

# IMMUNOPATHOGENESIS OF ATOPIC DERMATITIS

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Atopic dermatitis (AD) is a chronic relapsing, highly pruritic, inflammatory skin disease that frequently predates the development of allergic rhinitis and asthma.<sup>45</sup> It is an important skin condition with significant costs and morbidity to patients and their families. Population studies suggest that the prevalence of AD has been increasing steadily since World War II, and in most countries it affects more than 10% of children.<sup>85</sup> There are wide variations in prevalence within and between countries inhabited by similar ethnic groups, suggesting that response to environmental factors is critical in determining disease expression. This article examines the cellular and immunologic mechanisms that are thought to affect the pathogenesis of chronic AD (Fig. 1).<sup>40</sup> An understanding of these mechanisms has important implications in the approach to the management of AD and the development of new therapies for patients with this common illness.

## IMMUNOLOGIC FINDINGS

### Systemic Immune Response

Most patients with AD have elevated numbers of circulating eosinophils and increased serum immunoglobulin E (IgE) levels. Other systemic findings in AD include the following:

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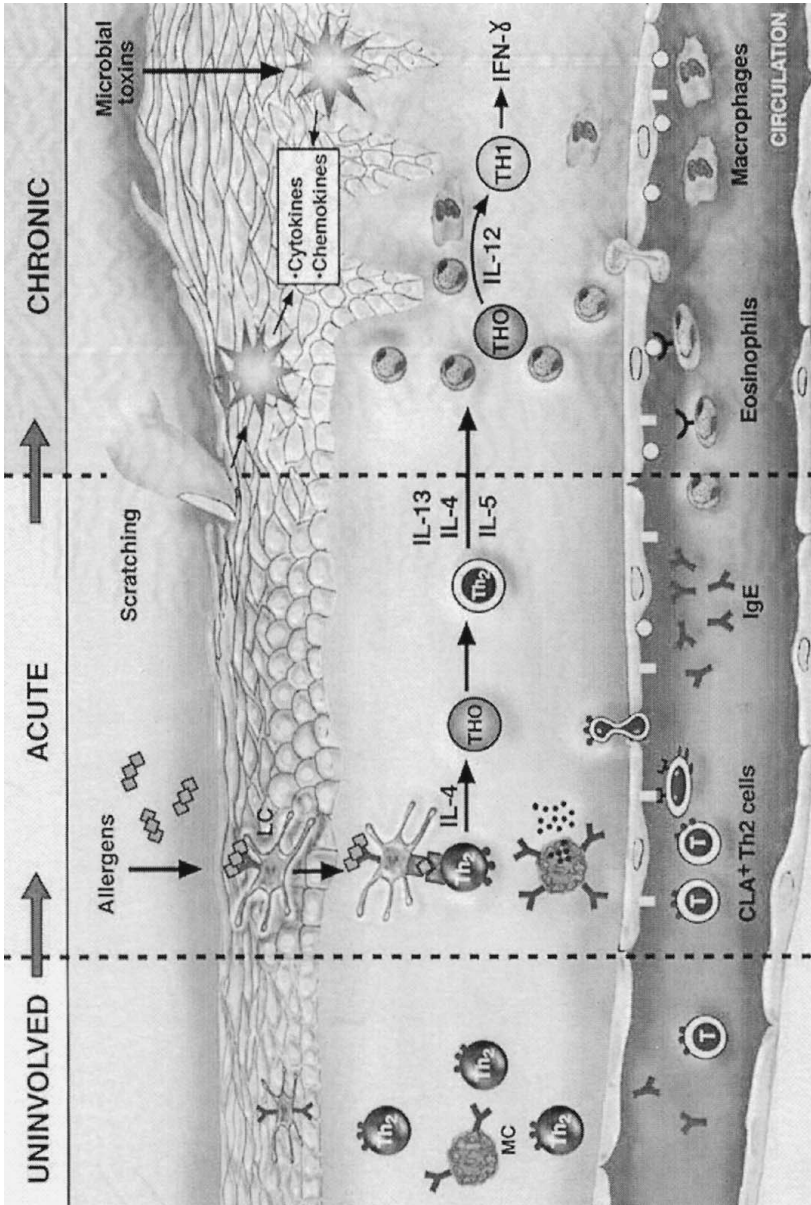


**Figure 1.** Immunologic pathways involved in the progression of atopic dermatitis. The biphasic switch from Th2 to Th1 responses is paralleled clinically and histologically by acute population and spongiosis followed by the development of lichenification, epidermal hyperplasia and dermal fibrosis. LC = Langerhans cells; MC = mast cells; CLA = cutaneous lymphoid antigen; Th = T helper cell type; IFN= interferon. (From Leung DYM: Atopic dermatitis: New insights and opportunities for therapeutic intervention. *J Allergy Clin Immunol* 105:860–876, 2000; with permission.)

- Increased basophil spontaneous histamine release
- Increased expression of CD23 on mononuclear cells
- Chronic macrophage activation with increased secretion of granulocyte macrophage colony-stimulating factor (GM-CSF), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), and interleukin-10 (IL-10)
- Expansion of IL-4-, IL-5-, and IL-13-secreting Th2-type cells
- Decreased numbers of interferon- $\gamma$  (IFN- $\gamma$ ) secreting Th1-type cells
- Increased serum sIL-2 receptor levels
- Increased serum eosinophil cationic protein, eosinophil-derived neurotoxin levels, and eosinophil major basic protein levels
- Increased urinary eosinophil protein X

Nearly 80% of children with AD eventually develop allergic rhinitis or asthma, suggesting a common systemic link between respiratory allergy and AD. This finding raises the question of whether allergen sensitization through the skin predisposes to respiratory allergic disease because of its effects on the systemic allergic response. When mice are sensitized epicutaneously with protein antigen, it induces a localized allergic dermatitis, elevated serum IgE, airway eosinophilia, and hyperresponsiveness to methacholine, which suggest that epicutaneous exposure to antigen in AD may lead to the development of asthma.<sup>73</sup>

The elevated IgE responses and eosinophilia observed in AD is thought to be caused by increased expression of Th2-type cytokines. Peripheral blood mononuclear cells (PBMC) from patients with AD have been found to have a decreased capacity to produce IFN- $\gamma$  in response to a number of allergenic and mitogenic stimuli. There also have been a number of studies demonstrating increased frequency of allergen-specific T cells that produce increased IL-4, IL-5, and IL-13 but little IFN- $\gamma$  in the peripheral blood of patients with AD.<sup>31, 32</sup> Peripheral blood monocytes from patients with AD have an abnormally low incidence of spontaneous apoptosis and are unresponsive to IL-4-induced apoptosis following stimulation.<sup>8</sup> The inhibition of apoptosis and nonresponsiveness to IL-4 was caused by increased production of GM-CSF by circulating monocytes of patients with AD.

These observations are important because IL-4 and IL-13 are the only cytokines that induce germline transcription at the C $\epsilon$  exon, thereby promoting isotype switching to IgE.<sup>54</sup> In fibroblasts, IL-4 or IL-13 stimulates RANTES, eotaxin, and MCP-1 expression,<sup>51</sup> which likely contributes to local eosinophil infiltration. Because T cells do not express IL-13 receptors, exogenous IL-13 does not promote Th2 responses or suppress Th1 differentiation in allergen-stimulated cultures in the same way as IL-4 does. IL-5 and GM-CSF promote the differentiation, vascular endothelial adhesion development, and survival of eosinophils.<sup>17</sup> In contrast, IFN- $\gamma$  inhibits IgE synthesis, the proliferation of Th2 cells, and expression of the IL-4 receptor on T cells.

### Skin Localization of Allergic Disease

The mechanisms that determine the location of allergic disease (e.g., skin versus lung in the case of AD versus asthma) is understood

incompletely but likely is determined in part by route of allergen sensitization, tissue chemokine expression, and expression of homing receptors on memory effector T cells. Tissue-selective homing is regulated by interaction of differentially expressed T-cell homing receptors with vascular endothelial-cell surface antigens. The cell adhesion molecule that results in T-cell homing to the skin is termed *cutaneous lymphocyte-associated antigen* (CLA). An important proof of concept is that T cells in the skin of allergen-induced reactions express significantly higher levels of CLA than T cells isolated from the airways of asthmatics. These data suggest that the propensity of patients to develop AD as opposed to asthma is associated with differences in the skin- versus lung-homing ability of their T cells. Patients with AD have an increased number of activated CLA+ T cells in their circulation. Santamaria Babi et al analyzed the reactivity of CLA+ T cells in patients with AD versus asthmatics, who all were sensitized with house dust mite.<sup>65</sup> When CLA+ T cells were separated from CLA- T cells, the mite-specific T-cell proliferation response in patients with AD sensitized to dust mite was localized to CLA+ T cells. In contrast, mite-sensitive patients with asthma had a mite-dependent proliferation response in their CLA- T cells consistent with the concept that airway T cells have a low level of CLA expression. A further link between CLA expression and skin disease-associated T cells in AD was shown by demonstrating that CLA+ T cells in patients with AD, but not normal controls, expressed the HLA-DR activation antigen and spontaneous production of IL-4 but not IFN- $\gamma$ . Akdis et al<sup>3, 4</sup> also demonstrated that CLA+ T cells in AD that express either CD4 or CD8 spontaneously secrete IL-5 and IL-13, functionally prolong eosinophil survival, and induce IgE synthesis. As a further step for selective recruitment of T cells to the skin, the chemokine CTACK (CCL27), which is produced primarily by keratinocytes, may be involved in the attraction of CLA+ T cells into the skin.<sup>50</sup> Although inflammatory cells such as eosinophils are not known to have specific tissue-homing receptors, studies indicate that local tissue expression of chemokines likely is involved in the localization to sites of inflammation.<sup>17</sup>

## Immunohistology

Clinically normal-appearing skin of patients with AD is not histologically normal but contains a sparse perivascular T-cell infiltrate.<sup>16</sup> Acute papular skin lesions are characterized by marked spongiosis (intercellular edema) of the epidermis. Antigen-presenting cells, such as Langerhans' cells and macrophages, in lesional skin of AD exhibit surface-bound IgE molecules,<sup>37, 44</sup> and there is a marked perivenular T-cell infiltrate. The lymphocytic infiltrate consists predominantly of activated memory T cells that bear CD4, HLA-DR, and CD45 RO. Eosinophils, basophils, and neutrophils rarely are present in acute AD. Mast cells are present in various stages of degranulation.

Chronic lichenified lesions are characterized by a hyperplastic epi-

dermis, prominent hyperkeratosis, and minimal spongiosis. There is an increased number of IgE-bearing Langerhans' cells in the epidermis, and macrophages dominate the dermal mononuclear cell infiltrate. The number of mast cells are increased in number but generally are granulated fully. Increased numbers of eosinophils are observed in chronic AD. These eosinophils undergo cytolysis with release of granule-protein contents into the upper dermis of lesional skin.<sup>12</sup> Eosinophils are believed to contribute to skin inflammation in AD by secreting cytokines and mediators that induce tissue injury in AD through the production of reactive oxygen intermediates and the release of toxic granule proteins.<sup>10</sup> Eosinophil major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin are elevated in AD sera and correlate with disease severity.<sup>29</sup> Urinary eosinophil protein X also has been found to correlate with AD disease activity.<sup>59</sup>

## **Cytokine Expression Pattern in Atopic Dermatitis Skin Lesions**

### *Th2- and Th1-type Cytokines*

Th2- and Th1-type cytokines contribute to the pathogenesis of skin inflammation in AD, with the relative contribution of each cytokine dependent on the stage of skin inflammation. As compared with the skin of normal individuals, uninvolved skin of patients with AD has an increased number of cells expressing IL-4 and IL-13, but not IL-5, IL-12, or IFN- $\gamma$  messenger RNA (mRNA).<sup>19, 20</sup> Acute and chronic skin lesions, when compared with normal skin or uninvolved skin of patients with AD, have significantly greater numbers of cells expressing IL-4, IL-5, and IL-13 mRNA; however, acute AD does not contain cells that express IFN- $\gamma$  or IL-12 mRNA.

Chronic AD skin lesions have significantly fewer cells that express IL-4 and IL-13 mRNA but increased numbers of cells that express IL-5, GM-CSF, IL-12, and IFN- $\gamma$  mRNA compared with acute AD. Acute T-cell infiltration in AD is associated with a predominance of Th2-like cytokines (IL-4 and IL-13), whereas maintenance of chronic inflammation is associated with an increase of Th1 and Th2 cytokines (IL-5, GM-CSF, IL-12, and IFN- $\gamma$ ) accompanied by the infiltration of eosinophils and macrophages. The increased expression of IL-12 in chronic AD skin lesions is of interest because cytokine plays a key role in Th1 cell development, and its expression in eosinophils and macrophages is believed to initiate the switch to Th1 cell development in chronic AD.<sup>18</sup>

The activity of cytokines is dependent on the expression of their receptors. Acute AD lesions contain a significantly higher number of cells that express the alpha subunit of IL-4 receptor (IL-4R- $\alpha$ ) mRNA compared with chronic AD lesions and normal and uninvolved atopic skin, whereas chronic AD lesions contain significantly more cells that

express the IL-5R- $\alpha$  and GM-CSFR- $\alpha$  mRNA when compared with acute AD lesions and normal and uninvolved atopic skin.<sup>76</sup>

Using an animal model of AD, Spergel et al<sup>74</sup> examined ovalbumin-elicited allergic skin inflammation in mice with targeted deletions of the IL-4, IL-5, and IFN- $\gamma$  cytokine genes to assess the role of these cytokines in atopic skin responses. Their data suggested that IL-4, IL-5, and IFN- $\gamma$  play important roles in the skin inflammatory response of AD. Allergen-sensitized skin from IL-5 knockout mice had no detectable eosinophils and exhibited decreased epidermal and dermal thickening. IL-4 knockout mice displayed normal thickening of the skin layers but had a drastic reduction in eosinophils. Sensitized skin from IFN- $\gamma$  knockout mice was characterized by reduced dermal thickening.

A subset of patients with AD has been found to have normal serum IgE levels.<sup>2</sup> Skin biopsies from patients with the nonallergic form of AD have similar numbers of T cells as found in patients with allergic AD; however, skin T cells from nonallergic AD express lower IL-5 and IL-13 levels compared with those from allergic AD. T cells isolated from skin biopsies of patients with nonallergic AD produced significantly lower levels of IgE than T cells from patients with allergic AD. In addition, B-cell activation with high CD23 expression was observed in the peripheral blood of patients with allergic AD, but not in patients with nonallergic AD.

### *Chemoattractant Factors*

The C-C chemokines, RANTES, monocyte chemotactic protein-4, and eotaxin have been found to be increased in AD skin lesions and likely contribute to the chemotaxis of eosinophils and Th2 lymphocytes into the skin.<sup>77, 87</sup> IL-16, a chemoattractant for CD4+ T cells, is more highly expressed in acute than chronic AD skin lesions.<sup>36</sup> Studies suggest a role for cutaneous T-cell-attracting chemokine (CTACK or CCL27) in the preferential attraction of CLA+ T cells to the skin.<sup>60</sup> The chemokine receptor CCR3, which is found on eosinophils and Th2 lymphocytes and can mediate the action of eotaxin, RANTES, and MCP-4, has been reported to be increased in nonlesional and lesional skin of patients with AD.<sup>87</sup> Leukotriene B4 (LTB4) also is released on exposure of AD skin to allergens and may act as a chemoattractant for the initial influx of inflammatory cells.<sup>33</sup> These cytokines, chemokines, and mediators reinforce the influx of inflammatory cells into the skin.

### *Mechanisms of Chronic Skin Inflammation*

Chronic AD results from the prolonged survival of eosinophils and monocyte-macrophages in atopic skin. Increased IL-5 expression during the transition from acute to chronic AD likely contributes to the prolongation of eosinophil survival and function. In chronic AD, there is increased GM-CSF expression.<sup>8</sup> GM-CSF plays an important role in maintaining the survival and function of monocyte-macrophages, Lang-

erhans' cells, and eosinophils.<sup>17</sup> Enhanced production of GM-CSF by epidermal keratinocytes and infiltrating macrophages has been shown in AD lesions.<sup>8, 58</sup> Supernatants from cultured keratinocytes of patients with AD induce a significantly higher proliferative response in PBMC than supernatants from control keratinocytes of nonatopic individuals, and this proliferative response can be abrogated totally by an anti-GM-CSF monoclonal antibody. Supernatants from PMA-stimulated keratinocytes of patients with AD, together with exogenous IL-4, also support the maturation of monocytes into dendritic cells. Epidermal keratinocytes, when stimulated simultaneously with IFN- $\gamma$  and TNF- $\alpha$ , have been found to produce increased levels of RANTES, which enhances the chemotaxis of eosinophils.<sup>57, 86</sup> This may serve as one mechanism by which the rise in IFN- $\gamma$  during chronic AD enhances the severity of eczema.

Increased IFN- $\gamma$  secreted by activated T cells that infiltrate into the skin lesions of chronic AD may also play a role in keratinocyte apoptosis. Trautmann et al<sup>79</sup> demonstrated that keratinocytes normally express low levels of Fas receptor that can be enhanced substantially by the presence of IFN- $\gamma$ . Subsequently keratinocytes can undergo apoptosis induced by supernatants from activated T cells or direct contact between T cells and keratinocytes. Other cytokines did not induce keratinocyte apoptosis. This finding may represent a common mechanism between AD and allergic contact dermatitis that accounts for clinical and histologic similarities between various eczematous conditions.

The environmental triggers that contribute to chronicity of AD are unknown; however, it is well established that chronic exposure to allergens can contribute to atopic skin disease.<sup>69, 84</sup> Furthermore, chronic AD frequently is associated with colonization by superantigen-producing *Staphylococcus aureus*.<sup>43</sup> To examine a potential role for microbial superantigens in the prolongation of monocyte-macrophage survival, Bratton et al,<sup>9</sup> incubated peripheral blood monocytes from patients with AD with the toxic shock syndrome toxin-1 (TSST-1; a prototypic superantigen) and examined its effects on the incidence of apoptosis. TSST-1, in a concentration-dependent manner, significantly inhibited monocyte apoptosis and stimulated production of the prosurvival cytokines GM-CSF, IL-1 $\beta$ , and TNF- $\alpha$ . In this experimental setting, GM-CSF was the primary cytokine responsible for inhibition of apoptosis.

## **FACTORS CONTRIBUTING TO Th2 CELL DEVELOPMENT IN ATOPIC DERMATITIS**

A number of factors support acute Th2 cell development in the atopic skin process and in the systemic immune response of AD. These factors include the cytokine milieu in which T-cell development takes place, the host's genetic propensity to produce Th2-type cytokines, pharmacologic factors, the costimulatory signals used during T-cell activation, and the antigen-presenting cell.

## Role of Cytokines

Interleukin-4 promotes Th2 cell development, whereas IL-12, produced by macrophages, dendritic cells, or eosinophils, induces Th1 cell development.<sup>63</sup> The IL-12  $\beta_2$  subunit, which is the binding and signal-transducing component of the IL-12R, is expressed on Th1 but not Th2 clones.<sup>62</sup> It is of interest that IL-4 inhibits the expression of IL-12R $\beta_2$  on T cells. In contrast, IL-12 induces expression of the IL-12R $\beta_2$  chain, providing a basis by which this cytokine induces differentiation of Th1 cells. IL-18 activates the IFN- $\gamma$  promoter at an activation protein (AP-1) binding site and induces IFN- $\gamma$  synthesis, enhancing Th1 cell development.<sup>14</sup> IL-4 also has been shown to inhibit IFN- $\gamma$  production and down-regulate the differentiation of Th1 cells. Mast cells and basophils also provide a source of Th2-type cytokines that can be released on cellular activation.<sup>48</sup> The increased systemic and local skin expression of IL-4 by T cells, mast cells, and basophils in AD would be expected to promote Th2 cell development. It should be noted, however, that because Th2 cells still can develop (albeit at a lower level) in IL-4 knockout mice, other factors also could contribute to Th2 cell development.

## Genetics

Although many genes likely are involved in the development of allergic diseases, there has been particular interest in the potential role of genes on chromosome 5q31-33, which determines expression of Th2-type cytokines (i.e., IL-3, IL-4, IL-5, IL-13, GM-CSF).<sup>18</sup> Kawashima et al examined linkage between markers at and near the IL-4 gene and AD in 88 Japanese nuclear families.<sup>30</sup> A case-control comparison suggested a genotypic association between AD and the T allele of the -590C/T polymorphism of the IL-4 gene promoter region. Because the T allele is associated with increased IL-4 gene promoter activity compared with the C allele, their data suggest that genetic differences in transcriptional activity of the IL-4 gene influence AD predisposition. Hershey et al<sup>25</sup> reported an association of AD with a gain-of-function mutation in the IL-4R- $\alpha$ . The authors speculated that the R576 allele may predispose persons to allergic diseases by enhancing the signaling function of the receptor. Overall, these data support the concept that IL-4 gene expression plays a critical role in the expression of AD. An IL-13 coding-region variant also has been associated with increased total serum IgE levels and AD, supporting the concept that IL-13 has a key role in some of the immunologic features of AD.<sup>47</sup> Lee et al<sup>39</sup> identified a major susceptibility locus for AD mapping to chromosome 3q21. Although the actual gene involved was not identified, these findings support the concept that distinct genetic factors contribute to susceptibility to AD.

## Pharmacologic Factors

Monocytes from patients with AD have increased cyclic AMP-phosphodiesterase (cAMP PDE) enzyme activity. This cellular abnormality contributes to the increased IgE synthesis by B cells and IL-4 production by T cells in AD, because IgE and IL-4 production can be decreased in vitro by PDE inhibitors.<sup>21</sup> The elevated cAMP PDE in atopic monocytes also contributes to the secretion of increased IL-10 and PGE<sub>2</sub>. Monocyte-derived IL-10 and PGE<sub>2</sub> inhibit IFN- $\gamma$  production by T cells and may contribute to the decreased IFN- $\gamma$  production by PBMC cultured from patients with AD. PDE inhibitors also have been found to reduce superantigen-induced, IL-12-dependent expression of the CLA skin-homing receptor on T cells from patients with AD.<sup>64</sup>

## Costimulatory Signals

Complete activation of resting T cells requires costimulatory signals independent of the engagement of T-cell receptors with the MHC plus peptide complex on antigen-presenting cells. In mice, the generation of Th2 cells has been reported to depend on the interaction of CD28 with B7.2.<sup>35</sup> To determine the potential role of B7.2 molecules in AD, the author compared the expression of B7.1 versus B7.2 on B cells from patients with AD.<sup>27</sup> The expression of B7.2 on B cells of patients with AD was significantly higher than that found in normal subjects or patients with psoriasis. In contrast, there was no significant difference in B7.1 expression among the three subject groups. Total serum IgE from patients with AD and normal subjects correlated significantly with B7.2 expression on B cells, suggesting a role for B7.2 + B cells in IgE synthesis. Antihuman B7.2, but not B7.1, monoclonal antibodies (mAb) significantly decreased IgE production by PBMC stimulated with IL-4 and anti-CD40 mAb. IL-4 and IL-13 also have been found to induce B7.2 expression on B cells, providing an amplification loop for IgE synthesis in AD.<sup>26</sup>

Langerhans' cells in the lesional skin of AD predominantly express B7.2 compared with B7.1.<sup>55</sup> Antibodies to B7.2 completely inhibited T-cell proliferation stimulated with *D. pteronyssinus* in the presence of Langerhans' cells. These data suggest that CD86 expression on Langerhans' cells has an important role co-stimulatory molecules for T-cell activation and may account for the increased Th2 responses that occur after repeated antigen presentation by Langerhans' cells.<sup>24</sup>

## Antigen-Presenting Cells

Atopic dermatitis skin contains an increased number of IgE-bearing Langerhans' cells that seem to have an important role in cutaneous allergen presentation to Th2 cells.<sup>56</sup> In this regard, IgE-bearing Langer-

hans' cells from AD skin lesions are 1000-fold more efficient than Langerhans' cells that lack surface IgE in presenting house dust mite allergen to T cells. These results suggest that cell-bound IgE on Langerhans' cells facilitate the capture and internalization of allergens into Langerhans' cells before their processing and antigen presentation to T cells. Langerhans' cells that bear IgE and have captured allergen likely activate memory Th2 cells in atopic skin but also may migrate to the lymph nodes to stimulate naïve T cells to further expand the pool of systemic Th2 cells.

Binding of IgE to Langerhans' cells occurs primarily through high-affinity IgE receptors. The importance of these IgE receptors on Langerhans' cells is supported by the observation that the presence of Langerhans cells' that express FcεRI and bear IgE molecules is required to provoke eczematous skin lesions by application of aeroallergens on the skin of atopic patients.<sup>37</sup> In contrast to mast cells and basophils, in which the FcεRI is a tetrameric structure constitutively expressed at high levels, the FcεRI on Langerhans' cells lacks the classical beta chain and its expression varies depending on the local skin inflammatory environment. Normal individuals and patients with respiratory allergy have low-level surface expression of FcεRI on their Langerhans' cells, whereas FcεRI is expressed at high levels in the skin lesions of patients with AD.<sup>34</sup> High-level FcεRI expression enhances binding and uptake of allergens and the activation of Langerhans' cells on receptor ligation.<sup>28</sup> Surface expression of FcεRI has been found to correlate with IgE serum levels. IL-4 strongly induces the cytoplasmic expression of the alpha chain of FcεRI in dendritic cells and up-regulates the expression of the skin-homing structures E-cadherin and CLA.<sup>16</sup> In contrast, IFN-γ inhibits expression of FcεRIα and E-cadherin.

## IMMUNOLOGIC TRIGGERS

Atopic dermatitis can be triggered by a variety of immunologic triggers (see article by Jones elsewhere in this issue). These triggers include food allergens,<sup>69</sup> aeroallergens,<sup>37</sup> *S. aureus* toxins,<sup>71</sup> and autoallergens.<sup>80</sup> Double-blind, placebo-controlled food challenges have demonstrated that nearly 40% of infants and young children with moderate-to-severe AD have food allergy.<sup>70</sup> Furthermore, food allergen-specific T cells have been cloned from lesional skin and peripheral blood of patients with AD.<sup>66, 82</sup> Patients with food-induced AD have been studied to analyze the relationship between tissue specificity of a clinical reaction to an allergen and the expression of skin-homing receptors on T cells activated in vitro by the relevant allergen.<sup>1</sup> In these studies, the expression of CLA and L-selectin on T cells from children with casein-induced AD were assessed and compared for their CLA expression following stimulation in vitro with casein to T cells collected from patients with milk-induced gastroenteropathy or healthy controls. Casein-reactive T cells from patients with milk-induced eczema were found to have significantly higher levels of CLA than *Candida albicans*-reactive T cells

from the same patients and either casein- or *C. albicans*-reactive T cells from nonatopic controls or noneczematous atopic patients.

Inhalant allergens also have been reported to exacerbate AD.<sup>84</sup> Aeroallergen-specific T cells have been isolated from the lesional skin and peripheral blood of patients with AD.<sup>60, 81</sup> Most reports, however, have focused on the epicutaneous application of aeroallergens using patch test techniques. In these studies, patch testing of uninvolved atopic skin with aeroallergens resulted in eczematoid reactions in 30% to 50% of patients with AD.<sup>13, 38</sup> Positive reactions were observed to various allergens, including dust mite, weeds, animal danders, and molds. In contrast, patients with respiratory allergy and healthy volunteers rarely have positive allergen patch tests.

Several studies have examined whether avoidance of aeroallergens results in clinical improvement of AD. Most of these reports have involved uncontrolled trials in which patients placed in mite-free environments (e.g., through use of acaricides or impermeable mattresses covers) were found to have improvement of their AD. One double-blind, placebo-controlled study using a combination of effective mite-reduction measures in the home has been reported.<sup>78</sup> Although both active and control groups decreased Der p 1 concentrations in carpeting, the reduction in the amount of dust was significantly greater on the mattresses in the active group, and the disease improved significantly more in the active treatment group.

These clinical studies suggest that inhalation or contact with aeroallergen may exacerbate AD. Laboratory data supporting a role for inhalants include the finding of IgE antibody to specific inhalant allergens in most patients with AD. One study found that 95% of sera from patients with AD had IgE to house dust mites compared with 42% of sera from asthmatic subjects.<sup>68</sup> The degree of sensitization to aeroallergens is associated directly with the severity of AD.<sup>67</sup>

Patients with AD have an increased tendency to develop bacterial and fungal skin infections. *S. aureus* is found in over 90% of AD skin lesions. In contrast, only 5% of normal subjects harbor this organism. The density of *S. aureus* on inflamed AD lesions without clinical superinfection can reach up to  $10^7$  colony-forming units per  $\text{cm}^2$  on lesional skin. The importance of *S. aureus* is supported by the observation that even patients with AD and without superinfection show a reduction in severity of skin disease when treated with a combination of antistaphylococcal antibiotics and topical corticosteroids.<sup>46</sup>

Studies suggest that one strategy by which *S. aureus* exacerbates or maintains skin inflammation in AD is by secreting a group of toxins known to act as superantigens which stimulate marked activation of T cells and macrophages. Several lines of investigations support a role for superantigens in AD (Fig. 2): (1) Over half of patients with AD have *S. aureus* cultured from their skin that secrete superantigens such as enterotoxins A, B, and TSST-1.<sup>10, 43, 52</sup> An analysis of the skin-homing CLA<sup>+</sup> T cells from these patients and their skin lesions reveals that the cells have undergone a T-cell receptor (TCR) V-beta expansion consistent

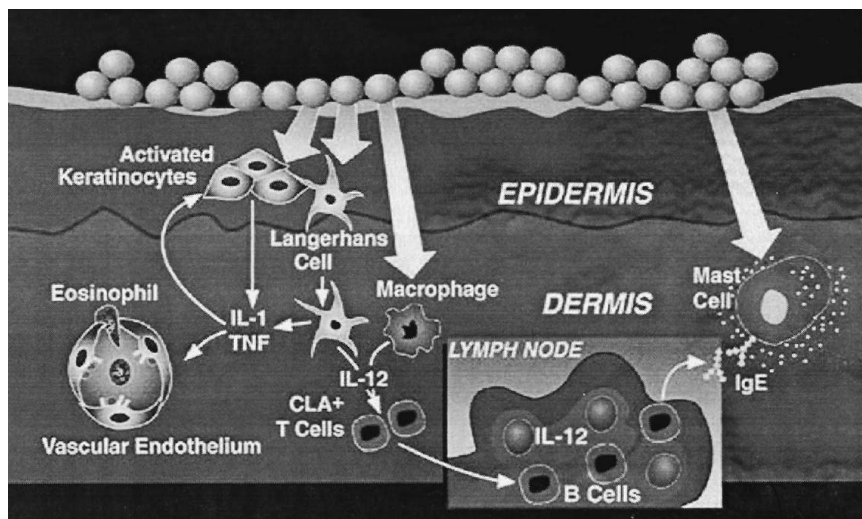


**Figure 2.** Immune mechanisms of staphylococcal superantigen action. (From Leung DYM: Atopic dermatitis: New insights and opportunities for therapeutic intervention. *J Allergy Clin Immunol* 105:860–876, 2000; with permission.)

with superantigenic stimulation.<sup>11, 75</sup> (2) Most patients with AD make specific IgE antibodies directed against the staphylococcal toxins found on their skin. Basophils from patients with antitoxin IgE release histamine on exposure to the relevant toxin but not in response to toxins for which they have no specific IgE.<sup>43</sup> (3) A correlation has been found between the presence of IgE antisuperantigens and severity of AD.<sup>10, 52</sup> Superantigens also augment allergen-specific IgE synthesis and induce corticosteroid resistance, suggesting that several mechanisms exist by which superantigens could aggravate the severity of AD.<sup>22</sup> (4) The superantigen staphylococcal enterotoxin B (SEB), when applied to the skin, can induce skin changes of erythema and induration, and the infiltrating T cells are selectively expanded in response to SEB.<sup>72</sup> Superantigens have been demonstrated to induce T-cell expression of the skin-homing receptor through stimulation of IL-12 production.<sup>42</sup> In the case of AD, the author has proposed that staphylococcal superantigens secreted at the skin surface could penetrate inflamed skin and stimulate epidermal macrophages or Langerhans' cells to produce IL-1, TNF, and IL-12. Local production of IL-1 and TNF induces the expression of E-selectin on vascular endothelium, allowing an initial influx of CLA<sup>+</sup> memory and effector cells. Secretion of IL-12 increases CLA expression on those T cells activated by allergen or superantigen and increases the efficiency of T-cell recirculation to the skin.

Studies also have demonstrated a potential role for autoallergens as a trigger for AD. In this regard, Valenta et al<sup>80</sup> reported that the majority of sera from patients with severe AD contains IgE antibodies directed against human proteins. One of these IgE-reactive autoantigens has

been cloned from a human epithelial complementary DNA (cDNA) expression library and designated Hom s 1, which is a 55 kDa cytoplasmic protein in skin keratinocytes. Although the autoallergens characterized to date mainly have been intracellular proteins, they have been detected in IgE immune complexes of AD sera, suggesting that release of these autoallergens from damaged tissues could trigger IgE- or T-cell-mediated responses.

Thirty percent of sera from patients with AD also have been found to have autoantibodies that react with tissue culture cells to display a characteristic pattern of nuclear distribution of dense fine speckles.<sup>53</sup> These sera react with a 70 kDa protein on Western immunoblots, so the antigen has been termed *dense fine speckles 70 kDa* (DFS70). Sixteen percent of asthmatics also have antibodies of the same specificities. A cDNA isolated from an expression library that encodes DFS70 has been found to be identical to a transcription coactivator called p75, which has been shown to be required for RNA polymerase II-dependent transcription. IgG and IgE antibodies to DFS70 are present in AD sera.

Overall, these data suggest that in addition to IgE immune responses elicited by environmental allergens, atopic skin inflammation can be maintained by human endogenous antigens, particularly in severe AD. These autoantigens are primarily nuclear or microsomal in origin. This finding raises the possibility that damage to the skin by infectious microbes or scratching can release intracellular antigens that elicit and sustain IgE and T-cell responses in AD.

## SUMMARY

Atopic dermatitis is a complex immunologic skin disorder that is expressed when genetically predisposed individuals are exposed to certain environmental stimuli. This results in an acute Th2 response in the skin followed by a combination Th1 and Th2 response in chronic skin lesions. The capacity of topical corticosteroids, tacrolimus, SDZ ASM 981, and phototherapy to inhibit the activation of multiple cell types and different cytokines likely accounts for the ability of these therapies to effectively reduce the chronic inflammatory skin response in AD.<sup>6, 23, 56, 61</sup>

More studies are needed to focus on strategies that prevent the initial development of AD. Given the central role of Th2-type cytokines and chemokines in the development of allergic skin inflammation, strategies directed at reducing Th2 responses and blocking the action of chemokines by way of antagonists of CCR3 and CCR4 are important. Further studies also are needed to examine the potential role of IFN- $\gamma$ , IL-12, and IL-18 in restoring the shift toward a more balanced T<sub>H</sub>0 response in the systemic immune response with equal production of Th1 and Th2 cytokines. There is also a strong rationale for examining the effect of therapeutic agents capable of blocking the actions of IL-4 and IL-5.<sup>7</sup>

The development of humanized anti-IgE antibodies<sup>49</sup> that are nonan-

aphylactogenic also may enable the elimination or reduction of IgE responses, although it will be more difficult to neutralize IgE in AD because of the high serum IgE levels. Elimination of the IgE response may have less importance in patients with ongoing Th2 cell-mediated allergic inflammatory responses. In animal models of AD, allergic skin inflammation was elicited to the same extent in wild-type and IgE knockout mice.<sup>74</sup> The combination of several anti-inflammatory approaches is needed to effectively interrupt the complex inflammatory cascades associated with allergic diseases.

## References

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