lacking and when done have yielded confusing results. The greatest benefit are likely in populations who have extremely low levels such as people living in upper latitudes during the winter or darkly pigmented individuals. In the current issue of JACI, Camargo and co-workers present results from a randomized, placebo-controlled trial demonstrating that winter related AD can be improved with vitamin D oral supplementation (13).

The importance of AD skin barrier dysfunction in driving allergen sensitization is highlighted by 3 papers in the current issue suggesting that severe AD drives sensitization with environmental peanut (6-8). In 2 of these papers, filaggrin mutations predicted increased association of AD with peanut allergy. These papers suggest the possibility that controlling environmental peanut in the household may reduce peanut allergen sensitization. Alternatively studies are needed to determine whether effective control of AD with barrier therapy and anti-inflammatory treatment to reduce AD skin severity will reduce absorption of environmental allergens and decrease onset of food allergies or respiratory allergy.

Considering the important role that skin barrier dysfunction plays in the initiation of AD, the current issue of JACI contains two different international investigations assessing early intervention with skin emollient therapy to prevent AD and allergic sensitization during infancy (see references 25 and 26). Simpson et al (25) performed a randomized controlled trial of 124 neonates at high-risk for developing AD. Parents in the intervention arm were instructed to apply full-body emollient therapy at least once per day starting within three weeks of birth. Parents in the control arm were asked to use no emollients. The primary outcome was the cumulative incidence of atopic dermatitis at six months. Their results demonstrated a statistically significant protective effect with the use of daily emollient on the cumulative incidence of AD with a relative risk reduction of 50%.

Horimukai et al (26) did a randomized, controlled trial with early moisturizer intervention conducted in 116 neonatal participants at high familial risk for AD. The primary outcome

was the cumulative incidence of AD, as of week 32, as evaluated by a dermatologist. The intervention with the moisturizer significantly lowered (by approximately 40%) the risk of AD compared to the controls ($P=0.002$) as of week 32. The two groups showed similar rates of allergic sensitization. However, the rate of allergic sensitization of infants with AD, was significantly higher than the rest of infants.

These 2 studies suggest that early intervention with emollient therapy from birth represents a safe and effective approach for AD prevention. If confirmed to be effective in future studies, emollient therapy from birth would be a simple and low-cost intervention that could reduce the global burden of allergic diseases. Whether or not, this form of intervention can prevent The Atopic March is unresolved and may require combination with intermittent anti-inflammatory therapy and environmental control.

Clinical Phenotypes of AD

AD is primarily defined by clinical criteria (107). There is, however, increasing recognition that AD is a complex syndrome with multiple etiologies and mechanistic pathways that clinically can be distinguished by age of onset, severity of illness, racial modifiers, response to therapy, and triggers (including infections, allergens, stress and irritant threshold). Table 2 lists some of the major clinical phenotypes of AD (15,16). These phenotypes often have overlapping features, but contain dominant characteristics that distinguish them from each other (Figure 4). The majority of 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 has also been increasingly reported 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 can be unreliable. Up to 50% but certainly not all AD have associated asthma, allergic rhinitis or food allergy. Identification of genetic and biomarkers of patients likely to undergo the atopic march would allow early intervention for prevention of mucosal allergy including food allergy and asthma.

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 (108-110). Other AD subsets exist including those who are prone to skin infection such as *Staphylococcus aureus* skin infections or eczema herpeticum (111-115). 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%. Less than 3% of AD are predisposed to eczema herpeticum. 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 controlled by environmental influences (9, 116).

Defining Endotypes in Atopic Dermatitis

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 therapies to patients most likely

to benefit from a mechanism-based treatment. In the future, AD may be stratified by genotype, and biomarkers reflecting immune polarization to complement their clinical phenotype. As noted in Table 1, filaggrin genotyping defines AD subsets with different mechanistic pathways. Importantly the severity of AD is related to filaggrin expression with a dose-dependent effect (45).

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, severe eczema. They often have palmar hyperlinearity, greater risk of allergen sensitization, and a history of food allergy and asthma. As well, they have increased pH in their stratum corneum, which may predispose them to *S.aureus* colonization. Patients who have heterozygous *FLG* mutations have an intermediate phenotype and can outgrow their AD in adolescence whereas homozygotes or compound heterozygotes can have lifelong disease (59). These patients may also serve as a target for filaggrin therapy (117).

Given the complex genetic milieu 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. In the future a combination of epidermal proteomics, genomics, gene transcriptomes, blood biomarkers in combination with the clinical phenotype will offer more precision in defining endotypes of AD (118-120). Approximately 80% of AD patients have elevated serum IgE levels, often with increased eosinophilia and serum levels of the Th2 chemokine thymus and activation regulated chemokine (TARC). Additional markers are needed to better monitor 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 (109, 110). 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.

The mechanisms underlying *S. aureus* and disseminated viral infections in AD is an active area of investigation. These patients are generally very atopic with increased serum IgE, and eosinophilia. This may reflect high level Th2 cytokine pathway activation which is known to reduce skin barrier function, enhance *S. aureus* skin colonization, reduce antimicrobial peptide (AMP) production and impair innate immune responses. However, since eczema herpeticum is extremely rare and HSV exposure is very common, it is likely that additional immunologic and genetic factors contribute to AD associated with a history of eczema herpeticum (ADEH+). To identify novel gene signatures, in the current issue of JACI, Bin et al (121) used a RNA-sequencing (RNA-seq) approach to evaluate global transcriptional changes in peripheral blood mononuclear cells (PBMCs) from ADEH+ and AD without a history of EH (ADEH-). They found that PBMCs from ADEH+, stimulated with HSV-1, were deficient in their anti-viral immune response involving interferon regulatory factor (IRF) 3 and IRF7 innate immune pathways in ADEH+. This likely contributes to the reduced interferon response in ADEH+ that predisposes to increased susceptibility to disseminated viral infection. Interestingly, DOCK8 deficiency which presents with eczema

and recurrent herpetic skin infections has recently been found to respond well to treatment of IFN-alpha 2b (122).

Disease severity appears to be related to the magnitude and polarity of immune activation as well as effects of immune cytokines on epidermal responses (21, 71, 95, 96, 123) (Table 3). Severe AD may thus be associated with systemic immune activation, including significant pathology in non-lesional (NL) skin (71), explaining the frequent need for systemic immune-suppressants and the inadequacy of treating only lesional (LS) skin with topical agents. In contrast, due to minimal systemic involvement, it may be most appropriate to treat mild disease with topical agents directed only to LS sites.

Immune studies suggest that different AD phenotypes are associated with distinct patterns of activation (or suppression) of polar immune axes and corresponding tissue responses. There are distinct differences in cytokine production in patients with intrinsic versus extrinsic AD (123). In intrinsic AD, which has normal IgE levels, there is significantly increased expression of IL-17, IL-23, IL-22 and their respective keratinocyte-induced products (i.e S100As, elafin/PI3, CCL20), suggesting a subset with potential of greater responsiveness to suppression of the IL-17/IL-23/IL-22 axes (Figure 5). Despite, high levels of IgE in extrinsic AD, similar expression levels of Th2-related products were observed in both extrinsic and intrinsic AD, suggesting that these phenotypes might have similar responses to IL-4R antagonism. Indeed, Beck LA and collaborators showed that responses to dupilumab treatment were similar in intrinsic and extrinsic AD patients (20).

Strong support for the changing pathogenic and therapeutic AD paradigm comes from a recently report that IL-4R alpha antagonist/dupilumab conducted in moderate-to-severe AD patients (20). This study showed major improvement (~70%) in disease activity in the higher dose (compared with only ~20% in the placebo group), coupled with large improvement in the AD genomic phenotype and reversal of the epidermal hyperplasia (as quantified by larger reductions in K16 expression) (20). In fact the reduction in hyperplasia was much higher in the 4-week trial than with 5 mg/kg CsA given for 12 weeks to patients with similar disease activity (95).

Concluding Comments: The translational revolution in AD

AD poses a large unmet need for more effective topical and systemic therapeutics. In addition to Th2 antagonists (i.e anti IL-4R/dupilumab), the key role of TSLP-receptor signaling (124, 125) and IL-22 (126) that clinical trials with agents targeting TSLP, Th22, and Th17/IL-23 will be of interest. Selection of immune targeted therapeutics for patients with different degrees of disease severity or recognized AD phenotypes should not be done by serendipity but should be guided by defining the extent of activation of polar immune circuits in skin and blood (Table 4). For example, anti IL-23/IL-17 might provide beneficial responses in AD, and particularly in intrinsic AD patients. The individual contributions of the Th22, Th17, and Th2 immune pathways to the disease phenotype will be clarified through clinical trials coupled with mechanistic studies that are currently in progress.

Acknowledgments

This work was funded in part by The NIH/NIAID Atopic Dermatitis Research Network contract HHSN272201000020C, NIAMS grant AR41256 and the Colorado CTSA/CCTSI grant UL1 RR025780 from NCRR/NIH and UL1 TR000154 from NIH/NCATS. Additionally, DYML wishes to acknowledge The Edelstein Family Foundation for their generous support of his work.

Abbreviations

AD	Atopic Dermatitis
ADEH	Atopic Dermatitis with a history of Eczema Herpeticum
AMP	Anti Microbial Peptides
CsA	Cyclosporin
DC	Dendritic Cells
EDC	Epidermal Differentiation Complex
Eos	Eosinophils
FLG	Filaggrin
HOME	Harmonising Outcome Measures for Eczema
HSV	Herpes Simplex Virus
IL	Interleukin
IRF	Interferon Regulatory Factor
IVL	Involucrin
LC	Langerhans Cells
LOR	Loricrin
LS	Lesional skin
MA	Matted
NB	Narrowband
NL	Non-Lesional
NMF	Natural Moisturizing Factor
PBMC	Peripheral Blood Mononuclear Cells
PRR	Pattern Recognition Receptor
SC	Stratum Corneum
SG	Stratum Granulosum
TARC	Thymus and Activation Regulated Chemokine
TEWL	Trans Epidermal Water Loss
TJ	Tight Junction

TLR Toll Like Receptors

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Figure 1.

Is it clinically relevant whether skin barrier dysfunction or an immune response occurred first? Once AD is established, the physician needs to address both aspects of AD pathophysiology! However, prevention of AD may require identification of patients with primary defects in barrier vs immune dysfunction. Figure courtesy of Boyd Jacobson, National Jewish Health, Denver, CO.

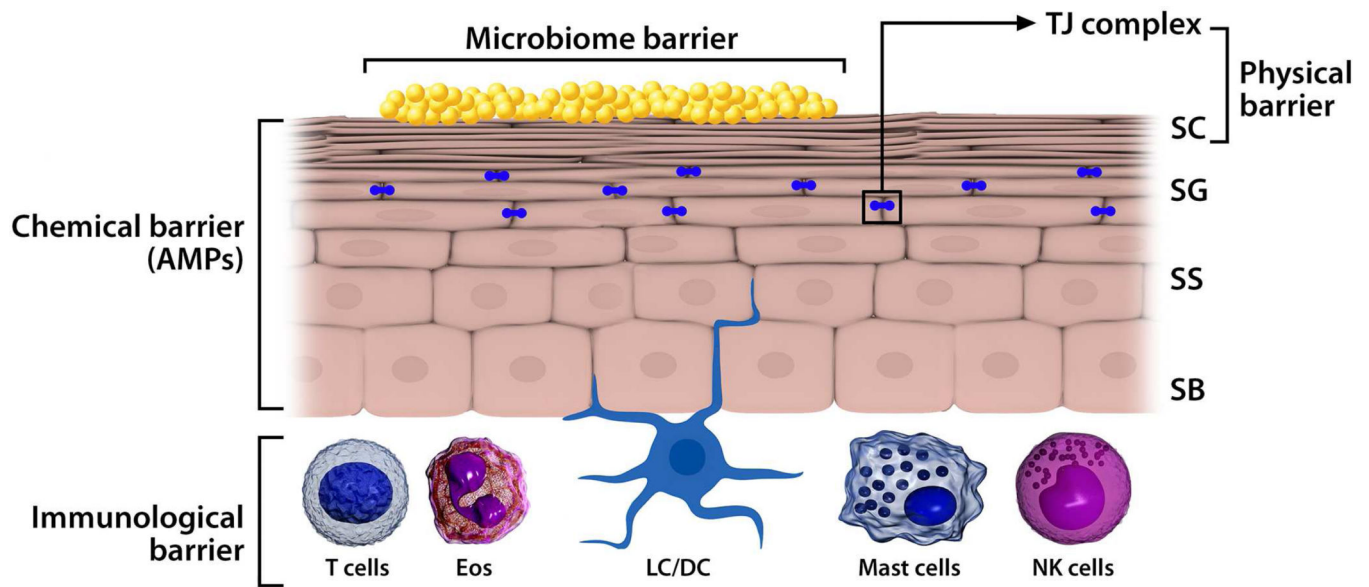


Figure 2.

The skin as a multi-tiered barrier. The stratum corneum (SC) is the first physical barrier protecting the skin from the environment. Gene mutations, e.g. filaggrin null mutations) or cytokines (e.g. IL-4, IL-13, IL-25, IL-33, etc) downregulating epidermal proteins including filaggrin, leads to allergen or microbial penetration through this barrier. Tight junctions (TJs) found at the level of the stratum granulosum (SG) provide an additional barrier. Disruption of both physical barriers enables the uptake of allergens, irritants, and microbes by Langerhans cells (LC)/DCs. Keratinocytes produce AMPs as a chemical barrier in response to pathogen colonization/infection. The skin surface is colonized with a diverse array of microorganisms (microbiome barrier), which regulates local immune responses and inhibits pathologic microbes. Infiltration of a number of cells into the AD skin lesion, including T cells, eosinophils (Eos), DCs, NK cells, and mast cells/basophils. Collectively, these cells constitute the cutaneous immunologic barrier. Pattern recognition receptors (PRRs) regulate the function of all of these barriers (physical, chemical, microbiome, and immunologic). SB, Stratum basale; SG, stratum granulosum; SS, stratum spinosum. This figure is modified from Kuo I, et al. *J Allergy Clin Immunol* 2013;131:266-78.

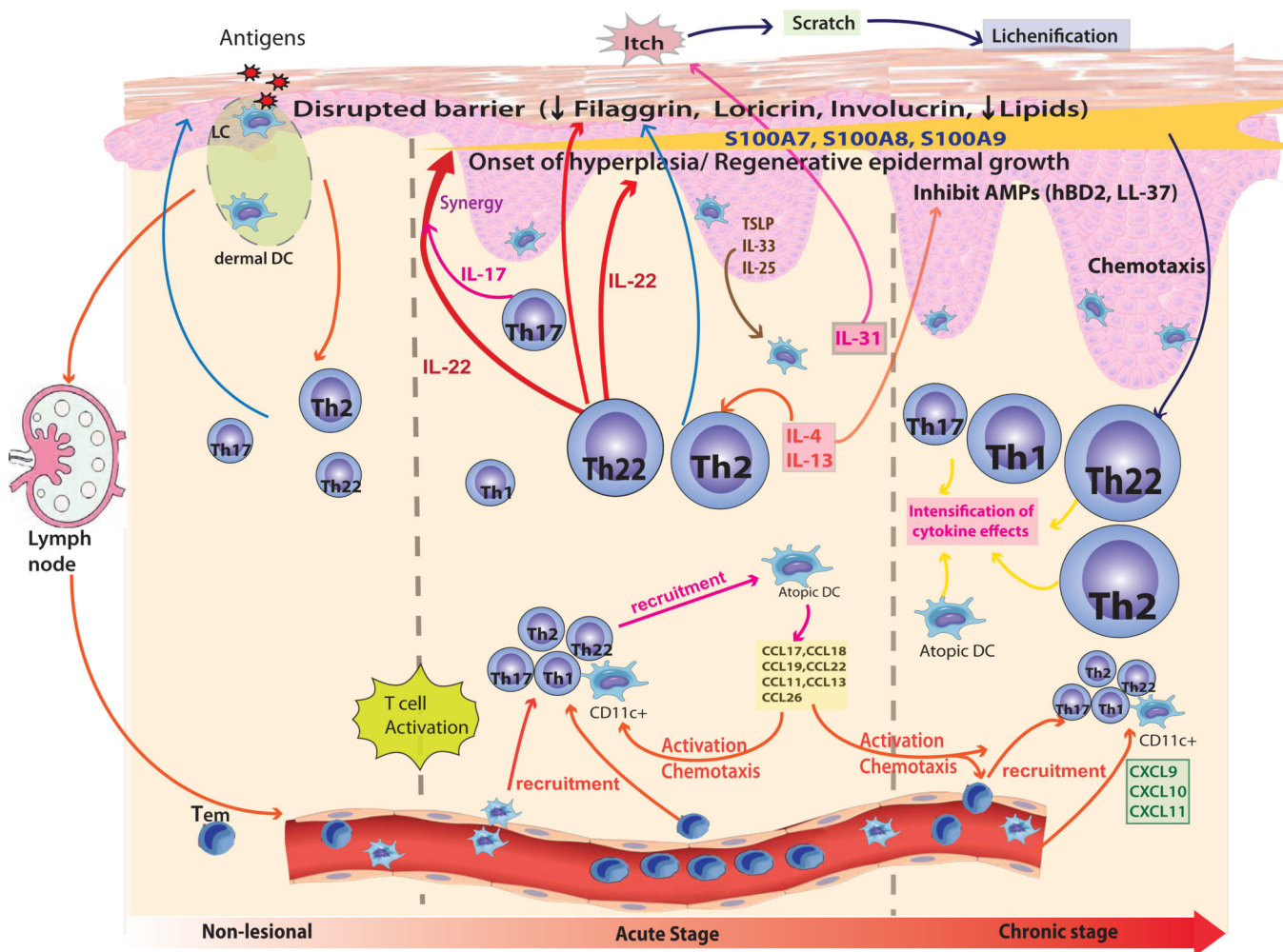
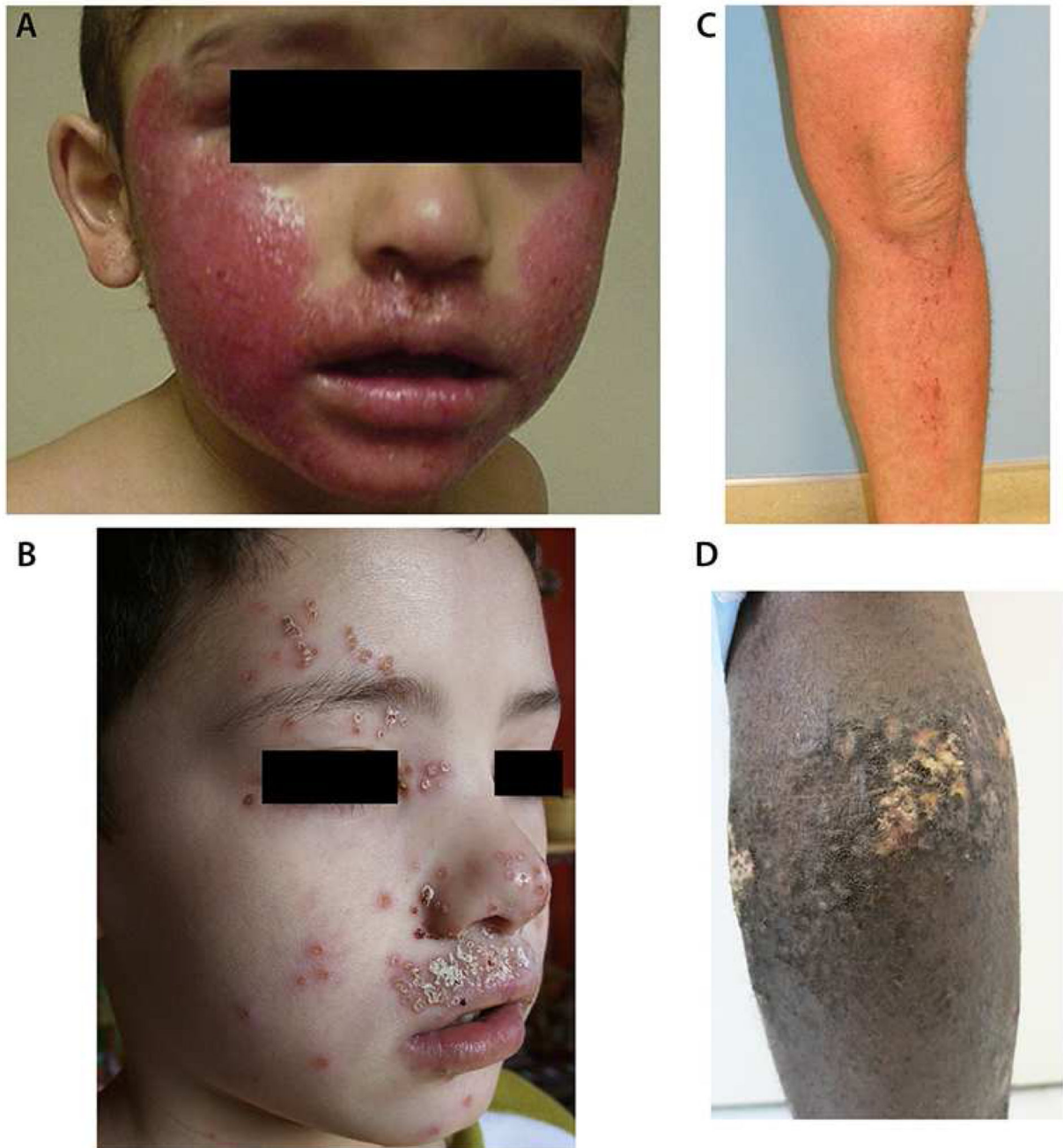


Figure 3. Immunologic Pathways involved in different phases of Atopic Dermatitis. Nonlesional AD skin lesions contain immune infiltrates that produce cytokines, e.g. IL-4 and IL-13, which contribute to a defective epidermal barrier. Barrier defects lead to penetration by epicutaneous allergens that encounter Langerhans cells in the epidermis and dermal DCs in the dermis to activate TH2 and TH22 cells involved in acute disease onset. Smaller increases in TH1 and TH17 immune axes are also found in acute lesions. A progressive activation of TH2 and TH22, as well as TH1, pathways is characteristic of chronic AD. IL-22 induces epidermal hyperplasia and, synergistically with the TH17 cytokine IL-17, drives an abrupt increase in a subset of terminal differentiation genes, specifically S100A7, S100A8, and S100A9 proteins. The increases in these barrier proteins contrast with the uniformly disrupted epidermal differentiation gene products (eg, filaggrin, loricrin, and corneodesmosin) throughout nonlesional, acute, and chronic AD skin. The TH2 and TH22 cytokines contribute to inhibition of the terminal differentiation proteins. IL-31 is thought to contribute to the itch in acute AD. Updated with permission from Gittler JK, et al. *J Allergy Clin Immunol* 2012;130:1344-54.

**Figure 4.**

Clinical Phenotypes in Atopic Dermatitis: Eczema herpeticum (panel A), *S. aureus* colonized AD (panel B), Mild AD (panel C), Severe AD (panel D). Panels A and B are from: Boguniewicz M and Leung DYM. *J Allergy Clin Immunol.* 2010; 125: 4-13; Panels C and D are contributed by Dr Emma Guttman- Yassky at The Icahn School of Medicine at Mt Sinai, NYC.

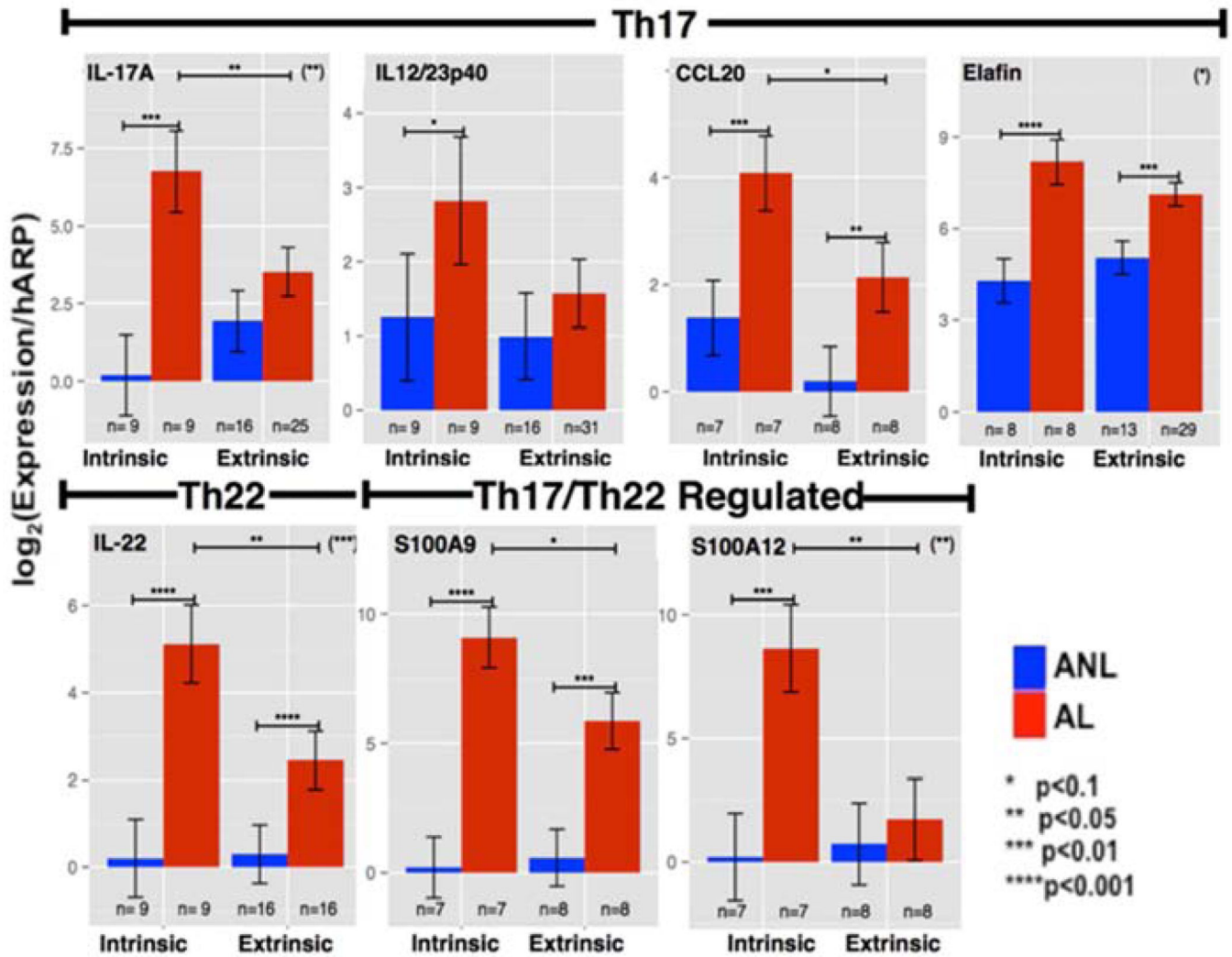


Figure 5. Measures of mRNA levels (normalized to hARP mRNA) for specific Th17/IL-23 and Th22 cytokines and inflammatory products in non-lesional (ANL) and lesional AD (AL) skin from patients with intrinsic versus extrinsic disease. From: Suarez-Farinas M, et al. *J Allergy Clin Immunol* 2013;132:361-70.

Table 1

Comparison of clinical and biophysical features of atopic dermatitis patients with (AD_{FLG}) and without (AD_{NON-FLG}) filaggrin mutations.

	Clinical Features	Biophysical Features
AD_{FLG}	Palmar Hyperlinearity More Persistent ↑Allergic Sensitization ↑Risk of Asthma ↑Severity of AD ↑Eczema Herpeticum	Severe Decrease in Natural Moisturizing Factor (NMF) pH IL-1β Type 1 interferon-mediated stress response
AD_{NON-FLG}	No Palmar Hyperlinearity Less Persistent Less Allergic Sensitization Lower Risk of Asthma	Mild Decrease in Natural Moisturizing Factor (NMF) pH Lower Compared to AD _{FLG} IL-1β Low Compared to AD _{FLG} Dysregulation of lipid metabolic processes

*Modified with permission from: McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. *J Allergy Clin Immunol* 2013;131:280-91.

Table 2

Clinical Phenotypes of AD

- Onset in infancy, outgrown in childhood
- Onset in infancy, persistent, severe eczema
- Adolescent-Adult onset, mild-moderate eczema
- Adolescent-Adult onset, persistent, severe eczema
- Increased IgE with food or aeroallergen sensitization (Extrinsic)
- Non-IgE mediated (Intrinsic)
- AD with *S. aureus* infection/colonization
- AD with history of disseminated viral infections e.g. eczema herpeticum

Table 3

Summary of cytokine effects on epidermis in AD

- Induce epidermal hyperplasia (IL-22)
- Induce spongiosis (Th2 cytokines IL-4/IL-13 and TNF)
- Inhibit keratinocyte terminal differentiation (IL-4, IL-13, IL-31, IL-25/Th2, IL-22/Th22, and TNF) with potential for feedback hyperplasia
- Inhibit Synthesis of Antimicrobial Peptides (Th2 cytokines IL-4, IL-13, IL-33)
- Inhibit Lipid Synthesis (Th2 cytokines IL-4/IL-13, IL-31, and TNF)
- Increase expression of S100A7, 8, 9 (IL-22+IL-17)
- Induce TSLP production in KCs (IL-4/IL-13, and TNF)
- Promote itch (IL-31, TSLP)
- Promote anti-viral responses (IFN gamma, IFN alpha, IL-29)

Table 4

Phenotypes of Severity and Treatment Response

- Pre-clinical: use skin barrier cream for prevention of AD
- Chronic AD in remission: use barrier cream in combination with maintenance topical corticosteroid or calcineurin inhibitors to prevent relapse
- Relapse of Mild-Moderate AD: use topical corticosteroids or calcineurin inhibitors for control of inflammation, identify and avoid triggers (irritants, allergens, infection), immunotherapy for allergen-driven AD
- Persistent Moderate-Severe AD not controlled on topical corticosteroids or calcineurin inhibitors: Wet Wrap Therapy, Allergen Immunotherapy, Non-specific immunosuppressives (cyclosporine, methotrexate, narrow band UV phototherapy, mycophenolate)
- Future targeted therapies for Moderate-Severe AD (anti-IL-4 receptor alpha, anti-IL-22, anti-IL-23/IL-17 or other biologics that interrupt polarized immune pathways)