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Which way do we go? Complex interactions in atopic dermatitis pathogenesis

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Abstract

Atopic dermatitis is a common, chronic, inflammatory skin condition characterized by recurrent and pruritic skin eruptions. Multiple factors contribute to the pathogenesis of atopic dermatitis including skin barrier dysfunction, microbial dysbiosis and immune dysregulation. Interactions between these factors form a complex, multidirectional network that can reinforce atopic skin disease, but can also be ameliorated by targeted therapies. This review summarizes the complex interactions between contributing factors in atopic dermatitis and the implications on disease development and therapeutic interventions.

INTRODUCTION

Atopic dermatitis (AD) is the most common inflammatory skin disorder, with an estimated worldwide prevalence of 3–5% in adults and 15–20% in children (Asher et al. 2006; Weidinger et al. 2018). AD is characterized by eczematous, pruritic skin patches and plaques that can severely affect quality of life and result in high socioeconomic costs (Chung and Simpson 2019). AD has also been proposed to initiate the “atopic march”, a sequential development of allergic disorders including food allergies, allergic rhinitis, and asthma, though this concept has been challenged as a clustering of diseases rather than a sequential march (Dharmage et al. 2014; Gustafsson et al. 2000; Paller et al. 2019)._Therefore, a

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

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deeper understanding and targeted treatments against the pathogenic mechanisms in AD could have implications in the prevention of other allergic diseases.

Several models have been proposed to explain the pathogenesis of AD. Initial studies focused on the role of altered immune responses, especially Th2 and IgE responses, to be major drivers of the disease (van der Heijden et al. 1991; Vestergaard et al. 1999). The so-called “inside-out” hypothesis postulated that immune dysregulation leads to compromised skin barrier function, thus permitting allergens and pathogens to penetrate the skin (Leung 1999). However, the discovery of inherited defects in factors that contribute to the skin barrier posited the alternative “outside-in” hypothesis, where an underlying barrier dysfunction allows antigen penetration to induce altered immune responses (Proksch et al. 2006). Recently, models have incorporated aspects of both, including an “outside-inside-outside” model where the skin microbiome and environmental factors penetrate the body from the outside through epidermal barrier defects and trigger immune dysregulation, which further exacerbates skin barrier defects (Elias 2008).

The complexity of current AD models indicates significant potential for interaction and crosstalk between epidermal barrier defects, the skin microbiome and immune dysregulation. This review will summarize the current state of research into the complex interactions of these factors in the immunopathology of AD and the implications of this complexity for the development of therapeutics.

CONTRIBUTING FACTORS: INSIDE AND OUT

Barrier dysfunction

The skin provides a key barrier between the body and the outside world, preventing transepidermal water loss (TEWL) and excluding pathogens and environmental antigens (De Benedetto et al. 2012). A major component of this barrier function is the multifunctional epidermal protein filaggrin. Filaggrin is produced as the large, insoluble profilaggrin in the keratohyalin granules of keratinocytes (Brown and Irwin McLean 2012). These granules form liquid-liquid phase separation droplets that contribute to barrier formation as they reach the skin surface (Quiroz et al. 2020). Additionally, profilaggrin undergoes processing and crosslinking to ultimately contribute to a tightly interwoven lipid/protein matrix that acts as the “mortar” that holds keratinocyte bricks together in a strong, impermeable “brick and mortar” structure (Nemes and Steinert 1999). In addition to this structural role, filaggrin is degraded by proteases to release its component amino acids as one component of the so called natural moisturizing factors (NMF) that help to keep the epidermis hydrated (Rawlings and Harding 2004).

Lipids play an important role in barrier formation by maintaining lubrication and preventing dehydration, as well as having antimicrobial activity (Bhattacharya et al. 2019). Epidermal lipids are mainly composed of ceramides, cholesterol and free fatty acids, though the composition and amount vary across different body surfaces (Greene et al. 1970; Pappas 2009). These lipids make up a significant proportion of the extracellular matrix surrounding the crosslinked filaggrin, helping to make up the “mortar” of the brick and mortar structure (Elias and Friend 1975).

Disruption of barrier function can have profound implications for the development of AD. Filaggrin mutations are the strongest genetic risk factor in the development of AD (Palmer et al. 2006), and correlate with increased disease severity, allergic sensitization, and overall higher healthcare costs (Heede et al. 2017; Soares et al. 2018). Filaggrin mutations have also served as the basis for AD mouse models, including the flaky tail model (ft/ft mice) and the monogenic filaggrin-knockout mice ($Flg^{ft/ft}$ mice) (Nakajima et al. 2019). Despite this strong association, filaggrin mutations are only present in a minority of the population and are unevenly distributed across racial and ethnic groups. For example, filaggrin mutations are present in approximately 30–50% of European Americans with AD, 27% of Asians with AD and 3–6% of African Americans with AD (Margolis et al. 2012; Czarnowicki et al. 2019), and the R501X and 2282del4 mutations account for 80% of filaggrin mutations in Ireland but only 1% in Singaporean Chinese (Chen et al. 2011).

In addition to filaggrin, other components of the skin barrier have been implicated in AD, including tight junction proteins (Zaniboni et al. 2016). For example, decreased claudin-1 expression in the affected skin of AD patients correlated with disease severity (De Benedetto et al. 2011). The skin also produces host defense peptides (HDPs) to regulate and control skin microbes and trigger host immune responses including inflammatory cytokine production (Schauber and Gallo 2008). Levels of these skin barrier proteins are decreased or dysregulated in atopic skin, further disrupting the barrier (Kuo et al. 2013). Furthermore, alterations in skin lipid composition are associated with barrier dysfunction in AD, including decreased ceramide chain length (Ishikawa et al. 2010; Janssens et al. 2012), increased cholesterol-3-sulfate levels (Li et al. 2017), and increased short chain and mono-unsaturated free fatty acids (Macheleidt et al. 2002; van Smeden et al. 2014)._A delicate balance between proteases, both intrinsic and environmental, and host-derived protease inhibitors regulate barrier formation through cleavage of structural proteins to induce desquamation (Veer et al. 2014). For example, excessive protease activity in the skin of patients with Netherton syndrome (that is caused by mutations in the protease inhibitor SPINK5) contributes to atopic skin disease and other systemic allergic conditions (Chavanas et al. 2000).

AD is an intensely pruritic condition driven by hyperinnervation, hypersensitivity and the release of pruritogens including IL-31, histamine, TSLP, bradykinin, and substance P (Furue et al. 2017; Hosogi et al. 2006; Kantor and Silverberg 2017; Kido-Nakahara et al. 2017; Mollanazar et al. 2016). As a result, skin injury from scratching significantly contributes towards impairment of skin barrier function via mechanical damage and upregulation of host proteases (Hachem et al. 2006). Additionally, microbial and/or host proteases produced or induced by common environmental skin exposures to house dust mites, cockroaches, fungi, pollen and bacteria can degrade intracellular junctions, disrupt the epithelial barrier and decrease lamellar body secretion critical for recovery of the epidermis (Takai and Ikeda 2011) (Jeong et al. 2008). Weather conditions, especially cold temperatures and low humidity, can also increase the permeability of the skin through a variety of mechanisms including decreased skin hydration, decreased extensibility and increased sensation of itch (Engebretsen et al. 2016).

Dysbiosis

As part of the interface with the environment, the skin is normally colonized by diverse commensal microorganisms while also preventing penetration by pathogenic microorganisms (Byrd et al. 2018; Paller et al. 2019). The balance of microorganisms that compose the skin microbiome is dynamic and there are differences in composition, depending on the anatomic skin site, age, sex and disease state (Findley et al. 2013; Grice et al. 2009). AD is associated with drastic shifts of the skin microbiome, notably the loss of commensal diversity and the dominant colonization with pathogenic *Staphylococcus aureus* and commensal *S. epidermidis* (Byrd et al. 2017). AD skin lesions have an estimated 90% *S. aureus* colonization rate that correlates with increased disease burden (Higaki et al. 1999). Clonotypic analysis of *S. aureus* clinical isolates shows that highly pathogenic, antimicrobial resistant, toxigenic strains predominate in AD skin that correlate with disease severity (Guzik et al. 2005; Pascolini et al. 2011). Conversely, recovery of commensal diversity can precede and indicate resolution of disease (Kong et al. 2012; Shi et al. 2018).

Immune dysregulation

AD is an inflammatory skin disease in which immune dysregulation results in subsequent systemic immune complications (Gavrilova 2018). Atopic dermatitis is strongly associated with type 2 immunity_(Brandt and Sivaprasad 2011). Robust Th2 polarization is seen as early as in the cord blood of infants that develop AD and continues to be present through adulthood (Herberth et al. 2010). This polarization towards Th2 immunity promotes the development of IgE producing B cell and plasma cells, thus contributing to other allergic diseases like food allergies, allergic rhinitis and asthma (Dharmage et al. 2014).

Recent studies have expanded on this Th2 paradigm to include roles for other immune subsets (Berker et al. 2017), such as Th17 (Esaki et al. 2016; Sugaya 2020), Th22 (Gittler et al. 2012), T regulatory cells (Tregs) (Fyhrquist et al. 2012) and Th9 cells (Ciprandi et al. 2013; Ma et al. 2014) in AD pathogenesis. Even Th1 immunity, while downregulated in acute AD, plays a crucial role in the maintenance of chronic AD (Su et al. 2017). Components of the innate immune system contribute significantly to the development of AD skin inflammation, including IL-5 and IL-13 from group 2 innate lymphoid cells (ILC2s), IL-4 from basophils, and IL-25, IL-33, and TSLP from epithelial cells (Divekar and Kita 2015; Hussain et al. 2018; Mashiko et al. 2017; Salimi et al. 2013). This immune milieu is dependent on a patient's age, sex, and ethnic background, thereby adding to the complexity of this disease (Brunner et al. 2019; Brunner and Guttman-Yassky 2019; Kanda et al. 2019).

As an inflammatory skin condition, associations between human leukocyte antigen (HLA) loci and AD were thought to be likely. Multiple large studies have identified HLA loci including HLA-DRB1, HLA-DQA1, and HLA-DQB1, that demonstrate linkage to AD (Margolis et al. 2015; Paternoster et al. 2015; Saeki et al. 1995). Interestingly, all co-associated HLA loci between psoriasis and AD display opposing effects, in accordance with lower than expected concomitance of these two disparate diseases in patients (Baurecht et al. 2015; Nanda 1995).

MULTIDIRECTIONAL INTERACTIONS BETWEEN CONTRIBUTING FACTORS IN ATOPIC DERMATITIS PATHOGENESIS

Barrier dysfunction and dysbiosis

Barrier dysfunction alters the skin microbiome—One of the crucial roles of the skin barrier is to exclude pathogenic microorganisms and maintain a healthy layer of commensal bacteria (Gallo 2017). Disruptions to barrier function can result in deleterious changes to the microbiome known as dysbiosis (Figure 1a) (Zeeuwen et al. 2012). Patients with loss-of-function filaggrin mutations have profound shifts in their microbiome, including increased colonization with *S. aureus* as well as decreased microbial diversity (Clausen et al. 2017; Zeeuwen et al. 2017). Loss-of-function mutations in filaggrin results in increased surface accessibility of fibronectin and fibrinogen, which *S. aureus* uses for surface adherence (Cho et al. 2001). Additionally, filaggrin deficiency decreases skin hydrating natural moisturizing factors (NMFs), further disrupting the skin barrier and increasing accessibility of *S. aureus* binding proteins (Kezic et al. 2011). *S. aureus* clonotypes with increased avidity to adherence proteins are shown to be enriched in the skin of patients with filaggrin mutations (Clausen et al. 2017; Fleury et al. 2017). In addition to structural roles, filaggrin also plays a role in the expression and release of enzymes crucial to antimicrobial defense. Loss-of-function mutations in filaggrin results in decreased sphingomyelinase, an enzyme that can decrease levels of sphingomyelin. Sphingomyelin is employed by *S. aureus* in the binding of its pore forming α-toxin and the loss of sphingomyelinase results in increased lysis of keratinocytes and dermonecrosis (Brauweiler et al. 2013). In addition to the important role of filaggrin in impacting the skin microbiome, disruptions in the lipid envelope have also been implicated in promoting dysbiosis, including increases in *S. aureus* burden (Baurecht et al. 2018).

Microbiome composition affects skin barrier function—Dysbiosis can also have consequences for skin barrier function. Clinical studies have shown that TEWL is increased with *S. aureus* colonization and positively correlates with bacterial burden (Jinnestål et al. 2014), though the directionality of this interaction is unknown. *S. aureus* utilizes a variety of secreted factors to disrupt the barrier, including proteases that degrade intercellular connections and pore-forming toxins to induce dermonecrosis (Williams et al. 2019). *S. aureus* also induces the activity of host proteases, which exacerbate barrier dysfunction by degrading structural proteins such as filaggrin and desmoglein-1 (Williams et al. 2017).

Barrier dysfunction and immune dysregulation

Barrier dysfunction induces immune dysregulation—Defective barrier function also plays a role in the immune dysregulation seen in AD (Figure 1b). Classical AD immune responses are elevated in patients with filaggrin loss-of-function mutations, with increased Th2 polarization, IgE levels and enhanced responses to epicutaneous allergen challenge (Brough et al. 2014). In mice, filaggrin deficiency induced similar polarization (Fallon et al. 2009; Scharschmidt et al. 2009). For example, increased levels of thymic stromal lymphopoietin (TSLP) are seen in skin equivalent cultures with filaggrin deficiency, which resulted in increased Th2 polarization (Wallmeyer et al. 2017). Filaggrin inhibits

phospholipase A2 (PLA2) which participates in the generation of neolipid antigens that bind CD1a, resulting in a decrease in T cell proliferation and ultimately a decrease in Th2 immune responses (Jarrett et al. 2016). Conversely, patients with mutations in filaggrin lack inhibition of PLA2 dependent neolipid generation, resulting in significant increases in both total CD1a reactive T cells and percentage of those cells expressing IL-13 compared with patients without filaggrin mutations (Jarrett et al 2016). Excessive protease activity in filaggrin-deficient (ft/ft) mice may also play a role in TSLP production, with inhibition of the protease activating receptor 2 (PAR2) inhibiting this response (Moniaga et al. 2013). The excessive protease activity in Netherton syndrome (described above) also resulted in elevated skin TSLP and Th2 responses (Briot et al. 2009). In addition to filaggrin, other barrier deficiencies can induce immune dysregulation. Claudin-1, a tight junction protein, has been shown to be inversely correlated with Th2 polarization, though directionality is unclear (De Benedetto 2011). Tape-stripping of mouse skin is an experimental approach to artificially mimic skin barrier dysfunction from scratching behavior, which provides a model for the itch-scratch cycle in AD and results in induction of TSLP and polarizes dendritic cells to elicit Th2 responses in draining lymph nodes (Angelova-Fischer et al. 2010; Kondo et al. 1998; Oyoshi and Geha 2008).

Beyond the traditional Th2 paradigm, barrier dysfunction also induces other T cell subsets seen in AD. Children with loss-of-function filaggrin mutations have been shown to have increased peripheral Th17 responses, while filaggrin-deficient mice have been shown to have increased Th17 cells and IL-17-producing γδ T cells (Bonefeld et al. 2016; Jee et al. 2018; Oyoshi et al. 2009). Adults with loss-of-function filaggrin mutations also have decreased numbers of Tregs with impaired function and decreased IL-10 production (Moosbrugger-Martinz et al. 2019).

Immune dysregulation alters skin barrier function—Immune dysregulation can also have profound effects on skin barrier function. Treatment of keratinocytes with IL-4 and IL-13 decreases expression of filaggrin and other epidermal structural barrier proteins, including involucrin and loricrin (Howell et al. 2009; Kim et al. 2008). Filaggrin processing is also decreased by the downregulation of caspase-14, which processes filaggrin to profilaggrin (Hvid et al. 2011). Treatment of keratinocytes with IL-4 upregulates the production of proteases that contribute to desquamation, resulting in decreased barrier function as measured by TEWL (Hatano et al. 2013). Additionally, Th2-polarized skin has decreased levels of sphingomyelinase, an enzyme that depletes the sphingomyelin used by *S. aureus* α-toxin to cause keratinocyte lysis and skin barrier impairment (Brauweiler et al. 2013). The effect of inflammation on barrier function can also synergize with genetic defects. In filaggrin-deficient skin equivalent cultures there is upregulation of involucrin, loricrin and β-defeinsin-2, all of which are abrogated in the presence of Th2 cytokines (Hönzke et al. 2016). In addition to Th2 cytokines, other cytokines implicated in the pathogenesis of AD have been shown to downregulate filaggrin and other factors involved in skin barrier function, including IL-17 (Gutowska-Owsiak et al. 2012), IL-31(Cornelissen et al. 2012) and IL-22 (Gutowska-Owsiak et al. 2011).

Dysbiosis and immune dysregulation

Skin microbiome alters immune responses in AD—The pathogenesis of AD involves key interactions between immune responses and microbial communities (Figure 1c). The skin microbiome of AD patients has considerable variability, with various microorganisms associated with exacerbating or alleviating the skin inflammation (Byrd et al. 2017). Colonization with *S. aureus* is associated with both Th2 polarization and IgE levels in AD patients (Simpson et al. 2018). A variety of *S. aureus*-derived components have been implicated in Th2 polarization, including *S. aureus* superantigen B (SEB), protein A, δ-toxin and diacylated lipopeptides (Forbes-Blom et al. 2012; Nakamura et al. 2013; Terada et al. 2006). Penetration of the epidermis by *S. aureus*-derived proteases is crucial for this induction of Th2 immunity (Nakatsuji et al. 2016). In addition to *S. aureus*, *Corynebacterium bovis* induces Th2 polarization in a mouse model of AD (Kobayashi et al. 2015). Conversely, the secretome of *S. epidermidis* blocks CD4 proliferation and induces Tregs (Laborel-Préneron et al. 2015). Commensal skin microbiota also produce tryptophan metabolites that block Th2 induction through the aryl hydrocarbon receptor (Yu et al. 2019).

AD patients have been identified with antigen-specific IgE directed against *S. aureus* components, which correlates with increased disease severity (Sonesson et al. 2013). Specifically, IgE directed against *S. aureus* exotoxins can activate mast cells, basophils and other cells bearing FcεR1 to exacerbate the immune response (Leung et al. 1993).

In addition to inducing the canonical Th2/IgE responses, dysbiosis can promote other cell subsets implicated in AD pathogenesis. *S. aureus* exotoxins can induce IL-22 production from human PBMC-derived T cells, with increased production observed from AD patients when compared to healthy controls or psoriasis patients (Niebuhr et al. 2014; Niebuhr et al. 2010). Epicutaneous application of *S. aureus* induces AD-like skin inflammation in an IL-17 dependent manner (Liu et al. 2017; Nakamura et al. 2013). In addition to bacteria, commensal yeast (*Malassezia spp.*) can induce Th17 dependent skin inflammation on tape-stripped skin (Sparber et al. 2019)

Immune dysregulation alters the skin microbiome—Immune alterations can also influence the skin microbiome in AD. *S. aureus* binds more avidly to the Th2-polarized skin of AD due to increased accessibility of surface proteins fibronectin and fibrinogen as compared to skin in psoriasis or in healthy controls (Cho et al. 2001). Finally, expression of HDPs with anti-staphylococcal activity by cultured human keratinocytes, including human β-defensin 2 (HBD2), HBD3 and cathelicidin (LL-37), are inhibited by Th2 cytokines (Albanesi et al. 2007; Howell et al. 2008). Similar decreases in HDP expression were seen with AD skin explants and could be reversed with anti-IL-4, anti-IL-10 and anti-IL-13 neutralizing antibodies (Howell et al. 2009; Howell et al. 2006). The skin of patients with the Th2 predominant AD showed decreased levels of HDPs when compared to healthy controls and patients with psoriasis (Nomura et al. 2003; Ong et al. 2002).

Barrier dysfunction, dysbiosis, and immune dysregulation

Despite the interactions amongst barrier dysfunction, dysbiosis and immune dysregulation, relatively few studies have made the connection between all the contributing factors in a

single model. We recently found in a mouse model of AD-like skin inflammation mimicking tissue injury from scratching that: (1) filaggrin-deficient (ft/ft) mice exhibited homeostatic dysbiosis and IL-1α dysregulation in skin compared to wildtype mice, and (2) injury-induced skin inflammation was driven by dysbiosis-mediated release of keratinocyte-derived IL-1α (Archer et al. 2019). Therefore, we discovered a mechanism wherein the barrier dysfunction caused by filaggrin deficiency resulted in dysbiosis that along with skin injury led to IL-1α-mediated immune dysregulation and chronic AD-like skin inflammation (Figure 1d). The interconnectedness of these contributing factors demonstrates the importance of understanding the complex interactions in the pathogenesis of AD.

THERAPEUTICS: TAKING COMPLEX INTERACTIONS INTO ACCOUNT

The complex interactions of barrier dysfunction, microbial dysbiosis, and immune dysregulation are important considerations in the development and use of therapeutics for AD (Figure 2). Targeting barrier dysfunction has long been a major aspect of clinical therapy, with topical emollients being first line initial treatment for AD (Eichenfield et al. 2017). Topical emollients treatment can improve the dysbiosis present in AD, decreasing the prevalence of *S. aureus* and restoring the normally diverse skin microbiome that is also observed in unaffected skin of AD patients (Seite et al. 2014). Barrier directed topical therapies are often combined with topical corticosteroids or calcineurin inhibitors, helping to address the immune dysfunction in AD. However, these immunomodulatory compounds can compromise skin barrier function, an effect that must be balanced with their ability to suppress inflammation (Kao et al. 2003; Kim et al. 2010)

Numerous therapies attempting to target the microbial dysfunction have been attempted, though none have yet been included in clinical guidelines in the absence of clinical findings consistent with cutaneous bacterial superinfection (Eichenfield et al. 2017). Trials of topical antibiotics in AD have been performed but results have been mixed and the use of antibiotics raises concern for the development of antibiotic resistance (Błażewicz et al. 2017; Breuer et al. 2002; Broberg and Faergemann 1995; Hung et al. 2007). Dilute bleach baths have been suggested by several studies, but in comparative studies were found to not be more effective than water baths alone (Hon et al. 2016; Huang et al. 2009). In addition to reducing pathogenic bacteria, treatments addressing the role of commensals have been evaluated. Commensal bacteria can produce antimicrobial peptides, decreasing the colonization of *S. aureus*, improving barrier function and decreasing immune activation (Myles et al. 2016; Nakatsuji et al. 2017). Coagulase-negative staphylococci produce autoinducing peptides that inhibit *S. aureus agr*-regulated toxin and virulence factor production (Williams et al. 2019). Transplant with *Roseamonas mucosa*, a bacteria derived from the skin of healthy volunteers, showed a benefit in reducing disease severity and *S. aureus* burden (Myles et al. 2018).

Therapies targeting the immune dysregulation often involve broad, systemic immunosuppression, including the use of methotrexate, cyclosporine, mycophenolate mofetil and azathioprine, though these drugs are usually reserved for severe, refractory cases due to their adverse side effect profile (Megna et al. 2016). Therapies directed towards specific dysregulated immune pathways have also become important in the treatment of severe AD. Dupilumab is a fully human monoclonal antibody targeting the shared receptor

subunit for IL-4 and IL-13. Dupilumab is approved in the U.S. for the treatment of adults and children (above the age of 6 years-old) with poorly controlled AD (Gooderham et al. 2018; Licari et al. 2020). In phase III trials, AD patients treated with dupilumab achieved 36–38% improvement in the primary endpoint of the investigator global assessment (IGA) (compared with 8–10% of the placebo group) and nearly 50% of AD patients treated with dupilumab achieved at least 75% on the Eczema Area and Severity Index (EASI-75) (compared with ~15% of the placebo group) as a secondary endpoint (Simpson et al. 2016). Treatment has been shown to improve bacterial dysbiosis, reducing the prevalence of *S. aureus* and increasing microbial diversity (Callewaert et al. 2020). Dupilumab treatment also resulted in improved barrier function measures, including increased expression of filaggrin, loricrin, and claudins (Guttman-Yassky et al. 2019). However, the sizable population of partial or nonresponsive dupilumab-treated patients may be partially explained by the heterogenous nature of this disease and suggests a need for a personalized therapeutic approach (Hendricks et al. 2019).

Antibodies targeting additional cytokines have been attempted with varying degrees of success. For example, mepolizumab (anti-IL-5 mAb) is currently in phase 3 clinical trials after demonstrating improvements in pruritus whereas nemolizumab (anti-IL-31R mAb) also showed a significant benefit in pruritus in AD patients but little or no efficacy on the skin inflammation (Hajdarbegovic and Balak 2017; Oldhoff et al. 2005). Tralokinumab and Lebrikizumab, both anti-IL-13 mAbs though targeting different epitopes, have also shown efficacy in moderate to severe AD in phase 2 studies and are both currently undergoing phase 3 trials (Guttman-Yassky et al. 2020; Wollenberg et al. 2019). Fezakinumab, an anti-IL-22 mAb showed modest but significant efficacy in reducing skin inflammation in moderate to severe AD patients; however, the improvement persisted beyond the final treatment dose (Guttman-Yassky et al. 2018) Secukinumab (anti-IL-17A mAb) and MOR106 (anti-IL-17C mAb) both lacked efficacy against the skin inflammation in AD in phase II clinical trials (Galapagos NV 2020; Ungar et al. 2020). Furthermore, anti-IgE responses have been targeted in atopic dermatitis, but they either lacked efficacy or only had a modest effect in reducing skin inflammation in AD (Gomez et al. 2007; Krathen and Hsu 2005; Thaiwat and Sangasapaviliya 2011; Wang et al. 2016). Conversely, several clinical trials have shown potential for exacerbation of AD, including recombinant IL-4 therapy that increased Th2 polarization in psoriasis and the use of anti-TNF therapies that induced sporadic and worsening AD-like lesions (Flendrie et al. 2005; Nakamura et al. 2017; Rahier et al. 2010). However, additional studies are needed to understand how treatment efficacy is influenced by the variations in AD disease between patients.

CONCLUSIONS

The interactions between barrier dysfunction, dysbiosis, and immune dysregulation are crucial factors in the pathogenesis of AD. Further research is necessary into the roles and directionality of these interactions to better understand and treat this inflammatory skin disease. An improved understanding will help to usher in an era of directed, multifactorial treatments to this complex and heterogeneous disease.

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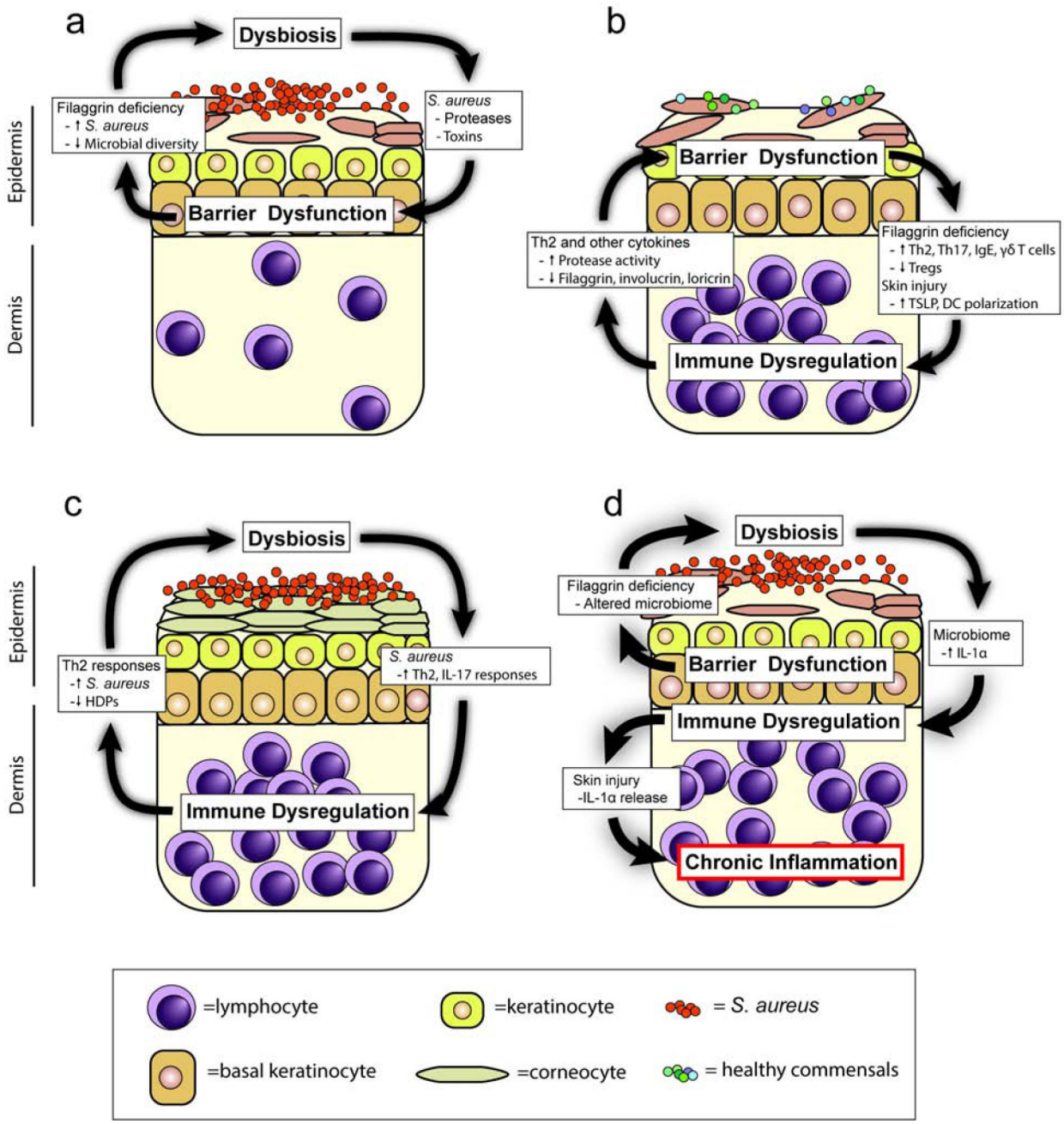

Figure 1. Complex interactions in atopic dermatitis.

Atopic dermatitis pathogenesis involves directional interactions between **(a)** dysbiosis and barrier dysfunction, **(b)** barrier dysfunction and immune dysregulation, **(c)** dysbiosis and immune dysregulation, or (**d**) barrier dysfunction, dysbiosis, and immune dysregulation. For example, barrier dysfunction mediated by filaggrin deficiency promotes dysbiosis, resulting in dysregulated IL-1α production that is released upon skin injury to drive chronic skin inflammation (Archer et al 2019). NMF=natural moisturizing factors; HDP=host defense peptides.

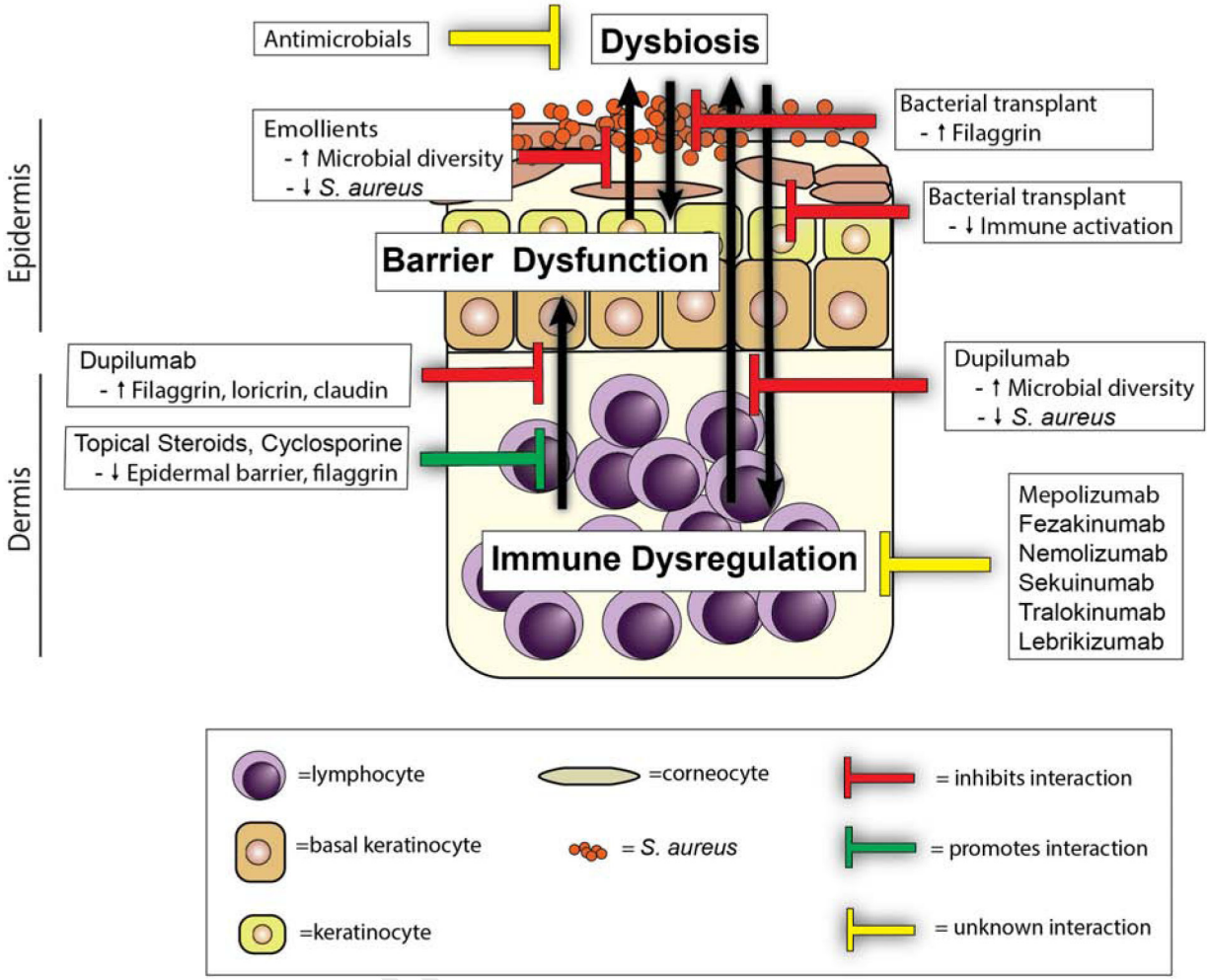

Figure 2. The role of therapeutics in regulating interactions in atopic dermatitis pathogenesis.

Therapeutic strategies can disrupt (e.g., dupilumab, bacterial transplant, and emollients) or strengthen (e.g., steroids and cyclosporine) the interactions between dysbiosis, barrier dysfunction, and immune dysregulation in atopic dermatitis pathogenesis, whereas the consequences of other therapeutics in these interaction are unknown (e.g., antimicrobials, mepolizumab, etc.).