Allergen sensitization through the skin induces systemic allergic responses

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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 epicutaneously, thereby influencing the systemic allergic response. It is well known that atopic dermatitis (frequently in association with food allergy) predates 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 epicutaneous 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(H)2 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(H)2 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.1,2 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.3 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.4,5 In this regard, Buffum and Settipane6 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 less severe asthma severity. In a study to more directly address this issue, Brinkman et al7 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

Abbreviations used

AD: Atopic dermatitis
BAL: Bronchoalveolar lavage
CLA: Cutaneous lymphocyte-associated antigen
CTACK: Cutaneous T-cell–attracting chemokine
HDM: House dust mite

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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. Similar-
ly, 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 con-
trast with 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-asso-
ciated antigen (CLA). This concept emerged from immuno-
histochemical 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+ subgroup. 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 activa-
tion 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
TH2-type cytokines consistent with the TH2 phenotype. This
expansion is thought to occur in response to relevant
allergens or superantigens. For example, casein stimula-
tion of peripheral blood mononuclear cells from patients
with AD who were milk responsive induced CLA expres-
sion 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 expan-
sion 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 manifesta-
tion, 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 macrovascu-
lar endothelial cells. Recent studies have implicated the
chemokine receptor CCR4 and 1 of its ligands, thymus
and activation-regulated chemokine (CCL17), in selec-
tive lymphocyte homing to the skin. High expression of
CCR4 was found in skin-homing lymphocytes, and high levels of thymus and activation-regulated chemokine
were detected on cutaneous endothelial cells of chroni-
cally inflamed skin. Another newly identified C-C
chemokine may also be of particular relevance: the cuta-
neous 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 ker-
atinocytes. In summary, the initial rolling of skin-homing
memory T cells along cutaneous vascular endothelial
cells is probably mediated by CLA/E-selectin interac-
tions. This is followed by firm adhesion induced by tis-
ssue-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
T_{H2} cytokines that will prime eosinophils and thereby
aggravate allergic inflammation at other tissue sites.

**Role of T_{H2} cytokines in eosinophil migration
in AD**

The literature supports the concept that increased
numbers of circulating eosinophils, activated by exposure
to T_{H2}-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 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 spongiosis 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 Th1 and Th2 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
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<tbody>
<tr>
<td>sIL-2R</td>
<td>Soluble IL-2 receptor</td>
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### TABLE II. Systemic eosinophil activation in AD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
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<tr>
<td>ECP</td>
<td>Eosinophil cationic protein</td>
</tr>
<tr>
<td>EDN</td>
<td>Eosinophil-derived neurotoxin</td>
</tr>
<tr>
<td>MBP</td>
<td>Major basic protein</td>
</tr>
<tr>
<td>LTC₄</td>
<td>Leukotriene C₄</td>
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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 spongiosis 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 Th1 and Th2 responses.3

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SENSITIZATION THROUGH THE SKIN ELICITS SYSTEMIC T\(_{h2}\) RESPONSES

In addition to data reported by Spergel et al,\(^30\) other investigators have demonstrated that epicutaneous sensitization with allergens elicits a T\(_{h2}\)-dominant systemic immune response.\(^31-33\) 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 T\(_{h2}\) response.\(^31\) 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\(^34\) observed that when T\(_{h}\) 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 epidermis that 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 HDM allergen to T cells. 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 T\(_{h2}\) cells in atopic skin but may also migrate to the lymph nodes to stimulate uncommitted T cells to further expand the pool of systemic T\(_{h2}\) 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.\(^35\) 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.\(^36\) 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 Th2 phenotype.37 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 Th2 cells that can stimulate IgE synthesis (Fig 1). To return to the skin, memory Th2 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 Th2 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 Th2-cell development, whereas IL-12 (produced by macrophages, dendritic cells, or eosinophils) induces Th1 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 Th2 cell development. It should be noted, however, that, because Th2 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 Th2 cell development.

In addition to the influence of local cytokines on Th1, Th2 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 (ie, IL-3, IL-4, IL-5, IL-13, and GM-CSF) expressed by Th2 cells.38 In particular, Kawashima et al39 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 al40 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 Th2 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,41 121 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 Th2 immune responses), it would be fascinating to evaluate these therapies in patients with AD before the onset of asthma.

REFERENCES


