Immune Dysregulation in Atopic Dermatitis

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Atopic dermatitis is a chronic inflammatory skin disease that causes significant morbidity in affected individuals. It is characterized by dysregulated immune responses that consist of an increased systemic Th2 response and a combination of Th2 and Th1 responses in the skin lesions. In this article, we review factors that contribute to these abnormal responses, including key effector cells of the immune system, chemokines, defective skin barrier, genetic predisposition, and environmental triggers. Understanding these pathomechanisms may improve our current therapies for atopic dermatitis.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is associated with genetic predisposition, cutaneous hyperreactivity to environmental triggers, and immune dysregulation [1•]. It affects approximately 10% to 20% of children and 2% of adults. Persistent AD is characterized by pruritus and an eczematous rash in the flexural areas. In young children, the rash may be distributed primarily on the extensor areas and on the face. In severe patients, the eczematous rash may be generalized, covering most of the body and extremities. AD patients, particularly those with moderate-to-severe disease, are affected by significant morbidity, including sleep loss, emotional abnormalities, social dysfunctions, and school or work loss. Because there is currently no cure for this disease, a precise understanding of the underlying mechanisms is critical for development of more effective treatments. In this review, we summarize the current progress in our understanding of the pathophysiology of AD and implications for therapy.

Systemic Immune Response in AD

In young children, AD is a major risk factor for the development of allergic rhinitis and asthma. AD is frequently the initial manifestation of a process known as the "atopic march," which progresses from AD to the development of allergic rhinitis and asthma. In experimental models of AD, the induction of allergic skin inflammation by epicutaneous application of allergens has been found to augment the systemic allergic response and airway hyperreactivity characteristic of asthma [2].

There are at least two forms of AD. The majority of patients have increased total serum immunoglobulin (Ig)E and allergic sensitization to food or inhalant allergens. This form of AD is known as extrinsic AD (EAD). This is in contrast to a minority (20%–30%) of patients with so-called intrinsic AD (IAD), who have normal total serum IgE without apparent allergen sensitization. EAD patients have been found to have a higher expression of the high- and low-affinity receptor for IgE (FcεRI and FcεRII/CD23) on their monocytes than IAD patients [3]. Because it is known that interleukin (IL)-4 plays a crucial role in upregulating IgE receptors on monocytes, these differences may be attributed to an increased frequency of genetic polymorphisms in the IL-4 and IL-4–receptor α chain (IL-4RA) of EAD as compared to IAD patients [3]. However, both forms of AD have increased eosinophilia and serum IL-13 [3], suggesting the importance of Th2 cells in the pathogenesis of atopic diseases. The reasons for the increased Th2 responses (eosinophilia and IL-13 production) in AD patients are not clear. Possible mechanisms include increased Th1 cell apoptosis or an increased expression of suppressor of cytokine signaling-3 (SOCS-3), which inhibits Th1 cell differentiation, skewing the immune responses in these patients toward a Th2 response [4].

Immune Responses in AD Skin

Clinically unaffected skin in AD demonstrates an increased number of Th2 cells expressing IL-4 and IL-13, as compared with normal nonatopic skin [5]. The predominance of Th2 cytokines in unaffected AD skin may be due in part to the presence of a specialized subtype of Th cells expressing the skin-homing receptor, cutaneous

lymphocyte-associated antigen (CLA). It has recently been shown that up to 98% of these CLA+ Th cells reside in the skin and that most of them are IFN-γ-expressing Th1 cells under normal conditions [6••]. In AD, however, CLA+ Th cells are predominantly Th2 cells, expressing IL-4 and IL-13. In addition, antigen-presenting cells (APC) in unaffected AD skin have been shown to have increased expression of FcεRI, compared to those in normal nonatopic skin [7]. Therefore, the presence of abnormal CLA+ Th2 cells and FcεRI-expressing APC are likely the main contributors to a Th2 predominance in unaffected AD skin.

The skin lesions of EAD patients contain a higher expression of Th2 cytokines (IL-5 and IL-13) than that of IAD patients [8]. However, both groups of patients have an increased expression of Th2 cytokines (IL-4, IL-5, and IL-13) in their skin lesions, compared to that in the normal skin of nonatopic controls [5,8]. In acute AD lesions, the expression of IL-4 and IL-13 has been shown to be significantly higher than that in chronic lesions. IL-4 is important for the differentiation of Th2 cells. IL-13 has also been shown to be important in generating a cutaneous Th2 response, independent of IL-4 [9•]. IL-13 may directly induce the expression of IL-5 and infiltration of eosinophils in the skin [9•]. IL-13 also induces keratinocytes to produce macrophage-derived chemokine (MDC/CCL22), which further attracts CCR4+ Th2 cells [10]. IL-16 and thymus and activation-regulated chemokine (TARC/CCL17), produced by epidermal APC, may also contribute to influx of Th2 cells into AD lesions [11,12].

Chronic AD lesions have been found to have an increased expression of both Th2 (IL-5) [5] and Th1 (IL-12 and IFN-γ) cytokines compared to normal skin. The chronic lesions of EAD patients also have an increased infiltration of eosinophils compared to that of IAD patients [13]. This difference may be due to an increased expression of IL-13 and IL-5 in EAD lesions [8]. IL-11, a cytokine associated with tissue remodeling, has been found to be increased in chronic AD lesions and may, therefore, be involved in collagen deposition and remodeling of AD skin lesions [14]. The expression of a chemokine, cutaneous T cell-attracting chemokine (CTACK/CCL27), is increased in the subacute lesions of AD [15]. The expression of this chemokine is induced in keratinocytes by the combined action of tumor necrosis factor (TNF)-α and TARC [16]. CTACK attracts a mixture of CCR10+ Th1/Th2 cells that are characteristics of chronic AD lesions [17]. Activation of keratinocytes by interferon (IFN)-γ leads to the production of other chemokines, including IFN-γ–inducible protein-10 (IP-10/CXCL10), monokine induced by γ-IFN (MIG/CXCL9), and IFN-γ–inducible α-chemoattractant (I-TAC/CXCL11) [18]. These chemokines, attract more Th1 cells via the CXCR3 receptor to perpetuate inflammation of chronic AD lesions. Another chemokine, fractalkine (FKN/CX3CL1), may also contribute to the chemotaxis of T cells into chronic AD lesions via its receptor, CX_3CR1 [19]. The increased expression of chemokines such as RANTES/CCL5, monocyte chemotactic protein-4 (MCP-4/CCL13), and eotaxin/CCL11 in AD lesions are likely to contribute to the infiltration of CCR3+ eosinophils, macrophages, and Th2 cells into AD lesions.

Key Effector Cells in AD Skin

T cells

These cells are a major source of cytokines that contribute to the pathogenesis of acute and chronic AD lesions. The sequential role of Th2 and Th1 cytokines in the development of acute and chronic AD lesions, respectively, was initially shown by atopy patch testing (APT) with house dust mite (HDM) allergens on AD skin: an initial phase with predominantly IL-4–expressing Th2 cells and a subsequent phase after 24 to 48 hours characterized by IFN-γ–expressing Th1 cells [20]. This switch in cytokine profile involves a local production of IL-12 from surrounding eosinophils and/or APC. IFN-γ produced by Th1 cells activates keratinocytes to express Fas (CD95), which predisposes keratinocytes to apoptosis, leading to the formation of eczematous lesions [21].

In addition to CD4+ Th cells, CD8+ T cells may also contribute to the pathogenesis of AD. In a murine model, CD8+ T cells account for a major fraction of IFN-γ expression in atopic skin lesions [22]. Recent data suggest that the influx of CD8+ into AD lesions may be mediated through the interaction between CCR8 chemokine receptors on these cells and the cutaneous expression of the chemokine I-309/CCL1 [23].

There is increasing evidence that the effector functions of Th cells in allergic diseases are downregulated by a specialized population of Th cells known as the T regulatory (Treg) cells. A subgroup of naturally occuring Treg cells are characterized by a CD4+CD25+ phenotype and their development under the control of the transcription factor gene, *FoxP3* [24,25]. Recently, it has been found that the AD lesions are deficient in this subgroup of Treg cells [26•]. Because it has been shown that Treg cells were capable of suppressing allergen-specific T-cell activation, it was postulated that the lack of CD4+CD25+FoxP3+ Treg cells in AD lesions may contribute to the cutaneous inflammation of AD [26•]. Although Treg cells from AD patients have been consistently shown to be capable of suppressing effector T-cell proliferation, CD4+CD25+ Treg cells and another subgroup of Treg cells, known as the adaptive Treg cells (high IL-10–expressing T cells) were shown to be ineffective in preventing T-cell–induced keratinocyte apoptosis [26•]. The reason for this failed function of Treg cells in AD is not fully understood, but one possible mechanism may be attributed to a subversion of Treg cell function by staphylococcal superantigens, which are frequently present on the lesions of AD patients [27].

Dendritic cells (DC)

There are two major subtypes of DC in AD lesions: Langerhans' cells (LC) and inflammatory dendritic epidermal cells (IDEC). These cells in AD lesions express an increased level of surface FcεRI, compared to other chronic inflammatory skin diseases, including psoriasis and contact dermatitis. They are highly efficient APC that present processed allergens to Th cells. Both LC and IDEC have been shown to be capable of inducing Th2 and Th1 polarization, respectively. LC induce Th cells to express predominantly IL-4, whereas IDEC induce Th cells to express predominantly IFN-γ [28•]. The ability of IDEC in inducing Th1 cells is partly mediated by their production of IL-12 and IL-18. The expression of FcεRI on IDEC is a late event in APT, further confirming the role of these cells in the development of chronic AD lesions [29].

A third subtype of DC is known as the plasmacytoid dendritic cells (pDC). These cells express relatively low levels of CLA [30] and were found to be deficient in AD skin, as compared to those in psoriasis and contact dermatitis [31]. Because these cells are important producers of the anti-viral cytokines, IFN-α and IFN-β, the lack of pDC in AD lesions may contribute to susceptibility of AD patients to viral infections [31].

Keratinocytes

Secondary skin infections are a common complication of AD. Compared to another chronic inflammatory skin disease, psoriasis, AD patients have a significantly higher prevalence of bacterial and viral skin infections. This is likely due to differences in the immune responses between these two diseases, as both diseases have similar defective skin barriers. The keratinocytes of AD patients have been found to be relatively deficient in the production of antimicrobial peptides (AMP) [32], which are crucial effector molecules of the innate immunity. One of the reasons for AMP deficiency in AD is suppression of AMP production by IL-4 and IL-13 [32]. However, because IAD patients also have significant skin infections, and the expression of Th2 cytokines is significantly lower in their skin lesions than in the skin of EAD patients [8], other factors may also account for the AMP deficiency in AD patients. IL-10, which is increased in both EAD and IAD lesions [26•], was shown to downregulate AMP expression in keratinocytes by shutting off proinflammatory cytokine generation in mononuclear cells [33•]. Therefore, this cytokine contributes to the AMP deficiency seen in AD patients [33•]. Decreased expression of AMP may predispose AD patients to frequent *Staphylococcus aureus* skin infections [32] and an increased propensity toward disseminated infections with herpes simplex or vaccinia virus [34,35].

Keratinocytes may also play an important role in the development of acute and chronic AD lesions. These cells are capable of producing a cytokine, thymic stromal lymphopoietin (TSLP), which activates DC to induce IL-4, IL-5, IL-13, and TNF-α expression in Th cells [36]. TSLP-primed DC also produce TARC/CCL17 and MDC/CCL22 [36], both of which further increase the infiltration of Th2 cells into AD lesions. Increased expression of TSLP was found in the keratinocytes of AD lesions and was associated with LC activation [36]. Keratinocytes may also contribute to the development of chronic AD lesions via their production of granulocyte-macrophage colony-stimulating factor (GM-CSF) [37].

Skin Barrier Dysfunction

AD is characterized by dryness and defective skin barrier function [38]. These abnormalities contribute to AD's susceptibility to inflammation induced by external triggers, including microbial pathogens, allergens, and irritants. Ceramides are a major constituent of the stratum corneum lipids that are responsible for both water retention and permeability functions. These lipid molecules have been found to be significantly decreased in both lesional and clinically unaffected AD skin, compared to normal skin. The reduction of ceramides in AD is likely due to a decrease in the activity of epidermal acid sphingomyelinase (A-SMase), which is a crucial enzyme in the formation of ceramides [39]. In addition to lipids, keratinocyte differentiation-associated proteins, including involucrin and filaggrin, also play a crucial role in skin barrier functions. The expression of these proteins is also known to be significantly decreased in AD, as compared to normal skin [39]. The reasons for the decreased expression of these proteins in AD are not clear, but may be related to genetic predisposition (discussed later).

Genetics

Genetics clearly plays an important role in the pathogenesis of AD, as the concordance rate for monozygotic twins with AD is 77% compared to 15% for dizygotic twins with AD [40]. Genome screens have shown that four chromosome loci in AD are associated with psoriasis susceptibility genes: 1q21, 3q21, 17q25, and 20p [41•]. Notably, 1q21 contains the epidermal differentiation complex (EDC), which is known to encode for proteins with proinflammatory and chemotactic functions. In addition, the genes for involucrin and filaggrin are also localized on 1q21. More recently, two loss-of-function mutations in the filaggrin gene have been associated with AD [42].

Both genome screens and candidate gene association studies have provided evidence of shared chromosome loci and genetic polymorphisms between AD, atopy, and asthma. 5q31 and 20p have been linked to AD children with high total serum IgE and asthma, respectively. Specifically, the 5q31 region contains a cluster of Th2 cytokine genes including *IL-4*, *IL-5*, and *IL-13*. Of note, single nucleotide polymorphisms (SNP) of the *IL-13* gene have been linked to AD populations in Canada, Japan, Germany, and Netherlands. An SNP of the *IL-12 p40* subunit gene, which is located on 5q31, has also been

Table I. Immune dysregulation and potential therapeutic targets in atopic dermatitis

Immune dysregulation	Treatment strategies
Increased CLA+ Th2 cells in the blood and skin lesions.	Preventing homing of CLA^+ Th2 cells into the skin.
Increased IL-13 expression and eosinophilia in the blood and skin lesions.	Neutralizing IL-13 activity or antagonizing IL-13 receptors.
Increased FcεRI expression on monocytes and dendritic cells.	Downregulating FcεRI expression.
Absence of $CD4^+CD25^+FoxP3^+$ T-regulatory cells in skin lesions.	Enhancing the presence or activity of T-regulatory cells in skin lesions.
Increased chemokine expression in skin lesions: I-309/CCL1, RANTES/CCL5, eotaxin/CCL11, MCP-4/CCL13, TARC/CCL17, PARC/CCL18, MDC/CCL22, CTACK/CCL27, fractalkine/CX3CL1, MIG/CXCL9, IP-10/CXCL10, and I-TAC/CXCL11	Use of chemokine or chemokine-receptor antagonists.
Increased thymic stromal lymphopoietin expression by keratinocytes.	Preventing thymic stromal lymphopoietin expression or action.
Decreased antimicrobial peptide expression by keratinocytes.	Using synthetic antimicrobial peptides or reducing immunosuppressive cytokines.

CLA—cutaneous lymphocyte-associated antigen; FcεRI—high-affinity receptor for IgE; IL—interleukin.

linked to AD, likely due to a loss-of-function of this SNP in AD. Other atopy-associated candidate genes for AD include the *IL-4RA* gene and serine protease inhibitor Kazal-type 5 (*SPINK5*), which contains mutations that are known to cause Netherton syndrome.

Factors Contributing to Flares of AD

Allergens

The role of food allergies in AD has been supported by multiple clinical studies. However, the mechanisms by which food triggers AD symptoms are not fully understood. More recently, food allergens have been implicated as the initial trigger for IgE autoreactivity in young AD children [43]. This autoreactivity may lead to skin tissue damage and symptoms seen in AD patients. A number of IgE-reactive human autoantigens have been characterized at a molecular level. Up to 80% of 2- to 13-year-old children with moderate-to-severe AD and total serum IgE levels higher than 1000 kU/L have IgE autoreactivity against various human epithelial autoantigens [43]. AD children with IgE autoreactivity were found to have a higher prevalence of food allergies compared to AD children without IgE autoreactivity [43].

The role of HDM as a trigger for AD has been supported by clinical studies and by the induction of eczematous lesions with HDM patch testing on the skin of HDM-allergic AD patients. Of interest, HDM subcutaneous immunotherapy (SIT) has recently been shown to be efficacious in HDM-allergic AD patients [44]. Epicutaneous application of HDM allergens on the unaffected skin of HDM-allergic AD patients induces the expression of pulmonary and activation-regulated chemokine (PARC/CCL18), which is produced mainly by DC in AD lesions [45]. The production of this chemokine, together with other chemokines (IL-16, TARC/CCL17, and MDC/CCL22) produced by DC, leads to the recruitment of CLA^+ memory Th cells into AD lesions. The presence of both HDM-specific Th2 and Th1 cells have been shown in AD lesions, suggesting the role of these allergen-specific Th cells in the induction of acute and chronic AD lesions.

Microbes

Almost all AD patients are colonized by *S. aureus* on their skin lesions. Increased binding of *S. aureus* to AD skin is driven by underlying skin inflammation. In experimental animal models, *S. aureus* binding was shown to be significantly greater at skin sites with Th2-mediated compared to Th1-mediated skin inflammation. Once *S. aureus* binds to AD skin, inadequate cutaneous innate immunity, including deficient AMP production, allows it to proliferate.

More than 50% of AD patients carry *S. aureus* strains that are capable of producing superantigens. The majority of these patients develop superantigen-specific IgE molecules, which bind superantigens and cross-link to activate mast cells, basophils, or other $Fc\varepsilon R^+$ cells. Staphylococcal superantigens have been shown to induce an increased expression of Th2 cytokines and a decreased expression of Th1 cytokines in AD patients, compared to that in healthy controls. IL-31 is a relatively new Th2 cytokine that has been shown in mice to induce pruritus and skin lesions that resemble those of AD. The expression of this cytokine and its receptor has recently been shown to be increased in AD lesions, compared to psoriatic lesions and normal skin [46••,47••]. Furthermore, IL-31 expression was found to be selectively induced in skin-homing CLA^+ T cells [47••] and upregulated by staphylococcal enterotoxin B (SEB), a prototypic staphylococcal superantigen [46••]. In addition to their direct proinflammatory roles, superantigens may also induce T cells in AD lesions to be resistant to apoptosis or suppression by corticosteroids.

A subgroup of AD is triggered by *Malassezia* yeasts. Like staphylococcal superantigens, these yeasts are capable of inducing IgE sensitization in AD patients and may be found in patients previously diagnosed as IAD. Specific IgE levels to *Malassezia furfur* (previously known as *Pityrosporum orbiculare*) have been correlated with the severity of AD and can cross-react with autoantigens in AD skin [48••]. APT with another species, *M. sympodialis*, showed that sensitivity to this yeast can be found in a significant number of patients with AD. Various *Malassezia* allergens have been characterized at molecular levels.

Conclusions

AD is a complex disease involving the interaction between genes, the environment, and immune responses. The current mainstay of treatment for AD relies on allergen avoidance, control of infection, routine skin care to enhance skin barrier function, and symptomatic use of anti-inflammatory medications, including topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI). These medications are highly effective in alleviating the symptoms of AD because they primarily target T cells, which are the major perpetrators of AD pathogenesis. But for AD patients with more severe symptoms, the increased need for these medications leads to a higher risk for potential side effects [49•]. Therefore, therapies that target other pathomechanisms of AD are needed as a replacement for TCS/TCI or as TCS/TCI-sparing agents (Table 1). These therapeutic approaches include: 1) downregulating DC functions by targeting FcεRI; 2) antagonizing CLA, chemokines, or their receptors that are responsible for the infiltration of inflammatory cells into AD lesions; 3) targeting keratinocyte functions such as inhibiting TSLP production or apoptosis; 4) clearing *S. aureus* by using synthetic AMP or by targeting cytokines that suppress AMP expression [50].

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