The skin is a unique immunologic organ that acts as an interface between the external environment and the systemic immune response. As such, it may react directly with allergens that are applied epiptaneously, thereby influencing the systemic allergic response. It is well known that atopic dermatitis (frequently in association with food allergy) predicts the development of asthma and allergic rhinitis by several years. The possibility that atopic dermatitis may influence the course of asthma is suggested by several interesting observations. First, children with atopic dermatitis and positive skin tests to allergens frequently have more severe asthma than asthmatic children without atopic dermatitis. Second, because total serum IgE is strongly associated with the prevalence of asthma, it raises the interesting question of whether allergen sensitization through the skin predisposes to more severe and persistent respiratory disease because of its effects on the systemic allergic response. Indeed, epicutaneous sensitization of mice to a protein antigen induces both a localized allergic dermatitis and hyperresponsiveness to methacholine, which suggests that epidermocyte exposure to antigen in atopic dermatitis may enhance the development of asthma. Finally, systemic immune activation in atopic dermatitis is supported by the observation that these patients have increased numbers of circulating activated T^eff cells, eosinophils, macrophages, and IgE. Many of the markers of leukocyte activation have been shown to correlate with the severity of atopic dermatitis disease. This systemic activation might facilitate local infiltration of primed T cells, eosinophils, and macrophages into the respiratory mucosa after inhalation of allergen in genetically predisposed hosts. The systemic aspects of atopic dermatitis, with an emphasis on respiratory effects, are summarized. (J Allergy Clin Immunol 2000;106:S258-63.)

Key words: Asthma, atopic dermatitis, eosinophil, T^eff cell, T lymphocyte

It is well established that the systemic immune response can affect the skin. This has best been shown after clinical challenges with either aeroallergens or foods. However, much less is known about the potential influence that skin challenges have on the systemic immune response, in particular whether sensitization through the skin causes effects on airway hyperreactivity or mucosal inflammation. Indeed, most studies of skin challenges have focused primarily on local responses in the skin and have pretty much ignored any systemic effects. The current review will therefore discuss the systemic effects of atopic dermatitis (AD), with an emphasis on respiratory allergy.

INFLUENCE OF AD ON RESPIRATORY ALLERGY

AD is usually seen in children before the age of 5 years, and approximately 80% of these children will ultimately experience either asthma or allergic rhinitis. Thus, AD frequently predates respiratory allergy. Although this does not necessarily mean there is a cause and effect relationship, there are a number of studies that indicate the severity of AD can influence the course of respiratory allergy. In this regard, Buffum and Settipane examined a group of more than 500 patients with asthma, with or without AD. The results of this study were intriguing because 12% of patients with asthma and AD had either severe asthma or actually died of their asthma. In contrast, the absence of AD was associated with a lesser asthma severity.

In a study to more directly address this issue, Brinkman et al examined whether the presence and severity of AD was predictive of the occurrence and magnitude of early and late asthmatic responses to inhaled allergens. They compared the bronchial effects of allergen inhalation challenge in 4 groups of patients who were allergic to either dust mites or animal dander (mild to moderate allergic asthma with no AD, 9 patients; mild to moderate allergic asthma and mild AD, 8 patients; severe AD and mild allergic asthma, 8 patients; and severe AD without allergic asthma, 8 patients). All patients exhibited an early asthmatic response or an immediate response to allergen, likely reflecting the fact that they all had positive skin tests to aeroallergens and IgE to specific allergens on the mast cells lining their airways. Interestingly, late asthmatic responses (ie, 3-8 hours after allergen challenge) were generally limited to
patients with severe AD and mild asthma. Only 3 of 8 patients (38%) with mild AD and allergic asthma had late asthmatic responses, and none of the patients with AD alone had a late-phase response, although some of the patients had immediate reactions. Overall, these data indicate that patients with severe AD and mild asthma are at higher risk for the development of pronounced late asthmatic cellular responses after allergen challenge.

**SYSTEMIC IMMUNE RESPONSE IN AD**

The mechanism that places patients with severe AD and mild asthma at risk for the development of cell-mediated late asthma responses requires further elucidation. It is known that patients with AD have a strong systemic allergic response associated with marked elevations in serum IgE, activated eosinophils, and T cells. Serum IgE and eosinophil infiltration are not organ specific; once secreted, IgE can passively sensitize mast cells, basophils, and dendritic cells throughout the body. Similarly, circulating activated eosinophils have an enhanced capacity to infiltrate into any inflamed tissue that expresses endothelial adhesion molecules and chemokine gradients selective for eosinophil migration. In contrast, eosinophil migration, memory T cells migrate nonrandomly to different tissues.

Memory T cells that infiltrate the skin express a unique skin-homing receptor called cutaneous lymphocyte-associated antigen (CLA). This concept emerged from immunohistochemical evidence that most infiltrating T lymphocytes (80% to 90%) in the skin of a wide variety of inflammatory and neoplastic conditions expressed CLA. In contrast, very few CLA-positive (CLA+) T cells are found at extracutaneous inflammatory sites. Santamaria Babi et al observed T-lymphocyte proliferative responses to house dust mite (HDM) in HDM-sensitized patients with AD only in the CLA+ subpopulation. In contrast, in patients with HDM-sensitized allergy and asthma, the HDM-dependent proliferation was observed in the CLA− subset. These data suggest that the propensity of patients to the development of AD rather than asthma depends, in part, on differences in the skin-versus the lung-homing ability of their memory T cells.

The expansion of CLA+ T cells occurs in patients with AD. These circulating T cells express increased activation markers, such as CD25, HLA-DR, and CD40L (Table I). Patients with AD have also been shown to have increased serum levels of soluble IL-2 receptor, another marker of T-cell activation that correlates with disease severity. These T cells spontaneously proliferate when they are cultured (even in the absence of mitogen) and selectively express IL-4, IL-5, or IL-13, cytokines consistent with the TH2 phenotype. This expansion is thought to occur in response to relevant allergens or superantigens. For example, casein stimulation of peripheral blood mononuclear cells from patients with AD who were milk responsive induced CLA expression that was not seen in patients with no allergy or in patients with milk-induced enterocolitis and no skin manifestations. Similarly, bacterial toxin-mediated superantigen stimulation through the skin can also expand CLA populations. Specifically, patients with AD who had toxic shock syndrome toxin-producing staphylococcus cultured from their skin had an expansion of V-beta-2 (a T-cell receptor known to respond to toxic shock syndrome toxin)-positive T cells in their peripheral blood CLA population. The former example demonstrates that antigen sensitization can occur in 1 organ (eg, gastrointestinal) although disease manifestation, including lymphocyte homing, can take place in a distant organ (ie, skin), as is the case in patients with AD and food allergy. Although there is no clear evidence that the induction of AD can occur through the respiratory tract, it appears likely that elicitation of or exacerbation of AD may occur through allergen inhalation in patients with a history of asthma.

CLA has recently been identified as a glycosylated form of P-selectin glycoprotein and has been found to bind to the endothelial adhesion molecule E-selectin in vitro. This binding partially explains the selective migration of CLA+ T cells to cutaneous sites because endothelial E-selectin expression is more prolonged in dermal microvascular endothelial cells than macrvascul ar endothelial cells. Recent studies have implicated the chemokine receptor CCR4 and 1 of its ligands, thymus and activation-regulated chemokine (CCL17), in selective lymphocyte homing to the skin. In contrast, CCR4 was found in skin-homing lymphocytes, and high levels of thymus and activation-regulated chemokine were detected on cutaneous endothelial cells of chronically inflamed skin. Another newly identified C-C chemokine may also be of particular relevance: the cutaneous T-cell-attracting chemokine (CTACK) selectively induces the migration of CLA+ T cells in vitro. Neither granulocytes, monocytes, B cells, nor CLA− T cells responded to CTACK (CCL27) in vitro. Additionally, CTACK appears to be expressed primarily by keratinocytes. In summary, the initial rolling of skin-homing memory T cells along cutaneous vascular endothelial cells is probably mediated by CLA/E-selectin interactions. This is followed by firm adhesion induced by tissue-specific chemokine gradients and is likely to be the most selective step of lymphocyte homing. Because these T cells are activated and expanded in the patient with AD, it is reasonable to hypothesize that they may secrete TNFα cytokines that will prime eosinophils and thereby aggravate allergic inflammation at other tissue sites.

**Role of TNFα cytokines in eosinophil migration in AD**

The literature supports the concept that increased numbers of circulating eosinophils, activated by exposure to TNFα-type cytokines, is 1 factor that predisposes patients with AD to airway inflammation (Table II). IL-5, in particular, plays a critical role in stimulating bone marrow differentiation of eosinophils. Additionally, IL-5 primes eosinophils for binding to vascular endothelial adhesion molecules and promotes eosinophil...
cell survival. It also enhances C-C chemokine-mediated chemotaxis of eosinophils. IL-4 and IL-13 play key roles in inducing vascular cell adhesion molecule-1 expression on endothelial cells that recognize eosinophils and initiate the multistep process that leads to trafficking of these cells into inflamed allergic tissues.21

Eosinophils from patients with AD differ from those in normal subjects; AD eosinophils are hypodense and have prolonged cell survival that is not further increased by the eosinophil-activating cytokines, IL-3, IL-5, and GM-CSF.22 In addition, eosinophils from patients with AD release higher levels of leukotriene C4 than normal eosinophils.23 They also have significantly increased migratory responses to N-formyl-methionyl-leucyl-phenylalanine and neutrophil-activating factor (an epithelial-derived chemokine) in vitro and to RANTES in vivo.24,25 IL-4 induces chemotaxis of blood eosinophils from patients with AD, but not from normal individuals.26 Furthermore, eosinophils from patients with AD spontaneously penetrate IL-4-activated vascular tissue constructs, whereas cells from normal individuals will only penetrate IL-4-activated constructs after eosinophil pretreatment with IL-5 or GM-CSF.27 Thus, circulating eosinophils in AD are primed for chemotaxis and transendothelial migration. Indeed, it is well established that eosinophil major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin levels are elevated in AD sera and correlate with disease severity.28

Resident cells (mast cells, dendritic cells, or macrophages) express high-affinity IgE receptors that can bind IgE directed to specific allergens and release proinflammatory cytokines on allergen stimulation. After allergen exposure in a patient with asthma and AD, the local release of cytokines, such as TNF-α and IL-1, could induce the expression of vascular endothelial adhesion molecules, which then promote the influx of activated eosinophils.29 The degree of tissue inflammation may be related in part to the number of activated eosinophils in the circulation.

EXPERIMENTAL INDUCTION OF AIRWAY HYPERREACTIVITY THROUGH SKIN SENSITIZATION

Although the results of early studies suggested an influence of AD on airway hyperreactivity, they did not directly address the issue of cause and effect (ie, whether or not epicutaneous sensitization can directly affect airway hyperreactivity). The relationship between epicutaneous sensitization and the development of systemic Th2 responses and airway reactivity has been examined by Spergel et al.30 In that study, the epicutaneous effect of ovalbumin applied by occlusive patch was compared with saline or intraperitoneal immunization with ovalbumin in BALB/c mice. As anticipated, total serum IgE did not increase significantly after intraperitoneal immunization with ovalbumin or epicutaneous application of saline. However, ovalbumin-specific IgE levels rose significantly after epicutaneous application of ovalbumin. In contrast, intraperitoneal injection of ovalbumin resulted in significantly higher levels of serum IgG2b than epicutaneous application. Skin biopsy results from the patch test site revealed dermatitis characterized by infiltration of CD3+ T cells and eosinophils. There were also epidermal thickening and spongiotic changes. Additionally, increases in IL-4, IL-5, and IFN-γ messenger RNA (by polymerase chain reaction) were reported and are consistent with the data in chronic AD that shows a mixture of Th2 and Th1 responses.3

Epicutaneous-sensitized mice were subsequently challenged with a single exposure to inhaled ovalbumin, and bronchoalveolar lavage (BAL) fluid was analyzed 24 hours later.30 In mice sensitized epicutaneously with ovalbumin, there was a significant increase in the total number of eosinophils in BAL fluid compared with saline-sensitized mice. More importantly, after challenge with inhaled ovalbumin, there was a significant increase in the number of eosinophils in the BAL fluid of ovalbumin-sensitized mice compared with saline-sensitized mice.

To determine whether epicutaneous sensitization can prime mice to develop airway hyperresponsiveness, Spergel et al.30 also examined whether inhalation of a single dose of ovalbumin elicits hyperresponsiveness to methacholine. In this study, pulmonary dynamic compliance to graded doses of methacholine was measured by plethysmography 24 hours after inhalation of a single dose of ovalbumin. They observed that ovalbumin-sensitized mice had a 10-fold greater sensitivity to methacholine than saline-sensitized control mice. This study showed that in epicutaneously sensitized mice, a single inhalation of protein antigen elicits a systemic allergic response, a local skin inflammatory response predominantly mediated by Th2 cells, and an increased airway response (ie, hyperresponsiveness) to methacholine.

### TABLE I. Peripheral blood T-cell activation in AD

| Increased serum sIL-2R levels |
| Increased expression of HLA-DR, CD25, and CD40L |
| Expansion of Tp2 cells expressing CLA |

### TABLE II. Systemic eosinophil activation in AD

| Elevated blood eosinophil count |
| Hypodense eosinophils |
| Increased serum ECP, EDN, MBP levels |
| Increased LTC4 generation |
| Delayed apoptosis and fas resistance not further enhanced by IL-5, IL-3, and GM-CSF |

| ECP, Eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; MBP, major basic protein; LTC4, leukotriene C4. |
SENSITIZATION THROUGH THE SKIN ELICITS SYSTEMIC TH2 RESPONSES

In addition to data reported by Spergel et al., other investigators have demonstrated that epicutaneous sensitization with allergens elicits a TH2-dominant systemic immune response. In these studies, increased serum IgE and local production of IL-4 and IL-5 were observed in the skin and draining lymph nodes after epicutaneous allergen sensitization. Although this response occurs in the absence of adjuvant, skin barrier disruption further enhances the TH2 response. This may be relevant to the clinical situation where scratching is a known prerequisite for the development of AD skin lesions.

The mechanism for this phenomenon is not well understood. Hauser et al. observed that when TH cells were grown with cultured Langerhans’ cells, the resultant T cells were large producers of IL-4, an important stimulator of IgE synthesis by B cells. In AD, there are increased numbers of IgE-bearing Langerhans’ cells in the skin and draining lymph nodes after epicutaneous allergen sensitization. Although this response occurs in the absence of adjuvant, skin barrier disruption further enhances the TH2 response. This may be relevant to the clinical situation where scratching is a known prerequisite for the development of AD skin lesions.

These results suggest that cell-bound IgE on Langerhans’ cells facilitates capture and internalization of allergens before their processing and presentation to T cells. IgE-bearing Langerhans’ cells that have captured allergen likely activate memory TH2 cells in atopic skin but may also migrate to the lymph nodes to stimulate uncommitted T cells to further expand the pool of systemic TH2 cells (Fig 1).

Binding of IgE to Langerhans’ cells occurs primarily through high-affinity IgE receptors. The importance of these receptors is underscored by the observation that the presence of FcεRI-expressing Langerhans’ cells that bear IgE molecules is required to provoke eczematous skin lesions after the application of aeroallergens to the skin of atopic patients. 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 inflammatory environment of AD. High-level FcεRI expression not only enhances the binding and uptake of allergens but also facilitates the activation of Langerhans’ cells on receptor ligation. Further, IL-4 potently induces the cytoplasmic expression of the alpha chain of FcεRI in dendritic cells and upregulates the expression of the skin-homing structures, E-cadherin and CLA.

In contrast, IFN-γ inhibits FcεRI and E-cadherin expression.
Studies have also shown that Langerhans’ cells in atopic skin predominantly express B7.2 (CD86), a costimulatory molecule thought to skew T-cell development toward the T_{H2} phenotype. When antigens or superantigens are introduced in the skin, they cause IgE-bearing Langerhans’ cells to migrate to the lymph nodes. In the lymph nodes, IgE-bearing Langerhans’ cells induce the expansion of T_{H2} cells that can stimulate IgE synthesis (Fig 1). To return to the skin, memory T_{H2} cells circulate throughout the body, even in the airway mucosa and bone marrow. In doing so, they can promote the systemic allergic response and activate eosinophils that are primed for tissue infiltration.

Other factors that contribute to T_{H2} cell development in AD include the host’s genetic background and the cytokine milieu in which the T cells develop. For instance, IL-4 promotes T_{H2}-cell development, whereas IL-12 (produced by macrophages, dendritic cells, or eosinophils) induces T_{H1} cells. In AD, the increased systemic and local skin expression of IL-4 by T cells, mast cells, and basophils would be expected to promote T_{H2} cell development. It should be noted, however, that, because T_{H2} cells can still develop (although at a lower level) in IL-4/STAT6 (signal transducer and activator of transcription-6) knockout mice, there must be other factors contributing to T_{H2} cell development.

In addition to the influence of local cytokines on T_{H1} cell development, many genes are likely to be involved in the T-cell phenotype and thus allergic disease. However, there has been particular interest in the potential role of chromosome 5q31-33 because it contains a clustered family of cytokine genes (i.e., IL-3, IL-4, IL-5, IL-13, and GM-CSF) expressed by T_{H2} cells. In particular, Kawashima et al examined the linkage between markers at and near the IL-4 gene in patients with AD. A case-control comparison showed a genotypic association between the T allele of the −590C/T polymorphism of the IL-4 gene promoter region and AD. Because the T allele is associated with increased IL-4 gene promoter activity compared with the C allele, data suggest that genetic differences in transcriptional activity of the IL-4 gene influence the development of AD. In addition, Hershey et al reported an association between AD and a gain-of-function mutation in the alpha subunit of the IL-4 receptor. These data support the concept that IL-4 gene expression plays a critical role in the expression of AD.

CONCLUSIONS

The current review examined the existing literature that supports the concept that skin challenges with allergen can effect the systemic allergic response. Thus, a link may exist between AD and asthma. Of note, both diseases are associated with elevated IgE, circulating activated T-cell levels, and eosinophilia. Furthermore, there is substantial data that indicate that epicutaneous sensitization with allergen can give rise to a systemic T_{H2} cell immune response, particularly elevated serum IgE levels. Epicutaneous sensitization can also induce airway hyperresponsiveness to methacholine. This is intriguing because patients with severe AD tend to have exaggerated airway responses to inhalation challenge with allergens, and most patients with AD experience the development of respiratory allergy.

With the increasing efforts to treat asthma early in childhood, the current observations suggest that infants and young children with AD should be a target population for the prevention of asthma. Perhaps by gaining control of the eczema, it would be possible to delay the onset or severity of asthma. Indeed, in an intriguing study by Ikura et al, 121 infants with AD were randomized to receive either ketotifen or placebo before the onset of asthma. After 1 year of study, children in the ketotifen treatment group had a significantly lower prevalence of asthma than children in the placebo treatment group. Finally, with the growing availability of therapies (such as anti-IgE, anti-IL-4, and other agents that can block T_{H2} immune responses), it would be fascinating to evaluate these therapies in patients with AD before the onset of asthma.

REFERENCES