

Pathogenesis of atopic dermatitis

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Atopic dermatitis (AD) is a common inflammatory skin disease with increasing prevalence since World War II. Recent studies have shed light on how the complex interrelation of genetic, environmental, immunologic, and pharmacologic factors contributes to the development of AD. The current review will examine the cellular and immunologic mechanisms underlying AD as well as the potential role of microbial superantigens in the pathogenesis of AD. An understanding of the relative contributions of allergens, IgE, T cells with skin homing capability, Langerhans cells, keratinocytes, eosinophils, and mast cells to the inflammatory process in AD may lead to improved treatments for this potentially debilitating disease. (*J Allergy Clin Immunol* 1999;104:S99-108.)

Key words: Atopic dermatitis, allergies, cytokines, skin, T cells

Atopic dermatitis (AD) is a chronic, highly pruritic, inflammatory skin disease frequently seen in patients with a history of respiratory allergy.^{1,2} Population studies suggest that the prevalence of AD in children has been steadily increasing since World War II and that it now affects more than 10% of children at some point during their childhood.^{3,4} The term atopic dermatitis was first introduced in 1933 by Hill and Sulzberger⁵ in recognition of the close association between AD and respiratory allergy. However, there has been considerable debate over whether AD is primarily an allergen-induced disease or simply an inflammatory skin disorder found in association with respiratory allergy. Recent studies, however, suggest that the mechanisms underlying asthma and AD have greater similarities than differences.

Overall, atopy can be defined as a familial hypersensitivity of skin and mucous membranes against environmental substances, associated with increased IgE production and/or altered nonspecific reactivity in different organ systems, for example, skin in the case of AD and lung in the case of asthma. It is evident that allergic reactions play a role in some patients but not necessarily in all. In many patients different factors such as a disturbance of skin function, infection, and stress are potentially more relevant. Immunologic disturbances are reflected in the elevated IgE production and T-cell dysregulation observed in AD. Nonspecific altered reactivity

Abbreviations used

AD:	Atopic dermatitis
CLA:	Cutaneous lymphocyte antigen
LPR:	Late-phase reaction
MAdCAM-I:	Mucosal addressin
PBMC:	Peripheral blood mononuclear cell
SEB:	Staphylococcal enterotoxin B

is reflected in increased releasability of mediator secreting cells and bronchial, nasal, and skin hyperreactivity. Each disease that forms the atopic triad has important immunologic parallels. However, they involve a different regional sphere of immunologic influence, for example, the skin-associated lymphoid tissue in AD as opposed to bronchial associated lymphoid tissue in asthma.

The current review will examine the cellular and immunologic mechanisms that are thought to play an important role in the pathogenesis of chronic AD. An understanding of the immunologic basis of AD is likely to have important clinical implications in our approach to the management of this common illness. Because the skin is readily accessible for tissue analysis, lessons learned from the immunopathogenesis of AD may also provide important insights into potential mechanisms that contribute to chronic tissue inflammation in other allergic diseases such as asthma.

SKIN REACTION PATTERNS IN AD

Intense pruritus and cutaneous reactivity are the cardinal features of AD. In 1891, the French dermatologist Jacquet first suggested that it was not the rash that itches but that the itch was the initial event. Subsequently, in 1936, while observing children undergoing food challenges Engman et al⁶ noted that skin trauma inflicted by scratching played an important role in the evolution of eczema. Importantly, if the skin could be protected from scratching, the eczematoid rash was prevented although the patient remained extremely pruritic.

Scratching may be intermittent throughout the day but is usually worse in the early evening and night. Disruption of normal sleep patterns is a common problem afflicting patients with chronic AD. The pathogenesis of cutaneous pruritus is poorly understood. Experimentally, pruritus can be induced by intradermal injection of various products of inflammatory effector cells such as histamine, neuropeptides, leukotrienes, and proteolytic enzymes. Patients with AD also have a reduced threshold for pruritus.⁷ Clinically, this is supported by the observation that allergens, reduced humidity, excessive sweating, and irritants such as wool, acrylic, soaps, and detergents can exacerbate pruritus and scratching.

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Supported in part by Public Health Services Research Grants HL36577, AR41256, HL37260, and 5 MO1 RR00051.

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0091-6749/99 \$8.00 + 0 1/0/99520

TABLE I. Peripheral blood findings in atopic dermatitis

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- Increased IgE levels
 - Eosinophilia
 - Increased basophil spontaneous histamine release
 - Decreased CD8 suppressor/cytotoxic number and function
 - Increased expression of CD23 on mononuclear cells
 - Chronic macrophage activation with increased secretion of GM-CSF, prostaglandin E₂, and IL-10
 - Expansion of IL-4- and IL-5-secreting T_{H2}-type cells
 - Decreased numbers of IFN- γ -secreting T_{H1}-type cells
 - Increased serum sIL-2 receptor levels
 - Increased serum eosinophil cationic protein levels
 - Increased soluble E-selectin levels
 - Increased soluble vascular cell adhesion molecule-1 levels
 - Increased soluble intercellular adhesion molecule-1 levels
-

Nassif et al⁸ tested graded dilutions of sodium lauryl sulfate to determine irritancy thresholds in patients with AD versus patients with either inactive AD or allergic respiratory disease with no dermatitis versus normal nonatopic subjects. Patients with active AD showed significantly greater irritant skin responses than the other control groups. Of interest, even patients with inactive AD and respiratory allergy had increased irritancy compared with normal control subjects. Thus the "atopic skin" is generally associated with a lowered threshold of irritant responsiveness.

Several skin lesions are commonly seen in AD. Acute skin lesions are characterized by intensely pruritic, erythematous papules over erythematous skin. These are associated with extensive excoriations, erosions, and serous exudate. Subacute dermatitis is characterized by erythematous, excoriated, scaling papules. Chronic dermatitis is characterized by thickened skin, accentuated skin markings (lichenification), and fibrotic papules. In chronic AD, all three stages of skin reactions frequently coexist in the same individual. At all stages of AD, patients usually have dry, lackluster skin. Distribution and skin reaction pattern varies according to the patient's age and disease chronicity. During infancy, AD is generally more acute and primarily involves the face, scalp, and the extensor surfaces of the extremities. In older patients the skin becomes lichenified and the rash localizes to the flexural folds of the extremities.

IMMUNOPATHOGENESIS OF AD

The concept that AD has an immunologic basis is supported by the observation that patients with primary T-cell immunodeficiency disorders frequently have elevated serum IgE levels, eosinophilia, and eczematoid skin lesions indistinguishable from AD. In patients with Wiskott-Aldrich syndrome, resolution of their skin rash occurs after correction of the immunologic defect by successful bone marrow transplantation.⁹ Furthermore, nonatopic recipients receiving bone marrow transplants from atopic donors have been reported to have positive immediate skin tests and atopic symptoms after success-

ful engraftment.¹⁰ These data suggest that AD is mediated by a bone marrow-derived cell.

Peripheral blood studies

A number of laboratory observations suggest an underlying immunoregulatory abnormality in AD (Table 1). It is generally thought that the elevated IgE responses and eosinophilia observed in the majority of patients with AD reflects the increased expression of T_{H2} cytokines, that is, increased IL-4, IL-5, and IL-13 with a concomitant decrease in IFN- γ expression. In this regard, peripheral blood lymphocytes from patients with AD have been reported to secrete increased amounts of IL-4 and express abnormally high levels of IL-4 receptor¹¹ as well as increased IL-13.¹² PBMC from patients with AD have also been found to have a decreased capacity to produce IFN- γ in response to a number of stimuli.^{13,14} A significant inverse correlation between IFN- γ generation in vitro and IgE serum concentrations in vivo in AD has been reported.¹³ There have also been a number of studies demonstrating increased frequency of allergen-specific T cells producing increased IL-4 and IL-5 but little IFN- γ in the peripheral blood and skin lesions of patients with AD.^{15,16} It should be pointed out, however, that the majority of allergen-specific T-cell clones are T_{H0}-type cells with the potential for development into either T_{H1} or T_{H2} cells after they have infiltrated into the skin.

Immunohistology of AD

The histologic features of AD depend on the acuity of the skin lesion.^{17,18} Uninvolved or clinically normal-appearing skin of patients with AD is histologically abnormal and demonstrates mild hyperkeratosis and a sparse perivascular cellular infiltrate consisting primarily of T lymphocytes. Acute lesions are characterized by marked intercellular edema (spongiosis) of the epidermis and a sparse epidermal infiltrate consisting primarily of T lymphocytes. In the dermis, there is a marked perivascular inflammatory cell infiltrate consisting predominantly of T lymphocytes and occasional monocyte-macrophages. The lymphocytic infiltrate consists predominantly of memory T cells bearing CD3, CD4, and CD45 RO (suggesting previous encounter with antigen).^{18,19} Essentially all T cells infiltrating into the skin lesion express high levels of cutaneous lymphocyte antigen (CLA), which functions as a skin homing receptor for T lymphocytes. Eosinophils, basophils, and neutrophils are rarely present in the acute lesion. Mast cells, in various stages of degranulation, are present in normal numbers.

In chronic lichenified lesions, the epidermis is hyperplastic with elongation of the rete ridges, 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 are generally fully granulated. Increased numbers of eosinophils are observed in chronic AD skin lesions. In support of a functional role of

eosinophils in chronic AD lesions, Leiferman et al²⁰ have found that eosinophil-derived extracellular major basic protein can be detected by immunofluorescence in a fibrillar pattern associated with the distribution of elastic fibers throughout the upper dermis. Extracellular major basic protein deposition was much more extensive in the involved areas than the uninvolved areas of skin. Although the role of eosinophils in the pathogenesis of AD is not completely understood, it is thought to contribute to tissue injury in AD through the production of reactive oxygen intermediates and release of cytotoxic granules. Eosinophil cationic protein is elevated in AD sera and correlates with disease severity, providing further evidence for eosinophil activation and involvement in AD.²¹

Biphasic cytokine expression pattern in AD skin lesions

Recent studies indicate that T_{H2} and T_{H1}-type cytokines contribute to the pathogenesis of skin inflammation in AD, with the relative contribution of each cytokine type dependent on the acuity or duration of the skin lesion (Table 2). Using in situ hybridization, Hamid et al^{22,23} investigated the expression of IL-4, IL-5, and IFN- γ mRNA in skin biopsies from clinically normal (uninvolved), acute (erythematous AD lesions of <3 days' duration) and chronic (>2 weeks' duration) skin lesions of patients with AD. As compared with normal skin, uninvolved skin of patients with AD had a significant increase in number of cells expressing IL-4 and IL-13 but not IL-5 or IFN- γ mRNA. Acute and chronic skin lesions, when compared with normal skin or uninvolved skin of AD patients, had significantly greater numbers of cells that were positive for mRNA for IL-4, IL-5, and IL-13. However, neither acute AD or uninvolved AD skin contained significant numbers of IFN- γ mRNA-expressing cells.

As compared with acute AD, chronic AD skin lesions had significantly fewer IL-4 and IL-13 mRNA-expressing cells but increased numbers of IL-5 and IFN- γ mRNA-expressing cells. These data indicate that although cells in acute and chronic AD lesions are associated with increased activation of IL-4, IL-5, and IL-13 genes, acute skin inflammation in AD is associated with a predominance of IL-4 and IL-13 expression, whereas maintenance of chronic inflammation is associated with increased IL-5 and IFN- γ expression accompanied by the infiltration of eosinophils and macrophages.

In addition, recent studies have demonstrated overexpression of IL-16 in acute skin lesions and IL-12 and GM-CSF overexpression in chronic AD lesions.²³⁻²⁵ These observations are of interest because IL-16 may promote the infiltration of CD4⁺ T cells into acute lesions and GM-CSF is likely to enhance cell survival of eosinophils and macrophages in chronic skin lesions (Reference 73). The increased expression of IL-12 in chronic AD skin lesions is of interest because that cytokine plays a key role in T_{H1} cell development, and its expression in eosinophils and/or macrophages is thought

TABLE II. Cells and cytokines in atopic dermatitis skin lesions

	Nature of skin lesion		
	Uninvolved	Acute	Chronic
Cell type			
T cells	+	+++	++
Eosinophils	—	+	+++
Macrophages	—	++	+++
Cytokine gene expression			
IL-4/IL-13	+	++++	+++
IL-5	—	++	+++
Interferon- γ	—	—	++
IL-12	—	—	++
IL-16	+	+++	++
GM-CSF	—	+	++

to initiate the switch to T_{H1} cell development in the chronic skin lesion.²⁶ The C-C chemokines, RANTES, monocyte chemotactic protein-3, and eotaxin have also been found to be increased in AD skin lesions and probably contribute to the chemotaxis of eosinophils into the skin.²⁷

The functional significance of these cytokine changes in acute versus chronic AD skin lesions is supported by recent studies of in vivo expression of cytokine receptor mRNA.²⁸ These studies have demonstrated that acute AD is associated with a high expression of IL-4 receptor, whereas IL-5 receptor and GM-CSF receptor mRNA are predominantly increased in chronic AD. These findings support the biphasic role of IL-4, IL-5, and GM-CSF in the pathogenesis of AD skin inflammation.

This biphasic pattern of T-cell activation has also been well demonstrated in studies on skin biopsies of atopic patch test reaction sites.²⁶ At early time points, for example, 24 hours after allergen application, increased expression of IL-4 mRNA and protein is observed, after which IL-4 expression declines to baseline levels. In contrast, IFN- γ mRNA expression is not detected in 24-hour patch test lesions but is strongly overexpressed at the 48- to 72-hour time points. This is consistent with studies demonstrating allergen-specific T_{H2} cell clones derived from early time points of evolving atopic patch test reactions, whereas the majority of allergen-specific T-cell clones derived from later patch test sites (>48 hours) exhibit T_{H1}- or T_{H0}-type cytokines profile. Interestingly, the increased expression of IFN- γ mRNA in atopic patch test lesions is preceded by a peak of IL-12 expression, implicating IL-12 in the development of the T_{H1}-type response. This increased IL-12 expression coincides with the infiltration of macrophages and eosinophils; both cell types are known to express IL-12. These observations have led to the proposal that initiation of AD is driven by allergen-induced activation of T_{H2} type cells, whereas the chronic inflammatory response is dominated by a T_{H1}-type response driven by the infiltration of IL-12 expressing eosinophils and macrophages that accompanies the initial T_{H2} response.

TABLE III. Factors contributing to the development of T_{H2} cells

• Genetic background (eg, IL-4 promoter polymorphism) • Cytokine milieu in which antigen presentation takes place (ie, IL-4) • Antigen-presenting cell (eg, Langerhans cells) • Nature of antigen (eg, allergens vs parasites) • T/B cell costimulatory signals (ie, CD28/B7.2) (CD86) interactions • Pharmacologic factors (ie, prostaglandin E₂, cAMP phosphodiesterase activity)

FACTORS CONTRIBUTING TO T_{H2} CELL DEVELOPMENT

The above data support an important role for T_{H2} cell development early in the atopic skin process. The ability of T_{H0} cells to develop into the T_{H1} or T_{H2} pathway is dependent on a number of determinants including the cytokine milieu in which T-cell development is taking place, the host's genetic background, pharmacologic factors, and the costimulatory signals used during T-cell activation (Table 3). There is supportive data for each of these determinants in AD.

Cytokine milieu

Cytokines present at the time of antigen exposure are one of the major determinants directing T_H cells toward the T_{H1} or T_{H2} phenotype. IL-4 promotes T_{H2} cell development, whereas IL-12, produced by macrophages or dendritic cells, induces T_{H1} cells. Recently, it has also been shown that the IL-12 receptor (IL-12R) β_2 subunit, which is the binding and signal-transducing component of the IL-12R, is expressed on T_{H1} but not T_{H2} clones.²⁹ Interestingly, IL-4 inhibits the expression of IL-12R β_2 on T cells. In contrast, IL-12, IFN- γ , and IFN- α induces expression of the IL-12R β_2 chain, thereby providing a mechanism by which these cytokines induce differentiation of T_{H1} cells. In this regard, T cells in unaffected skin and acute lesions as well as circulating T cells have been found to express increased IL-4, IL-5, and IL-13 but decreased IFN- γ . IL-4 has also been demonstrated to cause marked inhibition of IFN- γ production and down-regulate the differentiation of T_{H1} cells.³⁰ In such a milieu, polarization toward a T_{H2} response would be expected. Furthermore, mast cells and basophils also provide a source of T_{H2}-type cytokines that can be released upon cross-linking of their high-affinity IgE receptor.³¹

Genetics

Although more than 20 genes are likely to be involved in the development of allergic diseases, there has been particular interest in the potential role of chromosome 5q31-33 because it contains a clustered family of cytokine genes: IL-3, IL-4, IL-5, IL-13, and GM-CSF, which are expressed by T_{H2} cells. Indeed several studies have reported linkage between total IgE, bronchial

hyperreactivity, and asthma, with markers around the IL-4 gene cluster.^{32,33} In addition, there is an association in families with asthma between a polymorphism in the IL-4 promoter and elevated total serum IgE levels.³⁴ In the case of AD, Chan et al³⁵ found that abnormal IL-4 gene expression may be linked to alterations in nuclear protein interactions with IL-4 promoter elements. More recently, Kawashima et al³⁶ examined linkage between markers at and near the IL-4 gene and AD in 88 Japanese nuclear families. Transmission disequilibrium testing showed a significant preferential transmission to AD offspring of the T allele of the -590C/T polymorphism of the IL-4 gene. A case-controlled comparison suggested a genotypic association of the TT genotype with AD. 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. In addition, Hershey et al³⁷ studied a small group of patients with AD and reported an association of atopy with a gain-of-function mutation in the α -subunit of the IL-4 receptor. The authors speculated that the R576 allele may predispose persons to allergic diseases by altering 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 atopy.

Pharmacologic factors

Leukocytes from patients with AD have increased cAMP-phosphodiesterase enzyme activity.³⁸ This cellular abnormality appears to contribute to the increased IgE synthesis by B cells and IL-4 production by T cells in AD³⁹ as IgE and IL-4 production can be decreased in vitro by a phosphodiesterase inhibitor. The greatest phosphodiesterase abnormality is seen in AD monocytes, which have been shown to have a unique, highly active isoenzyme.⁴⁰ Of note, the elevated cAMP phosphodiesterase in atopic monocytes contributes to the secretion of increased levels of IL-10 and prostaglandin E₂.^{41,42} Both monocyte-derived IL-10 and prostaglandin E₂ inhibit IFN- γ production by T cells and may therefore contribute to the decreased IFN- γ production by cultured AD PBMC.

Costimulatory signals

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. Several studies in mice have reported that the generation of T_{H2} cells depend mainly on the interaction of CD28 with B7.2.⁴³ To determine the potential role of B7.2 molecules in AD, we recently compared the expression of B7.1 versus B7.2 on B cells from patients with AD versus normal subjects or patients with psoriasis.⁴⁴ The expression of B7.2 on B cells of patients with AD was significantly higher than that in normal subjects and patients with psoriasis. In contrast, there was no significant difference in B7.1 expression among the three subject groups. Interestingly, 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. Indeed, purified B7.2⁺ B cells produced significantly more IgE than B7.2⁻ B cells in vitro. Anti-human B7.2 but not B7.1 mAb significantly decreased IgE production by PBMC stimulated with IL-4 and anti-CD40 mAb. These data demonstrate the predominant expression of B7.2 in AD but not psoriasis and a novel role for this molecule in IgE synthesis. We have also found that IL-4 and IL-13 can induce B7.2 expression on B cells, therefore providing an amplification loop for IgE synthesis in AD.⁴⁵ In AD, presentation of aeroallergens by Langerhans cells may also be very important in sustaining T_{H2} and IgE responses because Langerhans cells predominantly express B7.2 rather than B7.1.⁴⁶ Indeed, repeated presentation of antigen by Langerhans cells has been found to predispose to T_{H2} responses characterized by a predominance of IL-4 rather than IFN- γ expression.⁴⁷

AD SKIN INFLAMMATION: MULTIFUNCTIONAL ROLE FOR IgE

There are several mechanisms by which IgE molecules can contribute to the inflammatory cell infiltrate in AD (Table 4). Clinically significant allergen-induced reactions are associated with an IgE-dependent biphasic response. After exposure to allergen, mast cells bearing IgE directed to the relevant allergen release various mediators, cytokines, and leukocyte chemotactic factors into local tissue within 15 to 60 minutes of allergen challenge. This immediate reaction probably contributes to the acute pruritus and erythema observed after exposure of patients with AD to relevant food and inhalant allergens.

Three to 4 hours after this immediate reaction begins to subside, there is the onset of an IgE-dependent late-phase reaction (LPR) characterized initially by expression of leukocyte adhesion molecules on postcapillary venular endothelium, followed by the infiltration of eosinophils, neutrophils, and mononuclear cells. Granulocytes reach their maximum cell accumulation at 6 to 8 hours, and by 24 to 48 hours after onset of the LPR, the cellular infiltrate consists predominantly of mononuclear cells. With the use of *in situ* hybridization, the cellular infiltrate in allergen-induced LPRs has been found to express increased mRNA for IL-3, IL-4, IL-5, and GM-CSF but no mRNA for IFN- γ .⁴⁸ These results suggest that the T cells infiltrating into the allergen-induced LPR, similar to allergen-specific T cells grown from AD skin lesions, are T_{H2}-like cells.

It has also been demonstrated that LPRs are associated with the release of cytokines such as IL-1 and TNF.⁴⁹ These cytokines, along with IL-4, can induce leukocyte adhesion molecules.⁵⁰ Of note, the AD skin lesion, as well as the cutaneous LPR, is associated with the expression of leukocyte adhesion molecules such as E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1.⁵¹ More importantly, the induction of adhesion molecules such as E-selectin in allergen-

TABLE IV. Multifunctional role for IgE in atopic dermatitis

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- IgE-dependent late-phase skin reaction
 - Allergen presentation by IgE-bearing Langerhans cells
 - Allergen-induced activation of IgE-bearing macrophages
 - IgG/IgM antibodies to IgE
 - IgE autoreactivity to human proteins
-

stimulated atopic skin explants can be blocked by neutralizing antibodies to IL-1 and TNF.⁵² Thus the release of these cytokines by resident skin cells probably represents an important initiating event in the local accumulation of inflammatory cells at the site of allergic reactions.

Additional evidence for the importance of IgE-mediated mechanisms in AD are derived from studies in patients with AD and food hypersensitivity, which demonstrate that plasma histamine levels rise in children after positive oral food challenges but not after placebo challenges.⁵³ Sampson et al⁵⁴ also reported higher rates of spontaneous histamine release from basophils in patients with AD and food hypersensitivity compared with that in control subjects. The increased spontaneous basophil histamine release was dependent on continued ingestion of offending food allergens. Mononuclear cells from patients with food allergy produced an IgE-dependent histamine-releasing factor in vitro that provoked histamine release from basophils of other food-sensitive patients but not from normal control subjects.

Langerhans cells and macrophages infiltrating into the AD skin lesion bear IgE antibody on their cell surface.^{55,56} Binding of IgE to Langerhans cells occurs primarily through high-affinity IgE receptors.⁵⁷ Macrophages can express low-affinity IgE receptors (CD23) in response to IL-4 or GM-CSF.⁵⁸ Allergens have been demonstrated to activate IgE-bearing macrophages in an IgE-dependent manner with the formation of leukotrienes, platelet-activating factor, IL-1, and TNF.⁵⁹ Patients with AD also contain circulating autoantibodies to IgE, which can also activate macrophages bearing IgE.⁶⁰ The activation of IgE-bearing Langerhans cells and macrophages by allergens and autoantibodies to IgE could thus contribute to atopic skin inflammation. Furthermore, IgE-bearing Langerhans cells in AD skin appear to play an important role in cutaneous allergen presentation to T_{H2} cells. In this regard, IgE-bearing Langerhans cells from AD skin lesions but not Langerhans cells that lack surface IgE are capable of presenting house dust mite allergen to T cells.⁶¹ These results suggest that cell-bound IgE on Langerhans cells facilitate binding of allergens to Langerhans cells before their processing and antigen presentation.

Although allergen challenges and experimental models suggest the participation of specific mechanisms of inflammation, it should be emphasized that an analysis of the AD skin lesion does not allow simple classification discretely into an IgE-mediated LPR or a T-cell-mediated immune reaction. Thus in all likelihood, the mononuclear cell infiltrate in the AD skin lesion reflects a combination of both IgE-dependent mast cell/basophil

degranulation and T_{H2} cell-mediated responses elicited during acute exposures to allergen and other antigens or superantigens.

Finally, recent studies have suggested that IgE autoreactivity may be a pathogenic factor in AD. In this regard, Valenta et al⁶² reported that the majority of sera from patients with AD contain IgE antibodies directed against human proteins. One of these IgE-reactive autoantigens has recently been cloned from a human epithelial cDNA expression library and designated *Hom s 1*, which is a 55 kd cytoplasmic protein in skin keratinocytes.⁶³ Such antibodies were not detected in patients with chronic urticaria, SLE, or graft-versus-host disease or in healthy control subjects. These data suggest that whereas IgE immune responses are initiated by environmental allergens, allergic inflammation is maintained by human endogenous antigens.

It should be noted that although the release of a variety of mediators into the skin after challenge by allergens trigger acute pruritus in AD, the actual development of eczematoid skin rashes is dependent on the skin trauma inflicted by scratching.⁶ Once the itch-scratch cycle is triggered, scratching likely promotes inflammation of the skin by inducing keratinocytes to release a variety of proinflammatory cytokines.^{64,65} This includes the release of IL-1, TNF- α , IL-4, and CC chemokines (eg, RANTES and eotaxin), which are critical cytokines in the induction of adhesion molecules such as E-selectin, intercellular adhesion molecule-1, and vascular adhesion molecule-1, as well as directing lymphocytes, macrophages, and eosinophils into cutaneous sites of inflammation. At this stage, a wide variety of resident and infiltrating cells are then capable of secreting cytokines and mediators, which sustain the inflammation. AD therefore results from a combination of different specific and nonspecific cellular mechanisms that serve to trigger and maintain skin inflammation.

AD AS A SKIN-DIRECTED T_{H2} -LIKE CELL RESPONSE

Allergic rhinitis or asthma eventually develops in nearly 80% of children with AD. Many of these patients outgrow their AD as respiratory allergy develops. This intriguing clinical observation is consistent with the concept that the clinical expression of allergic disease is determined in part from local tissue allergen sensitization and compartmentalization of the immune response in the skin versus the respiratory mucosa. Because allergic diseases involve organ-specific allergic inflammatory responses, the mechanisms that control recruitment of T_{H2} lymphocytes to different tissue sites are of considerable interest. Studies in animal models have demonstrated heterogeneity in the ability of memory T cells to migrate to different tissues.⁶⁶ This tissue-selective homing is regulated primarily by interaction of differentially expressed T-cell homing receptors with vascular endothelial cell surface antigens. The lymphocyte/endothelial cell adhesion molecule pairs that participate in T-cell homing

include (1) the CLA and its counter-receptor, E-selectin, which directs T-cell homing to skin; (2) L-selectin and its ligand, peripheral lymph node addressin, involved in lymphocyte homing to peripheral lymph nodes, and (3) the $\alpha 4\beta 7$ integrin and its ligand, MAdCAM-1 (mucosal addressin), which directs T-cell homing to Peyer's patch and intestinal lamina propria. In human beings, the CLA antigen has been the most comprehensively studied in the context of skin homing.

T cells migrating into the skin of allergen-induced reactions express significantly higher levels of CLA than T cells isolated from the airways of asthmatic subjects.⁶⁷ These data suggest the propensity of AD to develop as opposed to asthma depends on differences in T-cell skin-homing versus lung-homing characteristics. In this regard, we assessed the expression of CLA and L-selectin on T cells from children with casein-induced AD and compared their homing receptor expression after stimulation in vitro with casein with T cells collected from patients with milk-induced gastroenteropathy or healthy control subjects.⁶⁸ 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 casein-reactive or *C albicans*-reactive T cells from normal control subjects or noneczematous atopic patients.

The relation between CLA and cutaneous T-cell responses has also been studied by Santamaria-Babi et al.⁶⁹ These researchers analyzed the expression of CLA on circulating T cells in AD versus asthmatic subjects who were sensitized with house dust mite. When CLA⁺ T cells were separated from CLA⁻ T cells, they found that the mite-specific T-cell proliferation response in AD patients sensitized to dust mite was localized to CLA⁺ T cells. In contrast, patients with asthma who were sensitive to mites had a mite-dependent proliferation response in their CLA⁻ T cells consistent with our observation that airway T cells have low level CLA expression. A further link between CLA expression and skin disease-associated T cells in AD was shown by demonstrating that freshly isolated CLA⁺ T cells in patients with AD but not normal control subjects expressed the HLA-DR activation antigen and spontaneous production of IL-4 but not IFN- γ . More recently Akdis et al¹² has also demonstrated that CLA⁺ T cells in AD spontaneously secrete IL-5 and IL-13 and functionally prolong eosinophil survival and induce IgE synthesis.

The T-cell expression of CLA is regulated by various cytokines.⁶⁶ Transforming growth factor- β , IL-12, and to a lesser extent IL-6 increase CLA expression, whereas other cytokines such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-7, and IFN- γ lack CLA upregulatory activity. Furthermore, we have observed that when bacterial toxins with superantigenic activity are used to stimulate T cells, in the presence of accessory cells, CLA is upregulated in an IL-12 dependent manner.⁷⁰ Thus the nature of the antigen, the cytokine milieu in which the immune responses occurs, and the location of the response all contribute to the regulation of CLA. This observation is probably rel-

evant in patients with AD who are heavily colonized with *Staphylococci*-secreting superantigens.⁷¹

CUTANEOUS INFECTIONS: ROLE FOR SUPERANTIGENS

Aside from food and inhalant allergens (discussed elsewhere in this symposia), fungal and bacterial skin infections can exacerbate AD. Viral infections include Herpes simplex, vaccinia, warts, molluscum contagiosum, and papilloma virus. The most common viral infection is Herpes simplex, which tends to spread locally or can become generalized. Superficial fungal infections also appear to occur more frequently in atopic individuals. Jones et al⁷² found a 3-fold increased frequency of *Trichophyton rubrum* skin infections among patients with AD as compared with nonatopic control subjects. Recurrence of dermatophyte infections have occasionally been documented to coincide with flaring of AD. Recently there has been considerable interest in *Malassezia furfur* (also known as *Pityrosporum ovale* or *P orbiculare*) as a pathogen in AD. *M furfur* is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against *M furfur* is commonly found in patients with AD and most frequently in patients with head and neck dermatitis (but rarely outside of AD).⁷³ Positive allergen patch test reactions to this yeast have been demonstrated.⁷⁴ The potential importance of *M furfur* as well as other dermatophyte infections is further supported by the reduction of AD skin severity in such patients after treatment with antifungal agents such as ketoconazole.^{75,76}

The greatest attention has focused on the contribution of *Staphylococcus aureus* colonization and infection to the severity of AD. *S aureus* is found in more than 90% of AD skin lesions.⁷⁷ In contrast, only 5% of normal subjects harbor this organism, and its localization is mainly in the nose and intertriginous areas. The density of *S aureus* on inflamed AD lesions without clinical superinfection can reach up to 10⁷ colony-forming units per cm² on lesional skin.⁷⁸ The importance of *S aureus* in AD is supported by the observation that not only patients with impetiginized AD but also patients with AD without superinfection show clinical response to combined treatment with anti-staphylococcal antibiotics and topical corticosteroids.⁷⁹

Recent 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 (Table V).^{71,80,81} Several lines of investigation support a role for superantigens in AD. First, more than half of patients with AD have *S aureus* cultured from their skin that secrete superantigens such as enterotoxins A and B and toxic shock syndrome toxin-1. Second, most patients with AD make specific IgE antibodies directed against the staphylococcal toxins found on their skin.^{71,80} Basophils from patients with antitoxin IgE release histamine on exposure to the relevant toxin

TABLE V. Evidence for role of staphylococcal superantigens in atopic dermatitis

- Majority of *Staphylococcus aureus* isolates secrete superantigens
- Majority of patients with AD produce IgE antibodies to superantigens
- AD severity correlates with presence of IgE antibodies to superantigens
- Superantigens augment allergen-induced skin inflammation
- Superantigens induce dermatitis on application to skin by patch testing
- Chronic eczema develops in patients recovering from toxic shock syndrome
- Superantigens induce the CLA skin-homing receptor on T cells
- PBMC from AD, as compared with normal control subjects, have higher proliferative responses to superantigens
- Superantigens induce corticosteroid resistance
- Treatment with a combination of anti-staphylococcal antibiotics and topical corticosteroids is more effective than using either medication alone

but not in response to toxins to which they had no specific IgE. Third, a correlation has been found between the presence of IgE antisuperantigens and severity of AD.⁸¹ With the use of a humanized murine model of skin inflammation, *S aureus* toxin plus allergen was shown to have an additive effect in inducing cutaneous inflammation.⁸² Superantigens have also been shown to induce corticosteroid resistance, suggesting that several mechanisms exist by which superantigens could aggravate the severity of AD.⁸³ Fourth, SEB applied to the skin can induce skin changes of erythema and induration.⁸⁴ Furthermore, in a prospective study of patients recovering from toxic shock syndrome, it was found that in 14 of 68 patients, chronic eczematoid dermatitis developed, whereas no patients recovering from gram-negative sepsis had eczema.⁸⁵ These investigators concluded that superantigens may induce an atopic process in the skin. It is therefore of interest that superantigens have recently been demonstrated to induce T-cell expression of the skin-homing receptor through stimulation of IL-12 production.⁷⁰ In the case of AD, we have 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⁺ memory/effector cells. Local secretion of IL-12 could increase CLA expression on those T cells activated by allergen or superantigen and thereby increase their efficiency of T-cell recirculation to the skin. IL-12 secreted by toxin-stimulated Langerhans cells that migrate to skin-associated lymph nodes (and serve as antigen-presenting cells therein) could upregulate the expression of CLA and influence the functional profile of virgin T cells activated by the toxins, thereby creating additional skin-homing memory-effector T cells. Together, these mechanisms would tend to markedly amplify the initial cutaneous inflammation in AD and

perhaps also create conditions favoring staphylococcal skin colonization.

Finally, PBMC from children with AD have been reported to have a significantly higher proliferative responses to both *S aureus* and SEB as well as diminished production of IFN- γ in response to *S aureus* and SEB.⁸⁶ In contrast, PBMC from children with AD were more likely to produce IL-4 in response to *S aureus*. These investigators suggested that impaired IFN- γ production to *S aureus* in vivo may result in failure to eradicate this organism from the skin. Persistence on the skin could contribute to inflammation by causing continued T-cell activation, release of proinflammatory mediators, and corticosteroid resistance. Furthermore, by eliciting an IgE response, staphylococcal toxins could exacerbate AD by activating mast cells, basophils, or other Fc ϵ receptor-bearing cells. It should be noted, however, that other staphylococcal proteins/toxins such as protein A and α -toxin could also participate in the induction of skin inflammation by releasing TNF- α from epidermal keratinocytes or direct cytotoxic effects on skin keratinocytes.⁸⁷

IMPLICATIONS FOR MANAGEMENT OF AD

Current treatment of AD is directed at symptom relief, skin hydration, and reduction of cutaneous inflammation (reviewed in Reference 2). Factors that must be considered and eliminated include irritants, food and inhalant allergens, and emotional stresses. Maintenance of daily skin care with hydration of the skin and appropriate use of topical steroids to reduce skin inflammation is critical. Systemic antimicrobial therapy, particularly anti-staphylococcal antibiotics, is often necessary because AD skin is colonized with superantigen-producing *S aureus*, which enhances skin inflammation and inhibits responses to corticosteroids.^{82,83}

For patients who are resistant to therapy, alternative therapies should be considered because long-term treatment with oral or high-potency topical corticosteroids can lead to significant adverse events. Ultraviolet light (UVB or PUVA) therapy may be a useful adjunctive modality in the treatment of chronic recalcitrant AD. Therapeutic trials with several experimental immunomodulators have also been reported. In particular, IFN- γ , a cytokine that downregulates T_{H2} cell function, has also been found in placebo-controlled trials to reduce clinical severity associated with AD and decrease total circulating eosinophil counts.^{88,89} In addition, the new high-potency phosphodiesterase inhibitors may be useful in targeting the increased PDE activity in atopic monocytes and have demonstrated promising preliminary clinical results.³⁹ The response to many of these immunomodulators has, however, been modest or appears to act in only a subset of AD, presumably because patients are in different states of immune activation. Cyclosporin, a potent immunosuppressive drug that downregulates cytokine production, given orally has also been reported to be effective for AD, but concerns over systemic toxicity

have limited its use.⁹⁰ Topical therapy with cyclosporin has been attempted but patients failed to show significant improvement, probably because of insufficient penetration into the skin.

Tacrolimus or FK506, a macrolide lactone isolated from *Streptomyces tsukubaensis*, is a potent immunosuppressive agent with a spectrum of activity similar to cyclosporin. Its smaller molecular size and higher potency compared with cyclosporin suggested it could be effective as a topical agent. Although it is structurally unrelated to cyclosporin A, tacrolimus also interacts with a cyclophilin-like cytoplasmic protein, FK506-binding protein, and this complex in turn inhibits calcineurin, interfering with gene transcription of multiple cytokines including IL-2.⁹¹ Several uncontrolled studies and two multicenter, controlled studies suggest that FK506 in ointment form (tacrolimus) can effectively reduce the clinical symptoms of AD with markedly diminished pruritus within 3 days of initiating therapy with no evidence for systemic side effects.^{92,93}

The mechanism by which tacrolimus exerts its beneficial effects remains to be elucidated, although it probably involves the inhibition of IL-4 and IL-5 gene transcription.⁹¹ Indeed, skin biopsies performed after 3 and 7 days of treatment with topical tacrolimus have revealed markedly diminished T-cell and eosinophilic infiltrates. Tacrolimus also inhibits the transcription and release of other T-cell-derived cytokines such as IL-3, IFN- γ , TNF- α , and GM-CSF, which can also contribute to allergic inflammation. Of note, other cell types important in allergic skin inflammation including mast cells, basophils, eosinophils, keratinocytes, and Langerhans cells have tacrolimus (FK506)-binding proteins and downregulate their mediator or cytokine expression after treatment with tacrolimus. Recent studies suggest that the T-cell activation in AD is biphasic with activation of the T_{H2}-like cytokines during the acute phase and increased expression of the T_{H1}-cytokines in chronic lesions; therefore the capacity of tacrolimus to inhibit the activation of multiple cell types and different cytokines may account for its ability to effectively reduce skin inflammation in AD.

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