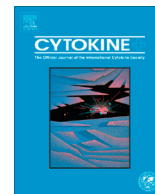




Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

New pathogenic and therapeutic paradigms in atopic dermatitis

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ARTICLE INFO

Article history:

Received 15 October 2014

Received in revised form 14 November 2014

Accepted 19 November 2014

Available online xxxxx

Keywords:

Atopic dermatitis

Translational medicine

T-cells

Immune antagonists

ABSTRACT

Atopic Dermatitis (AD) is a common inflammatory skin disease with increasing prevalence in industrialized countries. Up to one-third of adults with AD have moderate-to-severe disease, leading to a large, unmet need for effective treatments. While current therapeutics focus mainly on symptom control, major advances have been made in translational research, with the goal of developing drugs to eradicate disease.

A translational revolution is now occurring in AD, similar to the one that has occurred in psoriasis over the past decade. Research has focused on elucidating immune pathways responsible for AD, including Th2, Th22, and Th17 pathways, with testing of immune antagonists specific to these axes. An IL-4R antagonist, dupilumab, is the first drug that shows great promise in phase II trials. By studying clinical and molecular responses following treatment with specific immune antagonists, our understanding of and ability to treat AD will expand.

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1. Introduction

Atopic Dermatitis (AD) is the most common inflammatory skin disease, with rising prevalence in industrialized nations [1,2]. It is present in up to 25% of children in the U.S., and while only one-third of cases persist into adulthood, the vast majority of these children will go on to develop asthma or allergic rhinitis later in life [3,4]. This pattern of onset has been termed the atopic March, and atopic dermatitis represents the earliest possible point of intervention in this series of related diseases.

Abbreviations: AD, Atopic Dermatitis; ADASI, atopic dermatitis severity index; AMP, anti-microbial peptide; CCL, chemokine (C–C) motif ligand; CCR, chemokine (C–C) motif receptor; CsA, cyclosporine A; CTRH2, chemoattractant receptor-homologous molecule 2; DC, dendritic cell; DEFB1, defensin, beta 1/HBD1; EASI, Eczema Area and Severity Index; FcεRI, Fc receptor, IgE, high affinity; FLG, filaggrin; iDC, inflammatory dendritic cell; IDEC, inflammatory dendritic epidermal cell; IFN-γ, interferon-gamma; IgE, immunoglobulin E; IL-4R, interleukin-4 receptor; IVL, involucrin; K16, keratin 16; LC, Langerhans cell; LOR, loricrin; NOD, nucleotide-binding oligomerization domain; NB-UVB, narrow-band ultraviolet B; PBMC, peripheral blood mononuclear cell; PDE4, phosphodiesterase-4; SCORAD, scoring of atopic dermatitis; SPINK5, serine peptidase inhibitor, Kazal type 5; Th, T-helper; TLR, toll-like receptor; TMEM79, transmembrane protein 79/MATT; TSLP, thymic stromal lymphopoietin.

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The lifetime prevalence of AD in adults is 2–10%, but remains lower in rural and non-industrialized countries [5]. This observation has led to controversy surrounding the “hygiene hypothesis”, in which lack of exposure to antigens in early life creates immune imbalances favoring a pro-allergic Th2 response, leading to a pre-dilection for atopic disease [6–8]. Of all adults with AD, one-third are classified as having moderate to severe disease, representing a large and unmet need for safe, effective and reliable treatments [9].

Molecular medicine is radically changing the AD pathogenic and therapeutic landscape, similar to the process in psoriasis over the past decade [10,11]. Translational research accelerates therapeutic development by identification of pathogenic pathways that foster development of drugs to target specific components of these pathways. Efficacy can then be proven if suppression of the pathway is associated with improvement of clinical and tissue pathology.

However, several criteria are required for this translational approach to succeed in AD. First, investigators must have a well-defined cellular and molecular disease phenotype and a comprehensive understanding of immune circuits, although testing with targeted inhibitors can certainly contribute to this understanding. Additionally, well-established biomarkers of disease activity are vital to quantifying response to treatment, especially in a disease known to have high rates of clinical improvement in placebo cohorts [12] and diverse clinical phenotypes. Lastly, in order to test

<http://dx.doi.org/10.1016/j.cyto.2014.11.023>

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an immune-based hypothesis, researchers require access to drugs that will selectively target components of the immune system. The first example of the successful translational model in AD has been recently shown with the IL-4R antagonist, dupilumab [12,13]. This landmark trial marks an important turning point in the study and treatment of AD, demonstrating reversal of epidermal pathology with a specific immune antagonist targeting the Th2 pathway. Additional targeted therapies are currently being studied in the clinic, with the hope of shifting the paradigm of AD management from symptom control to disease eradication.

2. Clinical characteristics/clinical phenotypes

A diagnosis of AD is generally made on clinical criteria alone [14]. The disease is characterized by pruritic, eczematous, erythematous, often excoriated plaques with serous exudate and crusts (Fig. 1). The lesions are poorly demarcated, often involve the face and flexor surfaces, and are prone to development of cutaneous bacterial and viral infections [15]. The appearance of AD varies according to disease phase; the acute stage manifests as bright red, oozing lesions that transform into dull, pink-to-red lichenified plaques in chronic lesions.

With reports of increasing prevalence of AD in both adults and children around the globe [16], it is becoming clear that not all forms of AD are epidemiologically and/or clinically equal. Different AD phenotypes have unique characteristics, including age of onset, areas of involvement, increased skin thickness, levels of serum biomarkers (IgE), and rates of infectious complications [17–19]. For example, in infants AD is common on the face, while in adults, involvement of the hands and folds is often seen [20]. Additionally, roughly 80% of AD patients show reactivity to allergens based on elevated serum IgE or immediate skin test reactivity, while 20% have normal IgE levels and lack of sensitization toward environmental allergens [21]. These “intrinsic” patients have been shown to exhibit lower rates of atopic March and filaggrin mutations compared with their extrinsic counterparts [21,22], although recent studies suggest that these patients may show evidence of sensitization to uncommon antigens that are not assessed on standard panels, such as metal or microbial antigens [21,23]. We have also shown that while both intrinsic and extrinsic AD show similar Th2 polarization, much higher Th17 and Th22 activation is seen in intrinsic AD, with potential therapeutic relevance [24]. These variants are probably influenced by inherent genetic factors and environmentally controlled humoral and cell-mediated immune responses.

3. Genetics

AD has a strong familial component. One recent twin study showed that 82% of AD risk is determined by genetic factors, and only 18% by environmental factors [25]. Genes that have been associated with AD encode factors in the innate and adaptive immune systems as well as proteins that regulate the terminal differentiation of keratinocytes [26–28]. Adaptive immune response genes associated with AD include known Th2 cytokines and chemokines (IL4, IL4RA, IL13, TSLP, CCR5), while several genes have also been identified in the innate immune system, including NOD1, NOD2, TLR2, CD14, and DEFB1, which play an important role in the immune defense against infection. Several barrier genes were also associated with AD, including filaggrin/*FLG* (most common), loricrin/*LOR*, involucrin/*IVL*, *SPINK5*, and *TMEM79/MATT*. Loss-of-function mutations in *FLG*, which encodes an intermediate-filament protein filaggrin, have been found in 10–50% of AD patients, depending on the population [29–32]. AD patients with homozygous null mutations of *FLG* have earlier onset of disease, more

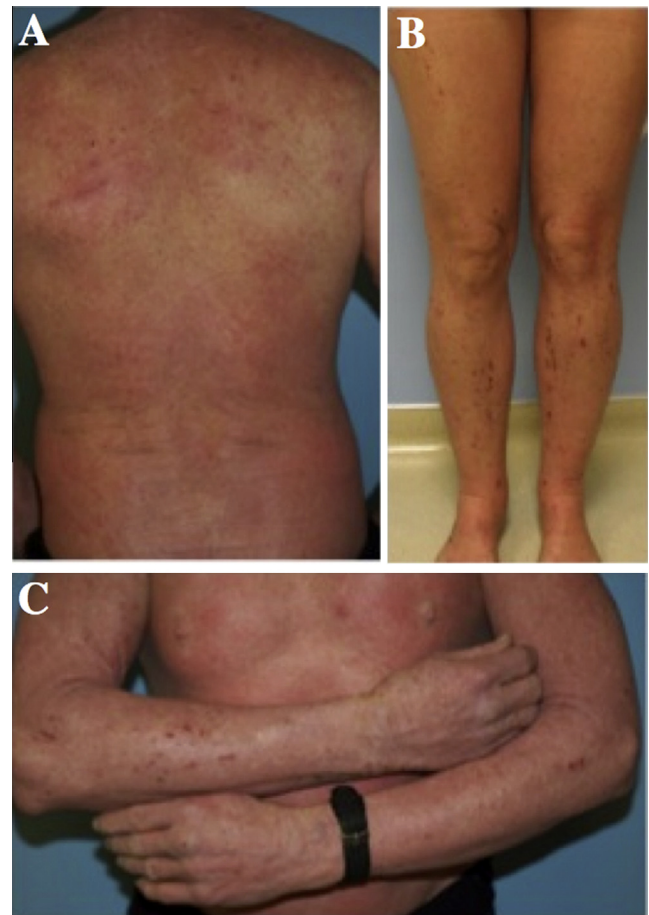


Fig. 1. Clinical images of AD patients with severe disease on the (A) back, (B) legs, and (C) trunk and arms. In contrast to psoriasis, the borders of the lesions are poorly demarcated and blend in with surrounding skin.

palmar hyperlinearity, greater risk of allergen sensitization, and increased pH in their stratum corneum in comparison to those with heterozygous *FLG* mutations. However, the rate of *FLG* mutations in the American AD population is only 10%, suggesting the predominance of other factors in creating the AD phenotype.

4. Epithelial skin barrier dysfunction in AD: “outside-in”

The association of *FLG* mutations with atopic dermatitis has prompted further support of the “outside-in” hypothesis, or the idea that functional disruption of the epidermal barrier is the primary pathogenic process in AD [30,33–35]. In mice, *FLG* mutations result in flaky skin on the tails, with a barrier abnormality that predisposes them to penetration of irritants and allergens, and resulting in increased inflammatory processes in the skin [36]. However, the precise cellular implications of this mutation in humans are still being elucidated. It is believed that loss-of-function mutations in *FLG* may change the shape of epidermal corneocytes, therefore disrupting their function and also altering the organization of extracellular lamellar bodies [30,33].

Patients with *FLG* mutations are not only predisposed to the formation of AD, but were also found to have early onset of recalcitrant AD, and disease that is more likely to be associated with asthma, food allergy, and cutaneous infections [37–39].

Recent studies in mice have stressed the interaction of *FLG* with other genes. Mouse models of AD have shown that the propensity to develop eczema spontaneously requires the *FLG* mutation and a

mutation in the *matted* (*matt*) gene, which independently gives rise to a matted hair phenotype [40,41]. This matted hair phenotype was found to be the result of mutations in the *Tmem79* gene, which encodes a component of the lamellar granule secretory system necessary for processing filaggrin, lipids, proteases, and antimicrobial peptides [41,42]. Single nucleotide mutations in *Tmem79* have been found to confer risk for AD in humans even when controlling for FLG [40], pointing to possible complex gene interactions in AD.

Additional mechanisms are present in normal skin to help preserve skin barrier function, particularly tight junctions. Claudins are tight junction proteins found directly below the stratum corneum on keratinocyte membranes in the stratum granulosum, and form an additional barrier should the stratum corneum become dysfunctional [43]. Claudins' expression is down-regulated in the epidermis of AD patients [43,44]. Expression of claudins was negatively correlated with that of Th2 cytokines [45], which were shown to down-regulate tight junction proteins in epithelia [46].

Microbial colonization plays an especially important role in AD. Longstanding *Staphylococcus aureus* colonization amplifies skin inflammation, ultimately worsening the AD symptoms [47,48]. Multiple mechanisms participate in this process. *S. aureus* colonization and the resulting release of exotoxin has been shown to induce T-cell proliferation, IL-31, and IL-22 in AD patients [49,50]. *S. aureus* also produces high levels of serine proteases, which are known to degrade the epidermal barrier [51]. Additionally, commensal skin flora are responsible for producing antimicrobial peptides that mitigate overgrowth of *S. aureus*; patients with AD who routinely use topical antibiotics may show decreases in commensal bacteria, allowing *S. aureus* the ability to colonize [52]. Compared to psoriasis, the epidermis of atopic patients has been shown to be deficient in producing antimicrobial peptides (AMPs) necessary for the destruction of both bacterial and viral microbes [15,53–58]. AD skin also produces increased amounts of molecules responsible for binding of *S. aureus*, compared to psoriasis [54,57,59,60].

While FLG defects are associated with barrier dysfunction, the primary abnormality in AD is still not clear. Most AD patients do not harbor a FLG mutation [29–31], and most FLG-deficient patients eventually clear the disease [61]. Additionally, vast suppression of many terminal differentiation proteins extending far beyond FLG (e.g. loricrin, involucrin, periplakin, and transglutaminase) has been demonstrated in both lesional and non lesional AD skin [62], suggesting a reactive epidermal response to an immune abnormality [63]. This concept is also supported by reports showing improvement in FLG expression with anti-inflammatory medications, including corticosteroids, gentamicin and calcineurin inhibitors [15,64,65].

5. Immune-mediated abnormalities in AD: “inside-out”

Despite the evidence supporting the fixed genetic barrier abnormalities in AD, growing evidence exists for the “inside-out” model [66,67], in which activation of specific cytokine pathways causes defective keratinocyte differentiation, ultimately resulting in barrier defects.

Several arguments exist in favor of immune abnormalities as the primary pathogenic process in AD. While the filaggrin mutation has provided an important piece of the pathogenic puzzle, the mutation is absent in most AD patients, and most patients with the mutation will eventually outgrow their disease [61,66,68,69]. Additionally, unlike other diseases associated with FLG mutations (e.g. ichthyosis vulgaris), which affect the entire skin surface area, individuals with AD display both lesional and nonlesional patches, suggesting that other factors play a role in creating the disease phenotype.

The effect of inflammatory cytokines on the epidermis supports the inside-out hypothesis, reproducing many components of the AD skin phenotype. The expression of terminal differentiation proteins (filaggrin, loricrin, involucrin) in human epidermal keratinocytes is suppressed after treatment with IL-4, IL-13, IL-22, IL-25 and IL-31 cytokines [55,70–72]. Cytokine imbalances, particularly increased Th2 and Th22 skewing, have been shown to reduce other terminal differentiation proteins, including loricrin and involucrin, and to upregulate human tissue kallikreins (serine proteases responsible for corneodesmosome protein degradation in the skin) [73–75]. The Th22 cytokine, IL-22, was shown to directly induce epidermal hyperplasia, which is a common feature of chronic AD skin [76,77].

Strong evidence for the inside-out hypothesis comes from recent clinical trials assessing the efficacy of immune therapy with broad agents (e.g. cyclosporine A, narrow band UVB), and particularly with specific immune antagonists in patients with moderate to severe AD. Although clinical reversal with NB-UVB and CsA was associated with both immune suppression and improvement of the epidermal pathology (consisting of hyperplasia and inhibition of barrier proteins), these studies suggested, but could not prove, the primary immune pathogenesis of AD since these treatments have indirect and direct effects on keratinocytes [12,78,79]. Recently, use of an IL-4R antagonist (dupilumab) in a phase 1B trial was shown to suppress inflammatory pathways and restore expression of key epidermal products in AD (claudins, lipids, and K16) in only 4 weeks of treatment [12]. However, longer and larger studies in AD patients are needed to fully evaluate the relationship between in vivo cytokine suppression and reversal of the epidermal pathology.

In addition to Th2 targeting, trials suppressing other cytokine pathways are now underway in AD. These studies will shed light on the immune imbalances in AD and the contribution of individual pathways to the disease.

5.1. Th1/Th2 imbalance

Historically, AD was considered to result from a Th1/Th2 imbalance. While Th1-mediated inflammation aims to fight infections through its main cytokine, IFN- γ , Th2-associated cytokines, such as IL-4, IL-5, and IL-13, are involved in allergic responses and mediate IgE class-switching, among other functions [80]. AD is associated with Th2 expansion in skin [81]. The Th2 cytokines have specific effects on the epidermis, including suppression of keratinocyte differentiation and AMP production, which contribute to the AD skin phenotype [15,82]. While acute AD lesions are skewed toward a Th2 response, chronic AD lesions also exhibit a significant Th1 component in addition to Th2 responses [70]. The accompanying rise in IFN- γ in chronic lesions is responsible for keratinocyte apoptosis and intensification of inflammatory responses [83,84].

5.2. The role of Th17 T-cells

Th17 cells are a unique subset of T-cells known to produce IL-17 and IL-22 [85]. Their role in the skin includes but is not limited to regulation of AMP production in keratinocytes [77]. While their role as vital mediators in the pathogenesis of psoriasis has transformed the treatment of this disease in the past decade, the role of these cytokines in AD is not fully elucidated.

Although there are increased numbers of IL-17 producing cells in acute skin lesions and peripheral blood of AD patients [86,87], these cells may be inactivated or inhibited by the predominant Th2 cytokine milieu in AD. Compared to psoriasis, a disease known for Th17-skewing, AD skin shows decreased production of IL-17 and AMPs [57,88,89]. The relative deficiency in AMPs in AD compared to psoriasis, along with relatively decreased expression of

IL-17, a known inducer of AMPs, provides a possible explanation for the increased rates of infections seen in AD patients [90]. Th2 cytokines, specifically IL-4 and IL-13, were reported to inhibit production of IL-17 and may be responsible for the relatively decreased IL-17 cytokine profile in AD [91]. Recent mouse data suggests a more complex interaction between Th17 and Th2 pathways, showing that IL-17 is necessary for IL-4 production and development [92]. The role of IL-17 in AD needs to be further clarified by studies with direct anti-IL-17 therapeutics.

5.3. The new frontier: Th22 T-cells

A distinct T-cell subset has been identified by our group in recent years; these T-cells produce the majority of IL-22 in humans, and are further subdivided into CD4+ “Th22” T-cells and CD8+ “Tc22” T-cells [75,93–96]. IL-22 and other cytokines in the IL-20 family are responsible for mediating epidermal hyperplasia and inhibiting terminal differentiation [76,97,98]. When examining the immune infiltrates in chronic AD lesions, there is a predominance of Th2 and T22 cells; even when compared to chronic plaque psoriasis, the numbers of Th22 and Tc22 cells in chronic AD lesions were significantly increased and showed correlations with disease severity, especially among Tc22 cells [75].

Thus, AD is a Th2/Th22 skewed disease, with additional contributions from Th1 cytokines occurring in the chronic stages of AD.

5.4. Dendritic cells

Distinct subsets of dendritic cells contribute to the inflammatory responses in AD. Initially, langerin + Langerhans cells (LC) and dermal dendritic cells (dDC) were characterized as the main subsets in human skin, but new subtypes of DCs have been identified as being associated with AD. Specifically, myeloid (CD11c+) DCs have been shown to be increased in patients with AD and make up the largest component of DCs [99,100]. Inflammatory dendritic epidermal cells (IDECs) are a subset of myeloid DCs that are involved in T-cell activation in AD [101,102]. Although IDECs were originally thought to be epidermal [103,104], CD1a+ DCs with known immune activating effects have also been observed in the dermis, and were found to have immunostimulatory effects including high levels of the thymic stromal lymphopoietin (TSLP) receptor, a known inducer of Th2 response [105]. Because these cells share similar markers with IDECs but are localized to the dermis, they are termed inflammatory dendritic cells (iDCs) [106]. In AD patients, these iDCs produce pro-inflammatory chemokines, including CCL17, CCL18, and CCL22 [107]. Additionally, LCs with activated FcεRI induce a Th2 response, and epicutaneous sensitization has been shown to activate this response [108,109].

5.5. Mast cells and eosinophils

AD is characterized by increased numbers of eosinophils in blood, with variable numbers in skin [24,110]. IL-5, as well as other Th2 cell cytokines, including IL-4 and IL-13, is responsible for eosinophil recruitment to affected sites [111–113]. However, a monoclonal IL-5 antagonist did not show efficacy in AD despite reduction of peripheral eosinophilia and promising results in the management of asthma [114–119]. This suggests a more minor role of eosinophils in AD compared to asthma.

While IgE was originally believed to be a vital modulator of AD, recent focus has shifted toward T-cell responses [22,24,102,120]. Interestingly, similar responses to dupilumab were observed in patients with high (“extrinsic AD”) and normal (“intrinsic AD”) IgE levels. This suggests the predominant role of T-cell activation, rather than B-cell or IgE status, in the pathogenesis of AD [12].

5.6. Innate lymphoid cells

Innate lymphoid cells (ILCs) are recently discovered non-T and non-B effector cells that lack antigen-specific receptors but release cytokines in known T-cell pathways and are classified according to cytokine profiles [121]. Type 2 ILCs express skin-homing receptors, infiltrate human skin after allergen challenge, produce the Th2 cytokines IL-5 and IL-13, and are activated by IL-33, whose receptor was recently found to be enriched in lesional skin biopsies in atopic patients [122]. The role of ILCs in AD still needs to be determined.

6. Emerging therapeutics

The treatment of psoriasis has undergone a revolution in the past decade, resulting in specific immune antagonists that are safer, more effective, and less toxic than broad immunomodulatory agents [11,123,124]. These translational developments in psoriasis have helped promote targeted therapeutics for AD.

Clinical trials with specific cytokine antagonists may help elucidate their individual contributions to the AD phenotype. To monitor responses to various interventions, it is vital to identify biomarkers that correlate with disease severity, generally measured as scoring of atopic dermatitis (SCORAD) or Eczema Area and Severity Index (EASI). We have identified a set of response biomarkers [62,63,79,125] that can provide an objective measure of efficacy for various therapies.

Measuring tissue responses is especially important in AD compared to psoriasis, given the strong placebo effect commonly encountered in clinical trials of AD therapeutics. Unlike a placebo response of ~3% in psoriasis [11,123,126–130], placebo responses in clinical trials for AD range between 15% and 23%, which can lead to difficulty in identifying significant responses [12,131]. Monitoring molecular responses to treatment provides an early measure of efficacy compared to the clinical response, and provides an important basis for comparison in AD trials. We have recently evaluated changes in the AD molecular signature following dupilumab treatment and found a dose-dependent improvement with treatment and a worsening of the AD transcriptome with placebo, which contrasts with the “improvement” in clinical responses observed with placebo [13]. This underscores the importance of biomarker studies in AD clinical trials.

6.1. Immune modulators: Th2 antagonists

Interleukin-4 (IL-4) is a Th2 cytokine that promotes differentiation of Th2 cells and IgE class-switching [132,133]. Mutations in IL-4 and its receptor have been associated with AD [132,134]. As above, the IL-4R antagonist/dupilumab, which inhibits signaling of IL-4 and IL-13, has shown good clinical efficacy in early clinical trials for moderate-to-severe atopic dermatitis [12]. Dupilumab not only reduced clinical disease activity, but also showed improvement in the AD genomic phenotype, including significantly reduced Th2 chemokines (e.g. CCL17, CCL18, and CCL6) and reversal of key epidermal markers (lipids, claudins, proliferation markers) [13].

Given the success of dupilumab, trials of other targeted biologics are underway [67]. IL-13 antagonists have shown efficacy in the treatment of asthma [135–137], and might provide a useful treatment for AD. IL-31 is a cytokine considered to be important for inducing itch, and targeted IL-31 agents are currently being tested in the treatment of AD (CIM331/NCT01986933) [138,139]. Thymic stromal lymphopoietin (TSLP) ligand and its receptor are responsible for mediating dendritic cell (DC) signaling in the induction of Th2 responses [70], and TSLP antagonists are also being

assessed for efficacy in AD (AMG-157/NCT00757042; MK8226/NCT01732510). Another molecule responsible for inducing the Th2 pathway is CTRH2, or chemoattractant receptor-homologous molecule, which activates Th2 cells to produce IL-4, IL-5, and IL-13 [140]. The efficacy of CTRH2 antagonists is currently being assessed in trials (NCT02002208). While IL-5 promotes eosinophil development and survival [141] and its inhibitor showed efficacy in the treatment of asthma [111,112], the lack of IL-5 inhibitor efficacy in AD has led researchers to examine other targets.

Omalizumab, a humanized IgG1 monoclonal antibody against IgE, has been also tested in AD patients although the role of IgE in the development of AD is unclear. While omalizumab has proven efficacy for both asthma and chronic idiopathic urticaria [142,143], it has not demonstrated clear efficacy in severe AD [144,145] despite displacement of FcεRI on target cells [146–148]. This finding, along with the success of dupilumab in all AD patients regardless of IgE levels, makes a strong argument against the pathogenic role of IgE in AD.

6.2. Other cytokine antagonists

Rather than aiming to correct immune dysregulation in AD by inhibiting Th2 responses, some researchers have hypothesized that boosting Th1 may instead restore the immune balance in these patients. Focus has been placed on interferon- γ (IFN- γ), the main Th1 cytokine, to restore Th1 polarization, as AD patients have been shown to produce lower levels of IFN- γ from peripheral blood mononuclear cells (PBMCs) [149–152]. However, recombinant IFN- γ treatment was shown to be effective only in a subset of patients with severe, unremitting AD [152,153]. Despite its lack of efficacy in trials, recombinant IFN- γ may have a role in the treatment of AD patients with recurrent skin infections, as it is known to promote antiviral and antibacterial activity [154–156].

IL-22 is a cytokine released by Th22 cells and shows increased mRNA expression in acute AD, while Th22 cells, which are responsible for the production of IL-22, are elevated in patients with chronic AD [75,157,158]. Now that it has been suggested that IL-22 possibly drives the AD phenotype, targeted therapy with anti-IL-22/ILV094 is currently being tested by our group in moderate-to-severe AD patients (NCT01941537).

The role of the Th17/IL-12/IL-23 is also being explored in both the pathogenesis and treatment of AD using an anti-IL-12/23p40 monoclonal antibody (ustekinumab). Increased expression of IL-17 has been showed to be associated with acute AD [75,157–161]; and therefore it has been hypothesized that agents that block IL-17, IL-23, or their receptors may be effective for patients with acute AD flares. Ustekinumab shows high efficacy in plaque psoriasis, and is currently being tested in clinical trials for the treatment of AD (NCT01806662) [10,11]. However, studies with direct anti-IL-17 activity are needed to clarify the role of this pathway in AD.

6.3. Phosphodiesterase inhibitors

AD patients are known to exhibit increased levels of phosphodiesterase-4 (PDE4) in PBMCs [162], and topical PDE4 inhibitors have shown benefit when applied to lesional skin in AD patients [163]. A pilot study of an oral PDE4 inhibitor, apremilast, in adult moderate to severe AD patients, showed dose-dependent improvements in AD severity index (ADSI) as well as other clinical endpoints [164,165]. A phase II trial with apremilast is now being conducted in AD patients (NCT02087943).

6.4. Barrier repair therapies

Much effort has been placed on interventions to correct barrier abnormalities, with mixed results. Recent studies suggest that

early protection of the skin barrier with frequent emollient use may actually prevent AD [166,167]. While emollients are a mainstay of therapy in AD, less common interventions have also been tested for barrier repair. Vitamin D3 has been shown to upregulate the production of antimicrobial peptides in the skin, which may reduce cutaneous infection rates and additional inflammation associated with *S. aureus* colonization [168–170]; however, clinical trials of these agents are lacking. Because abnormalities in the protease/antiprotease balance have been implicated in the pathogenesis of AD, topical protease inhibitors were studied for the treatment of AD but did not show any evidence of benefit [171,172].

Finally, efforts have been made to increase expression of deficient barrier proteins in AD, including filaggrin and loricrin, to ameliorate AD symptoms at a cellular level [107,172–174].

6.5. Allergen-directed immunotherapy

Most AD patients have elevated levels of IgE and a propensity toward reactions to inhalant and food allergens. For some patients with AD exacerbations following specific allergen triggers, immunotherapy may be considered [175]. The underlying mechanism of allergen-directed immunotherapy includes induction of Tregs in addition to suppression of basophils and Th2 cells [176]. In fact, randomized, double-blinded trials show improvement in those sensitized to dust mites [177,178] and studies are underway to assess implications for food allergy [179–181].

7. Looking forward

Atopic dermatitis is currently undergoing a pathogenic and therapeutic transformation. At the forefront of the paradigm shift is recently published work showing efficacy of a targeted inhibitor of the Th2 pathway in establishing clinical and mechanistic responses [12,13]. The exact contributions of Th17, Th22, and Th2 will be elucidated through trials of targeted immune antagonists coupled with molecular correlates.

Funding

D.M. was supported by the American Dermatological Association's Medical Student Fellowship.

Disclosures

E.G.Y. received research grants from Regeneron, Bristol Meyers Squibb, Janssen, Celgene, Dermira and Leo Pharmaceuticals. E.G.Y. is a consultant for and/or on the advisory board of Regeneron, Sanofi Aventis, GlaxoSmithKline/Steifel, Dermira, Celsus, Bristol Meyers Squibb, Celgene, Anacor, Leo Pharma, and Galderma.

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