Clinical Commentary Review

Skin Barrier and Immune Dysregulation in Atopic Dermatitis: An Evolving Story with Important Clinical Implications

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Atopic dermatitis is the most common chronic inflammatory skin disease. Its pathogenesis combines barrier defects, immune dysregulation, and increased skin infections; however, the relative contribution of each of these components is yet to be determined. Uninvolved atopic dermatitis skin also displays broad immune and barrier abnormalities, which highlights a role for proactive treatment strategy. The residual disease genomic profile that accompanies clinical resolution provides further support for proactive treatment approaches. Although intrinsic and extrinsic atopic dermatitis subtypes share a common clinical phenotype, they show some important differences in their Th22/Th17 cytokine profile, which opens the door for personalized specific therapeutics for each disease category. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)

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ATOPIC DERMATITIS PATHOGENESIS AND GENETIC STRUCTURAL COMPONENTS OF THE EPIDERMAL BARRIER

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease. Its prevalence has significantly increased in recent years, and it now affects approximately 3% of adults (5%-7% in Asia)[1] and up to 25% of children.[2] Disease pathogenesis, which combines both environmental and genetic factors, is still debated, with 2 alternate pathogenic hypotheses. The "outside-in," hypothesis suggests that epidermal-barrier dysfunction is the primary insult and a prerequisite to immune activation; whereas, the "inside-out" hypothesis indicates that AD is primarily a cytokine-driven disease with a reactive epidermal hyperplasia. Although originally perceived as 2 competitive mechanisms, there is accumulating evidence that supports their integrated role in disease development, but their relative contribution to the AD phenotype is still debated.[2-10]

The role and significance of barrier integrity in AD has been increasingly recognized.[11] Disrupted epidermal terminal differentiation and reduced lipids have all been implicated as part of the barrier defects.[3,4] The epidermal differentiation complex (EDC) locus[12,13] on chromosome 1q21 is a cluster of more than 60 genes that encode for major proteins involved in terminal differentiation and formation of the cornified envelope.[7,14] Among these genes are serine protease inhibitor, Kazal type 5(SPINK5), loricrin (LOR), involucrin, and filaggrin (FLG) as well as small proline-rich proteins and late cornified envelope proteins.[4,15] Proteins encoded by this complex have a significant functional overlap in maintaining the cornified envelope integrity.[16] Among them, Filaggrin (filament-aggregating protein)/FLG, a key protein involved in cornification and hydration (breakdown products act as osmolytes),[17] is the most commonly associated genetic component with a risk of AD development, severity, and increased propensity toward other atopic conditions.[7] Its deficiency has been postulated to increase pH (which causes serine protease activation and modification of microbial colonization)[18] and impair skin integrity, hydration, protease activity, and antimicrobial peptide (AMP) function. Multiple FLG mutations have been identified, with loss-of-function (null) mutations being the most abundant (mainly R510X and 2282del4).[19-21] FLG mutations are found in 10% to 50% of AD cases but also in 9% of the non-AD population, and 40% of the null-alleles carriers never develop AD.[20,22,23] Patients with FLG mutations also may outgrow their disease or have extended remissions.[22] Furthermore, in a genomic comparison among AD, psoriasis, and normal skin, we demonstrated that multiple cornification genes (beyond FLG) are downregulated in AD, with delayed coordinated expression of their proteins,[24] which possibly implies a secondary barrier abnormality in response to a primary immune activation.

ALTERED MICROBIOME CONTRIBUTES TO BARRIER DEFECT IN AD

Microbiome is a term coined by Lederberg in 2001 and defined as "the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space."[25] A 5-year National Institutes of Health project started in 2009,[26] the Human Microbiome Project aims at characterizing the microbiome in health and in different skin diseases, including evaluation of cutaneous microbiome in AD.[27] This project will expand our understanding regarding the effect of the microbiome on disease

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Abbreviations used
AD- Atopic dermatitis
AL- Atopic lesional
AMP- Antimicrobial peptide
ANL- Atopic nonlesional
CCL20- Chemokine, CC motif, ligand 20/macrophage inflammatory protein 3
CXCL5- Chemokine, CXC motif, ligand 5/epithelial-derived neutrophil-activating peptide 78
DC- Dendritic cell
EDC- Epidermal differentiation complex
FLG- Filaggrin
LOR- Loricrin
NB- Narrow band
RDGP- Residual disease genomic profile
S100A- S100-Calcium binding protein
SCORAD- Scoring of atopic dermatitis index
STAT- Signal transducer and activator of transcription
TCI- Topical calcineurin inhibitor
TCS- Topical corticosteroid
TEWL- Transepidermal water loss
TSLP- Thymic stromal lymphopoietin

development and its correlation with the immune and barrier defects. One of the most troubling features of AD skin is the susceptibility to localized and disseminated skin infections.[5,18] Ninety percent of patients with AD are colonized and/or infected with *Staphylococcus aureus (S aureus)*, with emerging methicillin-resistant *S aureus* strains imposing a therapeutic challenge.[28-30] As opposed to psoriasis and healthy skin, high levels of *S aureus* are found on AD nonlesional skin as well,[31] which stresses the significance of treating AD nonlesional skin. Several variables have been suggested to account for the high susceptibility to infections in patients with AD. The Th2 cytokines, IL-4 and IL-13,[32] have a permissive effect on microbial invasion, epidermal barrier,[33] cell-mediated immunity, lowering AMPs (β-defensins; human β defensins and cathelicidins; human cationic antimicrobial protein18/LL-37) production.[28,34] An association between AMPs and the skin barrier has been found, with the correlation of increased transepidermal water loss (TEWL) with high levels of human β defensin-2.[35,36] Recently, IL-4 and IL-13 also have been reported to increase *Staphylococcal* α toxin induced keratinocyte death through signal transducer and activator of transcription (STAT) 6 signaling.[37]

The *S aureus* superantigens staphylococcal enterotoxin B and toxic shock syndrome toxin 1 promote lymphocyte IL-31 production in patients with AD.[38] IL-31, in turn, has been shown to reduce FLG expression and mediate proinflammatory cytokines secretion.[39] IL-22 via STAT3 increases epidermal antimicrobial defense[40-42] but decreases terminal differentiation genes.[43] IL-17 holds an important role in regulatory innate immunity. It is involved in β-defensins upregulation[44] and in neutrophil recruitment.[45] As previously demonstrated,[46] Th17/IL-23 activation is reduced in chronic AD compared with psoriasis. IL-17 induces AMP keratinocyte gene expression, thus its relative deficiency in AD skin might contribute to the propensity toward skin infections. Further support to the IL-17 anti-infection role is provided by a recent publication that showed that Th17 harbors an antiviral capacity, which is conveyed through IL-29 production in patients with psoriasis.[47]

S aureus is involved on several levels in the pathogenesis of AD; It induces toxin-specific IgE secretion and basophilic activation,[48] mechanically disrupts epidermal integrity through protease activity,[49] inhibits terminal differentiation markers (KRT1, KRT10, LOR, and FLG) through IL-6 secretion[50] and directly activates eosinophils,[51] thus further compromising barrier integrity and function. Superantigen-producing *S aureus* colonization is correlated with serum IL-4 levels,[52] and staphylococcal exotoxins are strong inducers of IL-22 and IL-31 in AD (compared with psoriasis and healthy controls),[38,53] which all support a *S aureus* role in inducing and maintaining chronic skin inflammation in AD. A myriad of antistaphylococcal strategies have been tried so far. Among them are bleach baths, oral antibiotics, topical iodine, triclocarban 1.5%, fluticasone ointments with and without antibiotics, and fabrics with antibacterial properties.[54] Although these strategies reduce bacterial loads, there is the problem that the skin is rapidly recolonized by *S aurues.*[55]

Interestingly, barrier-directed treatments as well as anti-inflammatory medications (topical calcineurin inhibitors [TCI] and topical corticosteroids [TCS]) reduce the bacterial load and improve barrier function,[56-59] which suggests that neutralizing this component will recover the compromised innate immunity in AD.[60] Novel therapeutics directed at improving the bacterial overload include ceragenins (synthetic antimicrobial compounds), oral vitamin D, vaccines, and toxin-neutralizing agents (directed mainly staphylococcal enterotoxin B and toxic shock syndrome toxin 1), but yet the standard of care to reduce bacterial overload includes barrier repair by hydration and topical anti-inflammatory formulas.[5,61-65] There is a high need to identify more-effective treatments for *Staphylococcal* colonization because a Cochrane database systematic review concludes that results vary but global degree of improvement in symptoms and or signs after available treatments was only average.[54]

The microbiome individually affects the development and profile of the adaptive immune system and has an "imprint" on many of its aspects.[66] However, it has yet to be determined how *S aureus* colonization differentially drives cytokines polarization in different age groups and how its eradication will redirect these pathways and affect barrier integrity in AD. Better microbiome characterization by the Human Microbiome Project and parallel studies as well as application of different eradication protocols will help to better address these questions.

THE COMPLEX DIALOG BETWEEN THE IMMUNE DYSREGULATION AND THE EPIDERMAL BARRIER DEFECT IN AD: CHICKEN OR THE EGG?

The interplay between skin barrier and immune dysregulation in AD is complicated, and cytokine imbalance has a major impact on keratinocyte differentiation and other barrier features. AD is characterized by overexpression of the Th2 cytokines IL-4 and IL-13 as well as the Th22 cytokine, IL-22. As we recently showed,[9] acute initiation of AD is associated with overexpression of Th2 and Th22 cytokines genes, with intensification of these axes toward chronic disease, and the appearance of a significant Th1 component. Th17 also has some contribution in acute AD onset. During the acute disease phase, Th2 cytokines, notably IL-4, IL-5, IL-13, and IL-31, are detected in atopic lesional (AL) but also in atopic nonlesional (ANL) skin. The Th22 pathway genes IL-22 and S100-calcium binding proteins (S100A) 7-9 were also shown to be elevated in AL skin. Conversely, an