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Host–microbial dialogues in atopic dermatitis

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REVIEW

Abstract

Recent advances in sequencing technologies have revealed the diversity of microbes that reside on the skin surface which has enhanced our understanding on skin as an ecosystem, wherein the epidermis, immune cells and the microbiota engage in active dialogues that maintain barrier integrity and functional immunity. This mutual dialogue is altered in atopic dermatitis (AD), in which an impaired epidermal barrier, the skin microbial flora and aberrant immunity can form a vicious cycle that leads to clinical manifestations as eczematous dermatitis. Microbiome studies have revealed an altered microbial landscape in AD and genetic studies have identified genes that underlie barrier impairment and immune dysregulation. Shifting from the long-standing notion that AD was mediated by conventional allergic responses, emerging data suggest that it is a disorder of an altered host–microbial relationship with sophisticated pathophysiology. In this review, we will discuss recent advancements that suggest the roles of the skin microbiota in AD pathophysiology, genetic factors that mediate barrier impairment, dysbiosis and inflammation. Studies in mice, classic AD and monogenic disorders that manifest as AD collectively facilitate our understanding of AD pathophysiology and provide a foundation for novel therapeutic strategies.

Keywords: epidermal barrier, dysbiosis, microbiome, skin

Introduction

Our understanding on the complexity of the microbial landscape that inhabits the barrier surfaces of our bodies has significantly deepened in parallel with the advancement of sequencing technologies. 16S ribosomal RNA as well as shotgun metagenomic sequencing have demonstrated that the skin is inhabited by a plethora of micro-organisms including bacteria, fungi and viruses, collectively referred to as microbiota, which has fueled research on barrier immunity (1, 2). The host barrier and immune systems have evolved hand-in-hand with the microbiota, forming mutually beneficial relationships. While epithelia and immune cells form barriers that protect the body from microbial invasion, they also create a surface environment that allows for the stable colonization by commensal microbes. Recent emerging evidence has revealed crucial roles of skin commensals in priming and harnessing local immunity (3, 4). Altered host–microbe cross-talk leads to immune dysregulation and is believed to be a driving force in inflammatory skin diseases.

This review will discuss the pathophysiology that underlies atopic dermatitis (AD), with particular focus on dialogues that take place between the host and the microbiota. While the majority of AD patients in the European population harbor loss-of-function mutations in the gene encoding Filaggrin (FLG) (5), a structural protein crucial for proper epidermal barrier formation, the association is variable across different ethnic backgrounds (6), wherein the majority of non-European AD patients do not harbor *FLG* mutations. In this regard, monogenic diseases that manifest as AD deliver insight into the pathogenesis of AD and mechanisms that underlie dysbiosis, both from the epithelial and immunological perspectives. Lastly, this review discusses the possibility of future interventions using microbiome transplants.

Skin as an ecosystem of the body surface

The skin is a physical barrier that insulates our body from the environment. While protecting the body from pathogen invasions, research in the recent years has established that the skin surface is far from an uninhabitable, harsh terrain. Indeed, its dry, yet lipid-rich nature and the invagination of hair follicles provide aerobic and anaerobic niches for a variety of microbial communities, rendering skin as a large ecosystem supporting symbiosis between the host and microbes. Analyses utilizing next-generation sequencing of bacterial 16S rRNA genes have demonstrated taxonomic diversity, and metagenomic sequences have revealed yeast, viruses and bacteriophages as natural inhabitants of skin (7).

Commensalism of microbes is mutually beneficial for the host. During development, the colonization of *Staphylococcus epidermidis*, a gram-positive cocci ubiquitous on human skin, leads to the generation of regulatory T cells that enable stable commensalism of the bacteria without eliciting immune responses (8). During adulthood, *S. epidermidis* is recognized by the skin immune system through intact barriers, priming skin-resident $CD8^+$ T cells that confer heterologous protection against the yeast pathogen, *Candida albicans* (9, 10). While these studies were performed in mice using microbes that were derived from humans, they represent an example of how host and commensal bacteria communicate, and the broader picture of the interplay is an exciting field of research that is under active investigation.

The roles of skin barriers and immune cells have been well established in the setting of host-protective immune responses against pathogens. Recent studies have further unveiled homeostatic interactions between the immune cells and skin parenchyma that maintain structural, immunological and microbial homeostasis. Our previous studies highlight the hair follicles as control towers of skin immunity by producing chemokines to recruit and position skin-resident immune cells and to provide cytokines that enable their long-term persistence in skin (11, 12). We recently demonstrated that innate lymphoid cells (ILCs) exist in the upper parts of the hair follicles guided by a hair follicle-derived chemokine, CCL20, and that their residency was supported by Interleukin (IL)-7 and thymic stromal lymphopoietin (TSLP). There, the ILCs produced tumor necrosis factor receptor (TNFR) ligands that negatively controlled sebaceous gland function by suppressing the production of anti-bacterial lipids that restricted the commensalism of gram-positive cocci. This was in contrast to the actions of lymphocytes, whose absence led to the overgrowth of gram-positive cocci. Thus, the dynamic equilibrium of the skin microbiota is tuned by intricate dialogues between immune cells, epithelium and microbes (13). These fundamental mechanisms that regulate the skin microbiota provide insight into host–microbiota relationships, and further studies on how the dialogues go awry may provide better understanding of pathophysiology in inflammatory skin diseases such as AD.

Multifaceted pathophysiology of AD

AD is a chronic inflammatory skin disease that manifests as dry skin and eczematous dermatitis with relentless itch. Onset typically occurs during childhood and uncontrolled skin inflammation may lead to sequential onset of asthma, allergic rhinitis and food allergies, referred to as the atopic march (14). Other complications include cataracts, susceptibility to virus infections and mental health issues. Thus, significant comorbidities occur in AD, emphasizing the importance of understanding the pathophysiology involved. Note that while utilization of the term ‘eczema’ is not recommended from the clinical practice perspective, we herein utilize the term ‘eczematous dermatitis’ to reflect the spectrum of skin inflammation that may be observed in classic and monogenic AD, as well as in mouse models.

AD is a multifactorial, associated with impaired barrier formation, dysregulated type 2 immune response and increased susceptibility to *Staphylococcus aureus* colonization. Discoveries on genetic factors that underlie impaired epidermal barrier have provided momentum to the field, opening the door for detailed research also on immunological and microbiological aspects of the disease. Type 2 immune signatures and high levels of circulating IgE against inhaled allergens such as house dust and mite antigens have supported the notion that AD was an IgE-mediated allergic dermatitis elicited by chronic exposure to allergens. However, this long-held view is beginning to change with the observation that AD is closely associated with imbalanced balance of the skin microbiota, termed dysbiosis, which is predominated by *S. aureus* during the active phase of the disease (15).

These findings provide an opportunity for developing novel therapeutic strategies. A clearer picture on dysregulated immune networks has led to the emergence of new molecular targeting drugs such as IL-4R monoclonal antibody (16) and JAK inhibitors (17). Targeting the dysbiotic flora is also gaining considerable attention. However, there is still much to be learned to enable efficient and sustainable control of AD. Major unanswered questions include those regarding mechanisms that lead to exacerbated type 2 immune responses, cellular sources and targets of immune mediators, host-inherent factors that allow dysbiosis and characteristics of the dysbiotic flora themselves.

The skin microbiome in AD

It was first observed over five decades ago that AD skin was heavily colonized with *S. aureus* (18). More recently, 16S rRNA sequencing has revealed that the microbiome in AD skin is shifted toward an increased relative abundance of *Staphylococcus* species, particularly *S. aureus*. *Staphylococcal* colonization correlates with disease severity, suggesting the active involvement of *Staphylococcus* species during flares (15, 19). A study comparing *S. aureus* carrier and non-carrier AD patients has revealed that *S. aureus* carriers display higher disease severity and increased levels of type 2 immune biomarkers (20). Importantly, shifts in microbial compositions occur before the onset of AD (21, 22), suggesting microbial changes that are formed early in life may contribute to onset of AD.

It has been long debated whether the dysbiotic changes in AD were a consequence of chronic skin inflammation or whether they were actively involved in driving skin inflammation. This was, in part, due to the lack of mouse models that exhibited dysbiosis. Studies in mouse models have begun to reveal causal relationships. Mice deficient in a disintegrin and metalloproteinase 17 (ADAM17) spontaneously develop eczematous dermatitis with dysbiosis that was predominated by *S. aureus* and *Corynebacterium* species. Targeting the dysbiotic flora with an antibiotic cocktail in mice with pre-established eczematous dermatitis reversed dysbiosis and extinguished eczematous inflammation. Furthermore, the inoculation of *S. aureus* enhanced eczematous dermatitis and *Corynebacterium bovis* drove T helper 2 (T_h2) responses, which presumably leads to IgE responses, revealing crucial and distinct roles of dysbiotic flora during atopic inflammation (23).

The mechanisms by which *S. aureus* initiate or exacerbate atopic inflammation remain to be further explored. Interestingly, *S. aureus* express molecules that mediate

cytotoxic and immunological effects on host cells. α-Toxin is a pore-forming toxin that causes direct cellular damage to keratinocytes (24). Phenol soluble modulins (PSMs) are a family of *Staphylococcal* virulence factors that exert pro-inflammatory properties (25). In epicutaneous infection models of *S. aureus* in mice, PSM-α induces IL-17-dependent skin inflammation via IL-1R and IL-36R signaling (26, 27). PSM-δ (δ-toxin) induces skin inflammation by stimulating mast cell degranulation (28). Metagenomic analysis has revealed that particular strains of *S. aureus* dominate in individual patients during flares, and that the ability of *S. aureus* to induce immune responses is strain-dependent (19), warranting further investigations on whether strain-level differences in toxin production among *S. aureus* are associated with clinical phenotype and disease severity in AD.

Genetic factors in AD

Studies on host genetic factors may reveal candidate genes that underlie barrier impairment, exacerbated immune responses and the inability to regulate the skin microbiota. Genome-wide association studies of AD have demonstrated the association of single-nucleotide polymorphisms in a number of genes and loci that are related to type 2 cytokines, T-cell proliferation and survival, innate immune response and epidermal barrier functions, such as *IL4*, *IL13*, *IL18R1*, *IL6R*, *IL15RA*, *IL2RA*, *IL7R*, *CARD11*, *STAT3* and *FLG* (29–31). These results suggest that AD may either be impaired barrier-driven, immunity-driven or both. Multiple factors may synergistically trigger the development and exacerbation of AD, collectively contributing to the sophisticated pathophysiology. Importantly, single-nucleotide polymorphisms do not indicate functional alterations of the genes. In this regard, studies on monogenic diseases that manifest as AD with defined mutations in immune and non-immune genes are an attractive approach to elucidate the role(s) of single genes in the development of AD (Table 1; Fig. 1). The following sections will focus on dissecting molecular-level links between AD and dysbiosis from the genetic perspective.

Monogenic disorders manifesting as AD

The autosomal dominant hyper-IgE syndrome (STAT3-HIES; a.k.a. Job's syndrome), caused by dominant-negative mutations in signal transducer and activator of transcription 3 (*STAT3*), is a monogenic disorder that has been long associated with AD. STAT3-HIES patients present elevated serum IgE levels, eczematous dermatitis and recurrent *Staphylococcal* infections and mucocutaneous candidiasis (32, 33). 16S rRNA sequencing has revealed altered microbial compositions represented by the emergence of *Serratia marcescens*, an environmental microbe that has not been previously identified as a component of the normal skin flora (34). *Staphylococcus* and *Corynebacterium* are highly over-represented, and the disease severity is positively correlated with the prevalence of these bacteria. In addition, analysis of oral mucosa in STAT3-HIES reveals fungal dysbiosis with dominance of *C. albicans*, which is consistent with recurrent mucosal fungal infections in the patients (35). Importantly, eczematous dermatitis in STAT3-HIES is attenuated with *Staphylococcus* clearance measures, reinforcing the role of *S. aureus* in driving eczematous dermatitis (36).

STAT3 is a key transcription factor for T_h17 differentiation that is also involved in downstream signaling of IL-6, IL-21, IL-10 and IL-23 (37, 38). STAT3-HIES T cells show decreased expression of retinoid-related orphan receptor (ROR)-γt (a crucial transcription factor for T_h17 cell differentiation) and are unable to differentiate into T_h17 cells (39). Because IL-17 is an essential cytokine that promotes epithelial anti-microbial functions against extracellular bacterial and fungal infections, impaired T_h17 differentiation is considered to be a major mechanism underlying the susceptibility to dysbiosis and recurrent infections. Notably, STAT3 is also expressed by keratinocytes and may be involved in barrier functions. Keratinocyte-specific depletion of *Stat3* results in impaired hair cycling and wound healing in mice, which is associated with altered adhesion and migration of keratinocytes (40, 41). Intra-dermal lipopolysaccharide or epicutaneous ovalbumin challenge in mice that lack *Stat3* in keratinocytes leads to high IgE and type 2 immune responses (42). The finding that neither T cell- nor keratinocyte-specific depletion of *Stat3* leads to spontaneous onset of eczematous dermatitis suggests that impaired STAT3 signaling in immune cells and

Table 1. Monogenic conditions that manifest as AD in humans.

Affected cells or process	Gene mutations	Disease name
JAK-STAT signaling	Dominant negative mutations in *STAT3* (OMIM: # 147060)	Autosomal dominant hyper IgE syndrome
	Gain-of-function mutations in *STAT3* (OMIM: # 615952)	Infantile-onset multisystem autoimmune disease-1
	Gain-of-function mutations in *JAK1*	Not applicable
	Dominant negative mutations in *CARD11* (OMIM: # 617638)	Immunodeficiency-11B with atopic dermatitis
T cell functions	Loss-of-function mutations in *MALT1* (OMIM: # 615468)	Immunodeficiency-12
	Loss-of-function mutations in *DOCK8* (OMIM: # 243700)	Autosomal recessive hyper IgE syndrome
	Loss-of-function mutations in *WASP* (OMIM: # 301000)	Wiskott-Aldrich syndrome
Stratum corneum barrier	Loss-of-function mutations in *FLG* (OMIM: # 146700)	Icthyosis vulgaris
	Loss-of-function mutations in *SPINK5* (OMIM: # 256500)	Netherton syndrome
	Loss-of-function mutations in *CDSN* (OMIM: # 270300)	Peeling skin syndrome-1
Junctional barrier	Loss-of-function mutations in *DSG1* (OMIM: # 615508)	Severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome
	Dominant heterozygous mutations in *DSP*	
Keratinocyte differentiation	Loss-of-function mutations in *ADAM17* (OMIM: # 614328)	Neonatal inflammatory skin and bowel disease-1
	Loss-of-function mutations in *EGFR* (OMIM: # 616069)	Neonatal inflammatory skin and bowel disease-2

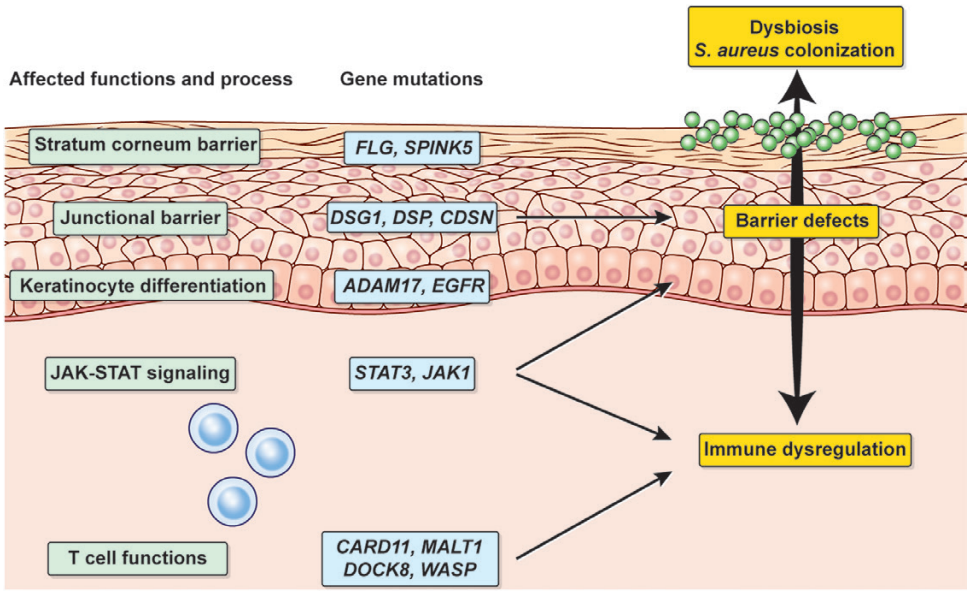

Fig. 1. Genetic factors that underlie the pathophysiology of AD. Monogenic diseases with defined mutations in genes associated with epidermal barrier, JAK–STAT signaling and lymphocyte functions manifest as eczematous dermatitis and *Staphylococcal* dysbiosis.

epithelial cells synergistically leads to eczematous dermatitis and dysbiosis (37, 43). Mice carrying the dominant-negative form of STAT3 as seen in STAT3-HIES exhibit elevated IgE and are susceptible to *Citrobacter rodentium* infection but do not develop eczematous inflammation, at least in SPF conditions (44), further suggesting that the involvement of additional environmental factors is required, such as signals from commensal microbes.

Interestingly, patients with gain-of-function mutations in *STAT3* also present eczematous dermatitis (45), indicating that the JAK–STAT signaling pathway must be tightly regulated to maintain skin homeostasis. A *JAK1* gain-of-function mutation also leads to systemic immune dysregulation and eczematous dermatitis in both humans (46) and mice (47), in which JAK inhibitors are efficacious. The use of JAK inhibitors in AD is under active investigation and preliminary results are promising (17). Further studies are required to understand how the JAK–STAT pathway operates in hematopoietic and non-hematopoietic compartments and contributes to the maintenance of skin barrier integrity and microbiome balance.

Mutations in genes involved in T cell receptor (TCR) signaling and T-cell responses also lead to atopic manifestations. Cytoskeletal remodeling proteins, Wiskott–Aldrich syndrome (WAS) protein and dedicator of cytokinesis 8 (DOCK8), mediate signaling during TCR-driven actin assembly in T cells (48). Both WAS- and DOCK8-deficient patients display elevated IgE, manifest eczematous dermatitis and have recurrent infections (49, 50). Similar to STAT3-HIES, skin microbiome analysis of WAS- and DOCK8-deficient patients has demonstrated significant shifts in the microbiome, represented by the predominance of *Staphylococcus*, *Propionibacterium* and *Corynebacterium* species (34). Strikingly, dysbiosis is not limited to bacteria and fungi. Deep metagenomic sequencing analysis of DOCK8-deficient skin revealed the predominance of DNA viruses with increased viral diversity and hundreds of novel human papillomavirus genomes (51). While DOCK8 is known to regulate T-cell function in anti-viral immunity, the shifts in the microbiome and virome of DOCK8-deficient skin underscore the importance of lymphocyte-mediated immune surveillance for micro-organisms. Why an atopic phenotype emerges as a result of impaired regulation of the actin cytoskeleton in T cells is not yet clear. Bias toward T_h2 in $CD4^+$ T cells from DOCK8-deficient patients might be related to enhanced IgE production and eczematous dermatitis (52). It is attractive to hypothesize that immune responses against the altered virome drive eczematous inflammation.

Mutations in genes encoding a signal complex that connects TCR signals to NF-κB activation result in immunodeficiency and atopic symptoms. Patients with defects in the caspase recruitment domain family member 11 (CARD11) (53, 54) and mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALT1) (55) present eczematous dermatitis and recurrent bacterial and viral skin infections. Taken together, these monogenic disorders due to dysregulated T-cell functions provide new insights into AD pathophysiology from an immunological perspective.

Epidermal barrier impairment underlying eczematous inflammation and dysbiosis

Mutations in a number of genes that are essential for epidermal barrier integrity have also been identified in both classic and monogenic AD (Table 1; Fig. 1). In particular, loss-of-function mutations in *FLG*, which were initially identified in patients with ichthyosis vulgaris, are a major predisposing factor for classic AD, particularly in the European population (5). FLG-derived peptides maintain structural integrity and hydration in

the stratum corneum, in part through degradation into natural moisturizing factors (NMFs). NMFs influence skin surface pH, affecting the keratinization process as well as microbial colonization. Acidic conditions in the presence of NMFs disfavor *S. aureus* growth (56). Atopic individuals tend to have alkaline skin conditions, suggesting that *S. aureus* colonization may be facilitated in part by pH shifts in FLG-deficient skin. The increased pH in epidermis also influences the activity of serine proteases that cleave IL-1 family cytokines. Indeed, increased IL-1 cytokines are correlated with FLG deficiency and reduced NMFs both in human patients and in FLG-deficient mice (57). Incisional damage to skin in *Flg*-mutant (*ft*/*ft*) mice induces the release of intracellularly stored IL-1α in keratinocytes, resulting in IL-1α-mediated skin inflammation and dysbiotic conditions. Topical antibiotic treatment reverses the skin inflammation, supporting the idea that both barrier deficiency and dysbiosis are crucial components of skin inflammation (58).

Cytokines that are abundant in AD skin, IL-4 and IL-13, act negatively on FLG expression (59). IL-4 and IL-13 also down-regulate the expression of anti-microbial peptides, suggesting that dysregulated immunity also confers susceptibility to bacterial colonization in AD skin (37, 38, 60, 61). A mutation of *Flg* in the BALB/c background (BALB/c *ft*/*ft*) facilitates *S. aureus* penetration into viable skin layers, which correlates with increased expression of IL-4 and IL-13. These observations suggest a pathogenic loop formed by increased type 2 immunity, FLG deficiency and *S. aureus* colonization (62). Interestingly, *S. aureus* inoculation onto C57BL/6 mouse skin with genomic ablation of *Flg* does not induce type 2 responses, but rather, type 17 responses, and does not lead to overt eczematous inflammation (23). Both genetic backgrounds and the nature of FLG deficiency (mutation versus deletion) could contribute to these differences.

In addition to bacterial dysbiosis, patients with AD are known to be susceptible to viral infections such as herpes simplex virus (HSV) infections and vaccinia virus infections. Disseminated cutaneous HSV infections, called eczema herpeticum, are a common complication in AD. *FLG* mutations associated with AD confer a greater risk for eczema herpeticum (63), suggesting that impaired barrier and/or altered immune responses in the absence of FLG predisposes to viral infections. Smallpox vaccination is contraindicated in AD and may result in extensive rash and systemic illness, called eczema vaccinatum. Although the mechanism that allows for the spread of vaccinia virus remains largely unclear, it is reported in human skin explants that IL-4 and IL-13 suppress the expression of an anti-microbial peptide cathelicidin/LL-37, thereby enhancing vaccinia virus replication, and that neutralizing IL-4 and IL-13 rescues LL-37 expression and inhibits viral replication (64). Consistently, BALB/c *ft*/*ft* mice display increased susceptibility to cutaneous vaccinia virus inoculation wherein virus disseminates to internal organs (65). Future research that further elucidates barrier and immunological alterations in the absence of FLG might enable identification of potential therapeutic targets that prevent susceptibility to microbes.

Rare genetic disorders with mutations in barrier-associated genes also manifest symptoms that resemble AD (Table 1; Fig. 1). Autosomal-recessive loss-of-function mutations in Kazal type 5 (*SPINK5*), encoding the serine peptidase inhibitor LEKTI, are responsible for causing Netherton syndrome, which is characterized by congenital icthyosiform erythroderma, atopic manifestations and *S. aureus* colonization (66). LEKTI inhibits kallikrein family proteases which regulate desquamation of epidermis. Loss of LEKTI thereby results in enhanced proteolytic activity in the epidermis, leading to impaired stratum corneum formation and *S. aureus* colonization. In addition, unregulated kallikrein activates proteinase-activated receptor 2 (PAR2) and induces NF-κB-mediated over-expression of TSLP, which can trigger type 2 immune responses that may contribute to eczematous dermatitis (67, 68).

Impaired keratinocyte cell–cell adhesion also leads to atopic manifestations. Severe eczematous dermatitis, multiple allergies and *Staphylococcal* skin infections occur in patients with mutations in desmosomal proteins, desmoglein 1 (*DSG1*) and desmoplakin (*DSP*) (69, 70). Loss of corneodesmosin (*CDSN*), an adhesion protein in corneodesmosomes, leads to development of eczematous dermatitis, allergies and *S. aureus* skin infections (71). In aggregate, these genetic disorders emphasize barrier disruption as a fundamental element that leads to eczematous dermatitis and dysbiosis in skin.

Epithelial barrier integrity relies on proper terminal differentiation of keratinocytes, which is controlled, in part, by signaling through epidermal growth factor receptor (EGFR) (72). EGFR signaling is regulated by an upstream proteinase via release of membrane-bound form of EGFR ligands. ADAM17 is a transmembrane proteinase that cleaves a variety of membrane-anchored molecules including EGFR ligands and plays a critical role in the regulation of tissue integrity (73). A loss-of-function mutation in *ADAM17* was reported in a patient who exhibited eczematous dermatitis and *S. aureus* skin infections (74). Three individual studies have demonstrated that keratinocyte-specific depletion of *Adam17* in mice results in chronic AD-like skin inflammation with barrier impairment (23, 75, 76).

We have demonstrated that *S. aureus* colonization precedes eczematous dermatitis formation in the Adam17-deficient skin (23), suggesting that dysbiosis is attributed to impaired ADAM17 deficiency in keratinocytes and that it is not secondary to chronic inflammation. Epidermal deletion of EGFR in mice also leads to dysbiosis and eczematous dermatitis, suggesting that impaired EGFR signaling is in part responsible for the phenotype observed in ADAM17-deficient mice (23, 75, 77, 78). Consistently, patients with loss-of-function mutations in *EGFR* share clinical features with ADAM17-deficient patients (79). Furthermore, patients treated with EGFR inhibitors during cancer therapy experience cutaneous adverse effects including dry and erythematous skin and bacterial skin infections (80), from which *S. aureus* is commonly isolated (78). Antibiotics have beneficial effects in ameliorating these skin conditions (81). Increased susceptibility to bacterial infections might be related to altered expression of anti-microbial peptides that are regulated downstream of EGFR (78). Collectively, these studies identify the ADAM17–EGFR axis as crucial for tuning epidermal barrier functions and in restricting dysbiosis. Further studies that elucidate detailed upstream and downstream events may have broad impact on the development of new therapeutic strategies in AD and EGFR antagonist-related skin toxicities.

Intervention with microbiome therapies

Despite accumulating evidence on the contribution of dysbiosis and *S. aureus* in AD, the clinical efficacy of anti-bacterial interventions in AD remains controversial (82). Given that antibiotics treatment can have systemic effects on the normal flora and lead to the emergence of antibiotics-resistant bacteria, skin-targeted approaches without the use of antibiotics would be better suited. A high-throughput anti-microbial screening of coagulase-negative *Staphylococcus* (CoNS) species against *S. aureus* has revealed new anti-microbial peptides that inhibit *S. aureus* growth. Importantly, these anti-microbial peptide-producing CoNS strains are less frequent in atopic individuals, and reintroduction of CoNS decreases *S. aureus* colonization (83). An open-label trial was recently conducted to evaluate the safety and efficacy of a strain of Gram-negative bacteria on AD (84). Topical application of *Roseomonas mucosa* reduced *S. aureus* colonization and decreased both disease severity and the use of topical steroids. While *R. mucosa* affects the innate immune response and barrier function (85), whether *R. mucosa* mediates its effects by restricting dysbiotic flora, or by directly modulating immunity, remains unclear. Further work will be needed to elucidate the mechanisms of action and to determine the efficacy and safety of biological agent-based therapies.

Conclusion

Extensive research over the past decade has highlighted dynamic interactions that take place between the immune system and the microbiota. These dialogues are essential for tissue development, homeostatic maintenance of epithelial barriers and functional immunity. The host has developed an array of sophisticated physical and immunological strategies to maintain the mutualistic relationship with the microbiota. Impaired dialogue leads to chronic inflammatory conditions as seen in AD. The mechanisms underlying dysbiosis, its roles in AD and novel therapeutic strategies that target upstream and downstream pathways are only beginning to be revealed. While more multifaceted research from clinical, immunological and microbiological approaches is needed, the recent development opens the door to an exciting field of research that should unveil links between the host and the microbiota in health and disease.

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