

Review article

Association between barrier impairment and skin microbiota in atopic dermatitis from a global perspective: Unmet needs and open questions

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Atopic diathesis encompassing atopic dermatitis (AD), allergic rhinoconjunctivitis, food allergy, eosinophilic esophagitis, and asthma is a widely prevalent condition with a broad heterogeneity in clinical course, age of onset, and lifespan persistence. A primary event in AD is the commonly inherited epidermal barrier dysfunction. Together with the host-microbiome interactions, barrier defect and allergen exposure modulate both innate and adaptive immunity, thus triggering and maintaining the inflammatory response. Microbiome diversity, together with the host's contact with nonpathogenic microbes in childhood, is a prerequisite for functional maturation of the immune system, which is in part mediated by microbiome-induced epigenetic changes. Yet, whether microbiome alterations are the result or the reason for barrier impairment and inflammatory response of the host is unclear. Exposure to locally prevalent microbial species could contribute to further modification of the disease course. The objective of this review is to reveal the link between changes in the skin microbiota, barrier dysfunction, and inflammation in AD. Addressing unmet needs includes determining the genetic background of AD susceptibility; the epigenetic modifications induced by the microbiota and other environmental factors; the role of globally diverse provoking factors; and the implementation of personalized, phenotype-specific therapies such as an epidermal barrier restoration in infancy and microbiota modulation via systemic or topical interventions, all of which open gaps for future research. (J Allergy Clin Immunol 2021;■■■■:■■■■-■■■■.)

Key words: Allergic, atopy, asthma, allergic rhinitis, atopic march,

phenotype, transepidermal water loss, hydration, Staphylococcus, epigenetic, interleukin

The first written evidence of a disease corresponding to atopic dermatitis (AD) dates back to Roman Empire times; however, it was not until 1923 that Cooke and Coca introduced the term *atopy*, originating from the Greek (meaning “with no place”).¹ Since then, the concept of clinicopathophysiologic connection between the diseases along the atopic spectrum (AD, allergic rhinitis/conjunctivitis, and asthma) has evolved dramatically. Today, the key role of IgE has been challenged in the context of atopic diseases. Evidence shows that type 1 sensitization is a secondary phenomenon, and epidermal barrier impairment, together with involvement of immune cells residing in the skin, is a prerequisite for the development of IgE-mediated allergies.^{2,3} The current understanding of AD immunopathology involves the dysfunction and skew in the T_H2 cell immunity, with the active contribution of IL-4 and IL-13, which are also involved in other diseases on the atopic spectrum, such as asthma and eosinophilic esophagitis.^{4,5} The intracellular signaling system consisting of 4 Janus kinases (JAKs) and 7 signal transducers and activators of transcription (STATs), known as the JAK-STAT signaling pathway, transfers extracellular signals to the cell nucleus and modifies the process of transcription and mediation of the effect of proinflammatory cytokines.⁴ The latter has been a major field of research for AD treatment since the introduction of systemic and topical JAK-inhibitors.^{6,7} Barrier deficiency, microbiota dysbiosis, and inflammation are the key players in atopic diseases. “The chicken or the egg” question is whether microbiome alteration is the result of or the reason for barrier impairment and inflammatory response in atopic diseases.

Classically perceived as a disease prevalent and explored in the White population, AD has ethnic- and geographic-dependent genetic, clinical, and immunologic heterogeneity. Exposure to locally prevalent microbial species could further diversify the disease anisotropy. With a lifetime prevalence of AD of almost 15% in industrialized countries, a trend toward increase in the prevalence of AD in developing countries has been witnessed.⁸⁻¹⁰ Environmental factors interact with the genetically susceptible milieu in atopic subjects, contributing to the increasing incidence of the disease.¹⁰ Among all factors, climate (cold, hard water, UV light exposure), air pollution, Western diet, antibiotic exposure in childhood, helminthic infection, and close contact with natural environments shape the disease epidemiology even in genetically indistinguishable subpopulations.¹⁰⁻¹³

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Abbreviations used

AMP: Antimicrobial peptide
 AD: Atopic dermatitis
 CoNS: Commensal staphylococci other than *Staphylococcus aureus*
 FLG: Filaggrin
 JAK: Janus kinase
 SC: Stratum corneum
 STAT: Signal transducer and activator of transcription
 TSLP: Thymic stromal lymphopoietin

Despite the general belief in the atopic march (the typical progression of allergic diseases from childhood to adulthood, which includes AD, allergic rhinitis, food allergy, eosinophilic esophagitis, and asthma),¹⁴ there is evidence that the march does not occur everywhere and phenotypic variability exists.¹⁵ On the other hand, the concept of the so-called adult onset has been questioned, as almost one-third of adults do not report a personal history of childhood eczema despite the AD diagnosis in their medical records.¹⁶ There is a solid body of evidence highlighting the need for early-life interactions between host (barrier, immune system) and microbiota, which together with environmental factors, contribute to the complex pathophysiology of AD.

The objective of this review is to reveal evidence regarding the link between skin microbiota, barrier dysfunction, and inflammation in AD. We focus on studies with human subjects and human cell lines that have been published since 2010.

SKIN BARRIER–IMMUNE SYSTEM INTERACTIONS

Epidermal barrier impairment is a prerequisite for the development of AD, despite the disease genotypes and endotypes.^{3,17} Dry skin and increased transepidermal water loss during the neonatal period until the age of 2 months increases the risk of AD development later in life.^{3,17} A major contributing factor to the inherited skin barrier defects is the mutation in the genes encoding structural epidermal barrier proteins, such as filaggrin (FLG).¹⁸ However, FLG mutations are not an obligate prerequisite for AD development, and not all carriers of FLG mutations develop AD.^{19,20} Wide geographic variability with regard to the most common FLG gene mutations has been witnessed, with the most prevalent European and Asian variants observed in no more than 5% of the African American population.²¹ As for other allergic diseases, the hereditary character of AD has long been suspected, and several studies have remarked on the importance of a family history in children with this disease.²² Studies of the genetic susceptibility to AD have discovered several associated variants and mutations in genes involved in the pathophysiology of the disease, with FLG being found in most original and replicated studies; however, a great number of other associated gene variants have been reported in genome-wide association studies, whole exome sequencing, and related meta-analyses,²³ although most of those associations are not supported by variant-related experimental functional studies. More recently, a whole genome sequencing–based investigation of the genetic basis of eczema herpeticum, a rare complication of AD, identified variants in the genes *SIDT2* (SID1 transmembrane family member 2) and *RBBP8NL* (retinoblastoma binding protein 8 N-terminal like) that are not only associated with the susceptibility to acquire

herpes simplex virus type 1 infection but, as has been demonstrated by experimental functional studies, are also able to modify the expression of genes influencing the differentiation of keratinocytes,²⁴ which is an important cellular component of the tissue alterations in AD. This research provides further evidence of the importance of genetic analyses for understanding the pathogenesis of AD; however, the potential usefulness of these and other genetic findings as biologic markers for personalized medicine remains to be determined.

Epidermal barrier function, residing almost entirely in the stratum corneum (SC), is impeded in AD, as has been revealed by multiple studies in skin physiology and morphology and at the molecular level. AD is characterized by increased transepidermal water loss and epidermal permeability, increased pH, and a reduction in the expression of structural SC proteins (eg, FLG), as well as by SC lipid abnormalities related but not limited to the chain length reduction in relation to barrier disruption in AD.^{25,26} The clinical consequences of hindered FLG synthesis and breakdown to natural moisturizing factor constituents (ie, transurocanic and pyrrolidone carboxylic acid) include dry, itchy, eczematous skin and increased skin surface pH.²⁷ In addition, an imbalance between proteases engaged in the proteolysis of extracellular corneodesmosome components and their inhibitors,²⁸ as well as tight junction defects in the deeper epidermal layers related to reductions in claudin-1 gene (*CLDN1*) expression,²⁹ further contribute to the skin barrier impairment in AD. Loss of FLG in the absence of inflammation alone changes the expression of inflammatory, proteolytic, and cytoskeletal proteins involved in AD pathophysiology.³⁰

FLG deficiency, resulting in increased skin surface pH, leads to the stimulation of serine proteases that cleave IL-1 secreted from corneocytes, thus facilitating inflammation.^{31,32} Epidermal barrier disruption, due to either mechanical injury (scratching) or FLG deficiency, leads to the secretion of alarmins from the keratinocytes and innate lymphoid cells such as the thymic stromal lymphopoietin (TSLP), IL-1 α , IL-25, and IL-33,^{32–34} which activate skin Langerhans cells and dermal dendritic cells, polarizes the immunity toward the T_H2 cell pathway with the key cytokines IL-4 and IL-13, and leads to the activation of IgE-producing B cells and mast cells through transcription modulation pathways.^{35–37} Despite the ongoing debate, TSLPs are able of recruiting basophils, at least partly via the IL-3 pathway,³⁸ and basophil homing from skin to gut is responsible for food intestinal allergy.³⁹ Therefore, migration of activated immune cells could be a plausible explanation for the atopic march.

Skewed immunity in the T_H2 cytokines is a hallmark of AD and a key driver in AD and its comorbidities.⁴⁰ T_H2 cytokines inhibit the production of structural SC proteins, namely FLG, loricrin, and involucrin.^{41,42} *In vitro*, IL-4 and IL-13 induce changes in skin lipids that are identical to those in AD.²⁵ These data reflect the 2-way interactions between barrier and inflammation in AD.

In acute and chronic eczematous lesions beyond T_H2 cytokines, an engagement of the T_H22 and T_H17 cytokines can be observed, whereas in chronic eczema the T_H1 cytokine pathway is activated.⁴³ In Asians, an increased polarity toward T_H22/T_H17 axes has been reported, whereas in African Americans suppression of the attenuation of T_H17/T_H1 cell pathways has been revealed.⁴⁴ An open gap for research is the search for a prompt biomarker and/or combination of biomarkers capable of differentiating between endotypes of AD and correlating with the disease activity.

SKIN BARRIER AND MICROBIOTA INTERACTIONS

The AD skin microbiome displays *Staphylococcus* spp–dominated dysbiosis with decreased microbial diversity and predominance of *Staphylococcus aureus* and *Staphylococcus epidermidis*.^{45,46} Microbiome changes have been shown to precede AD development in a culture-based analysis of longitudinal birth cohorts.⁴⁷ Furthermore, an increase in bacterial diversity precedes the disease amelioration during AD treatment.⁴⁸ Disease severity correlates with *S aureus* colonization, and patients with AD who are carrying *S aureus* display impaired skin barrier function and increased IgE sensitization rates compared with those in noncolonized atopic or healthy subjects.⁴⁹ On the other hand, not microbiome, but host transcriptome analysis, correlates strongly with AD clinical severity.⁵⁰

SC integrity disruption, as in FLG-deficient skin, is a key host factor for *S aureus* adhesion to the skin.⁵¹ FLG deficiency in healthy subjects results in skin microbiota closer to those in subjects with AD than to those in healthy subjects without FLG mutation, regardless of the skin site.⁵² Through fibronectin-binding protein B and clumping factor B, *S aureus* binds to the N-terminal glycine–serine-rich region of corneodesmosin. This adhesion is stimulated in low-hydrated, natural moisturizing factor–depleted, and more alkaline SC.^{51,53} SC lipid abnormalities have been linked to *S aureus* carrier status of patients with AD (ie, lower levels of certain ceramides, unsaturated free fatty acids [16:1 and 18:1], and triglycerides).⁵⁴ Although AD shows increased total ceramide, free fatty acid, and cholesterol levels, the levels of certain ceramide subtypes are decreased in association with *Staphylococcus* colonization.²⁶ A correlation between increased α -hydroxy ceramide level and *S aureus* abundance is reported at AD predilection sites.⁵² Finally, an inverse correlation for *S aureus* and a positive correlation for other commensal staphylococci was revealed for the expression of 4 genes encoding for tight junction proteins.⁵⁵ The present data are indicative that barrier defect could be the primary event in the skin–immune system–microbiome axis.

S aureus, in turn, exerts a deteriorating effect on the epidermal barrier. Following adhesion and through its α -toxin, it forms pores in the keratinocyte wall and in the formation of biofilm.⁵⁶ The defective skin barrier in AD facilitates the deeper penetration of *S aureus* into the dermis and subsequently the interaction with immune cells.⁵⁷ By stimulating epidermal kallikrein proteases or by synthesizing its own proteases, *S aureus* further perturbs the epidermal barrier. This process is facilitated by the absence of FLG (less acidic, dry compartment) and the availability of T_H2 cytokines.^{46,58}

Commensal staphylococci other than *S aureus* (CoNS), such as *S epidermidis* and *Staphylococcus hominis*, antagonize *S aureus* on account of the same inhabited ecosystem. Colonization with CoNS reduces development of AD at the age of 1 year.⁵⁹ Toll-like receptor ligands originating from CoNS decrease skin inflammation and enhance antimicrobial peptide (AMP) expression.⁶⁰ Therefore, the abundance of *S epidermidis* in acute AD lesions is seen as a compensatory mechanism rather than a virulence factor. The abundance of *S epidermidis* has been linked to enhanced cysteine protease activity, acting synergistically with the skin barrier damage caused by *S aureus*.⁶¹

Epigenetic studies support several of these findings. Epigenetic modifications in affected skin and immune cells from patients with AD have been reported, mainly influencing gene

expression through DNA methylation, noncoding RNA, and to a lesser extend histone acetylation.⁶² A number of epigenetic dysregulated signatures in skin homing CD4⁺CLA⁺ memory T cells from patients with AD, including differences in DNA methylation of protein coding genes and differentially expressed miRNA genes, have been described, providing a partial explanation of the mechanisms underlying the great influence of these cells on the skin inflammatory process of AD.⁶³ The inducers of these epigenetic modifications have not been clearly identified, but considering the strong AD association with urban life, it is possible that diverse factors such as diet and air pollution play a role. In addition, the effects of normal skin microbiota have also been explored. It has been reported that butyric acid, a fermentation product of *S epidermidis*, and one of its derivatives (BA-NH-NH-BA, which is potentially useful for topical therapy) induce the acetylation of histone 3 lysine 9 (AcH3K9) in human keratinocytes by inhibiting histone deacetylase. Interestingly, this derivative reduces the colonization of *S aureus* in the skin in a mouse model of AD, adding more specific tools for topical treatment of AD.⁶⁴ Still, the role of CoNS and their application as therapeutic strategy remains to be elucidated.

A loss of anaerobic bacteria such as *Lactobacillus* spp has been demonstrated in active AD lesions.⁵⁰ The switch toward aerobic metabolism is linked to the skin barrier breakdown and the increased skin surface pH. Clinically relevant nonbacterial infectious complications of AD require more extensive investigation of the changes in the mycobiome and virome.

MICROBIOTA AND INFLAMMATION INTERACTIONS

According to the widely discussed “hygiene hypothesis,” early-life communication and colonization with microbes is required for the immune system maturation and priming.⁶⁵ This colonization process should happen in a certain “window” of the early lifespan.⁶⁶ In a rodent model, a rapid influx of regulatory T cells into the skin following contact of neonate animals with commensal bacteria in this precise developmental window has been shown.⁶⁷

There is an increasing appreciation of skin and gut microbiota interactions in the genesis of atopic disease.⁶⁸ Body site differences in microbial communities are more pronounced in young infants than in adults. In young infants, for example, Proteobacteria are highly present in the gut but less prevalent in the skin.⁶⁹ In this regard, it is helpful to note that food sensitization during infancy is a first marker of the atopic march and is preceded by changes to gut microbiota.⁷⁰ The latter have been documented in a Canadian birth cohort⁷¹ and in a case-control study of 14-month-old infants in Taiwan⁷² as elevations of the Enterobacteriaceae (of the phylum Proteobacteria)-to-Bacteroidaceae abundance ratio in the gut microbiota of infants, and they are seen as early as 3 months after birth. Already within 1 month of birth, colonization of gut microbiota with an increasing number of *Escherichia coli* has predicted the development of AD in Dutch children at toddler age.⁷³ Importantly, a high Enterobacteriaceae-to-Bacteroidaceae abundance ratio in early and late infancy, which is characteristic of depleted Bacteroidetes species at both time periods, has been found to be a significant predictor of peanut sensitization in infants.⁷⁴ These gut

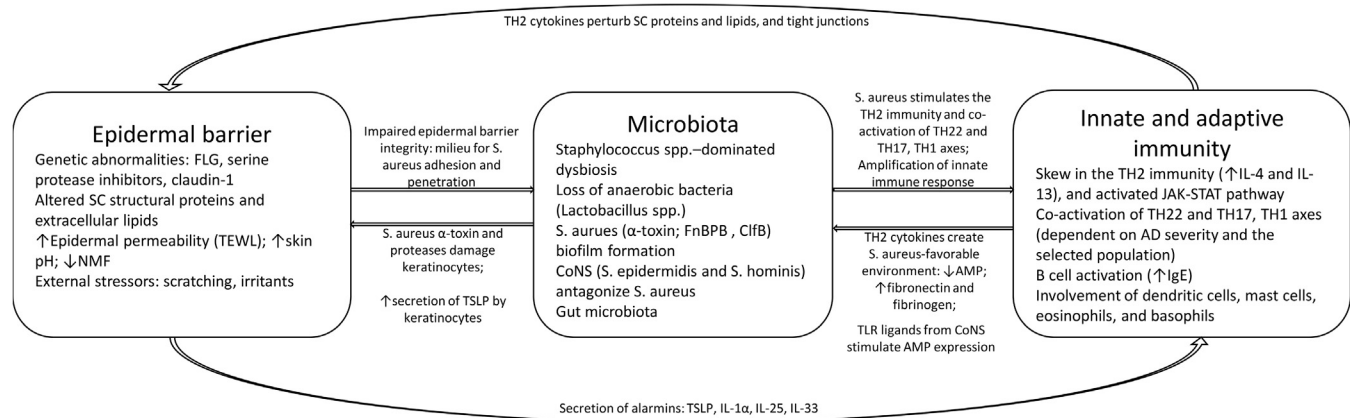


FIG 1. Schematic overview of the key alterations and interactions on the skin-immune system-microbiome axis. Downward arrow indicates a decrease, upward arrow indicates an increase. *ClfB*, Clumping factor B; *FnBPB*, fibronectin binding protein B; *JAK-STAT*, Janus kinase-signal transducers and activators of transcription; *NMF*, natural moisturizing factor; *TEWL*, transepidermal water loss; *TLR*, Toll-like receptor.

microbiota associations were mostly seen in Canadian infants of Asian ethnicity, which brings us back to geographic area determinants of atopic disease. AD is more severe among the offspring of Asian mothers who immigrate to industrialized countries.⁷⁵

Human-derived *S aureus* strains are able to induce AD-like skin lesions and immunologic abnormalities identical to those in AD (T_H2 and T_H17 cell axes), as witnessed in a mouse model.⁷⁶ Transcriptome analysis reveals that high *S aureus* quantities are associated with change in skin barrier genes (related to tight junction formation), certain metalloproteinases, and T_H2 pathway cytokines.⁵⁰

Breakage of the skin barrier by *S aureus* and its penetration correlate positively with T_H2 and T_H22 cytokines and TSLP expression and negatively with the expression of the AMP cathelicidin.⁷⁶ IL-4 and IL-13 are able to suppress genes encoding for specific β -defensins, thus decreasing the levels of the AMPs LL-37, β -defensin, and dermicidin, creating a milieu for the growth of pathogens such as *S aureus*.⁷⁷ In addition, T_H2 cytokines stimulate the expression of fibronectin and fibrinogen, both enhancing *S aureus* binding to the SC of AD skin.⁷⁸ Together, these findings support the hypothesis that the inflammatory milieu in AD facilitates *S aureus* binding to the SC.

The virulence factors of *S aureus* such as phenol soluble modulins are able to induce IL-36- and IL-36 α -driven $\gamma\delta$ T-cell-mediated inflammation in the epidermis.⁷⁹ Furthermore, they induce dermal innate lymphoid cell-incited T_H17 response and stimulate mast cell degranulation.⁸⁰⁻⁸² *S aureus* components induce the secretion of proinflammatory cytokines characteristic for type T_H1/T_H2 axis activation *in vitro* and in mouse models.^{83,84} Colonization with pathogenic *S aureus* results in secretion of TSLP from damaged keratinocytes, which activates dendritic cells and further polarizes immunity toward a T_H2 response.⁸⁵ Additional virulence factors such as protein A, staphylococcal superantigens, and most recently second immunoglobulin-binding protein induce T_H2 type inflammation.^{86,87} A vicious cycle, comprising immune imbalance and microbiome changes, underlies the pathophysiology of AD. Immune therapies blocking IL-4 and IL-13 from suppressing T_H2 inflammation decrease the abundance of *S aureus* and enrich the microbial diversity in patients with AD.⁸⁸ Data regarding

whether novel treatment agents targeting inflammation (ie, the JAK inhibitors) exhibit effects on microbiome composition are not yet available.

IMPLEMENTATIONS FOR PREVENTION AND MANAGEMENT

Recent investigations have revealed the possible preventive effects and management strategies in the context of the current understanding of the AD pathophysiology (ie, modulation of the skin-immune system-microbiome axis).⁸⁹ The widely used anti-inflammatory treatments focus mainly on immune abnormalities in AD, despite the fact that some beneficial effects on the skin microbiota have been observed for IL-4 and/or IL-13 antibody.⁸⁸

Etiologic treatment with emollients has been proved to be efficient in preventing the development of AD when introduced early in the neonatal period.^{90,91} Recent results from larger prospective cohort studies showed no efficacy of emollients alone in preventing infantile AD,^{92,93} with even a slight increase in skin infections in the treatment group. The authors concluded that combined interventions, namely, emollient use and dietary intervention (early introduction of potential allergens), could have a cumulative protective effect. This study is ongoing, and conclusive results are not yet available. Thus, multidimensional approaches, individualized to the disease genotype and phenotype as well as to patients' ethnic and cultural preferences, should be followed in AD prevention strategies.

Manipulation of skin and gut microbiota is a tempting target to prevent AD and the atopic march. The current meta-analysis revealed that the use of probiotics in the prenatal period and the first 6 months of infancy exerts protective effects against AD development.^{94,95} Because of the greater variability of the probiotic strains, dose regimens, duration of treatment, and mechanisms of action that are being used, we still see more open questions than answers.

Direct topical manipulation of the skin microbiota dates back to the 1980s, when Leyden successfully transferred axillary bacteria to the same subject's forearm.⁹⁶ Direct transfer of living bacteria raises questions related to harvesting techniques, selection of strains, the need for cultured growth, and immune reaction of the host.⁹⁷ In AD, transplant of cultured CoNS (*S epidermidis*

and *S. hominis*) capable of inhibiting *S. aureus* growth by AMP secretion resulted in decreased *S. aureus* colonization in patients with AD.⁹⁸ However, clinical efficacy was not assessed in this trial, which opens a window for further investigations.

In mice, fecal microbiota transplantation is associated with normalization of the T_H1/T_H2 cell imbalance and a decrease in levels of IgE, circulating eosinophils, and skin mast cells in relation to lower clinical dermatitis response.⁹⁹ These promising results need to be challenged in humans.

Novel strategies focus on the biotherapeutic approach, including quorum sensing inhibitors (agents targeted in the attenuation of bacterial virulence), anti-*S. aureus* endolysins (phage enzymes used by virions to destroy bacterial wall), and mAbs.¹⁰⁰

Contouring further environmental factors such as UV exposure (related to serum vitamin D levels), water hardness, air pollution, pollen exposure, urban versus rural lifestyle, and their role in primary prevention of the atopic march remains a global challenge for physicians and researchers.⁸⁹

CONCLUSION

As a disease with highly heterogeneous genotypes and endotypes, AD requires stratified management strategies and personalized approaches. The intimate mechanisms of interactions in the skin-immune system-microbiome axis (Fig 1) reflect the complex nature of the atopic diathesis and the atopic march. Globally diversified investigational and management approaches should be synchronized to reach the best standard of care and prevention. A demand for creation of a global atopic disease registry is imminent. Joint efforts by researchers and clinicians are required to decipher the enigma of AD.

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