

Does “autoreactivity” play a role in atopic dermatitis?

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The role of autoimmunity in atopic dermatitis (AD) is unclear. We sought to critically examine the occurrence, correlation with severity, and possible causative role of autoreactivity in patients with AD. Our systematic review of studies identified from MEDLINE included 31 experiments that described autoreactivity in patients with AD. We defined autoreactivity as *in vitro* or *in vivo* evidence of immune response to autologous human, generic human, or recombinant human proteins or other tissue/cellular components. Autoreactivity prevalence in patients with AD ranged from 23% to 91% in 14 studies involving 2644 participants, although it did not appear to vary with age, sex, or disease duration. In contrast to studies of AD, IgE autoreactivity was not found in healthy subjects or in those with allergic rhinoconjunctivitis, psoriasis, systemic lupus erythematosus, or other inflammatory diseases (8 studies of 816 participants). Two reports found a positive correlation between autoreactivity and AD severity. We suggest that autoreactivity might be playing a causative role in AD based on the magnitude and specificity of the associations found; plausible mechanisms through IgE autoantibodies, IgG autoantibodies, and T_H1 autoreactivity; and experimental elicitation of eczematous lesions after provocation. Whether autoantibodies contribute to AD chronicity now needs to be examined in longitudinal studies. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Autoreactivity, autoimmunity, eczema, atopic dermatitis, atopic eczema, IgE

The increase in symptoms of eczema or atopic dermatitis (AD) across the world suggests that environmental factors play a key role in determining disease expression.¹ The role of external factors, such as allergens capable of eliciting IgE antibodies, in determining AD disease persistence is not clear given that up to two thirds of all children with the clinical phenotype of AD have no identifiable, extrinsic, allergen-specific IgE antibody sensitization.² Moreover, chronic inflammation can be observed in allergic subjects, even in the absence of apparent exposure to known environmental allergens. Chronic infection has been

Abbreviations used

AD: Atopic dermatitis
ANA: Antinuclear antibody
SCORAD: Scoring Atopic Dermatitis

proposed as a possible factor contributing to disease perpetuation. Colonization with *Staphylococcus aureus*, which is found in more than 90% of AD lesions compared with less than 5% of healthy skin specimens, can cause persistent inflammation through T-cell activation.³ However, a systematic review of antistaphylococcal interventions for AD did not show any convincing clinical improvements in patients with AD, despite quantitative reduction in skin bacterial load.⁴

Another hypothesis for AD chronicity is the involvement of immune mechanisms against self-components. Two main observations have led to such a hypothesis. First, the pattern of chronic relapsing-remitting disease is similar to that of other autoimmune diseases, such as multiple sclerosis or psoriasis. Second, autologous or human components might elicit immediate hypersensitivity reactions in the skin of patients with severe AD. Qualitative changes of immunologic reactions have also been documented in chronic AD lesions. The acute phase of T_H2-predominant reactions has been observed to transit to a chronic phase of a mixture of type I- and type IV-like hypersensitivity reactions with T_H1-related cytokines (IFN- γ and IL-12) in abundance.⁵ Such a transit could result from the development of autoreactive T cells, potentially through epitope spreading secondary to inflammation.⁶ However, the possible role of autoreactivity in the pathogenesis of AD is far from clear and only hinted at in previous reviews, which might be open to publication bias.^{5,7} Demonstrating that autoreactivity plays a role in AD progression is important because such a finding might open up new therapies that inhibit the development and progression of autoimmunity. To more fully assess the possible role of autoimmunity in patients with AD, we sought to systematically review the literature to evaluate the prevalence and specificity of autoreactivity in patients with AD, to determine whether autoreactivity correlates with the clinical severity of the disease, and to systematically identify, summarize, and critically appraise the current evidence for a possible causative role of autoreactivity in AD pathogenesis.

METHODS

Systemic review

We searched MEDLINE from inception to the end of December 2011 to address the following 3 questions: (1) What is the prevalence of autoreactivity in patients with eczema? (2) Is autoreactivity a marker of disease severity? (3) What is the evidence for a potential role of autoreactivity in AD pathogenesis? We included *in vitro* or *in vivo* original studies with subjects of all ages and

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ethnic groups that investigated the phenomenon of autoreactivity in the context of AD or eczema. Autoreactivity in this review was defined as any *in vitro* or *in vivo* evidence of immune response to any human autologous, generic human, or recombinant human proteins or other tissue or cellular components. Such a definition includes all AD studies with an outcome measure to detect immune responses by, but not limited to, evidence of antibody-antigen binding, activation of innate or adaptive immune cells, and clinical immunologic responses. Our definition is deliberately broad to be inclusive of most of the studies in this field. Search terms included the Cochrane Skin Group search strategy for AD/eczema combined with the following search terms: "autoreactivity," "autoantigen," "autoallergy," "autoimmunity," and a list of known antigens that might cause autoreactivity in patients with AD (see Fig E1 in this article's Online Repository at www.jacionline.org). The online search was supplemented by scrutiny of citations listed in retrieved articles. All potential articles were scanned by the first author (T.S.T.). When a title or abstract could not be rejected with certainty, full-text articles were scrutinized. Each relevant article underwent standard *pro forma* data extraction by the first author, and all data were then critically assessed by the author panel.

Analysis

A formal meta-analysis was considered inappropriate because of the small number of studies related to each question and the heterogeneity in study design, types of participants, and diagnostic criteria.

In analyzing the correlation of disease severity and autoreactivity, we accepted any form of regression analysis, χ^2 tests, or Fisher exact tests performed by the report authors with a predefined significance level. To assess the potential role of autoreactivity in causation of AD, we used the following empirically derived criteria⁸: (1) strength and specificity of association between autoreactivity and AD; (2) biological gradient (evidence of dose response) in autoreactivity; (3) biological plausibility and concordance; (4) direct clinical experiment, such as reproducing an eczematous reaction on patch tests or intradermal injections in those who show *in vitro* autoreactivity with no reactions in those eczematous patients who do not exhibit such autoreactivity *in vitro*; (5) consistency of evidence across several studies; and (6) temporal relationship between autoreactivity and AD progression.

RESULTS

How common is autoreactivity in patients with AD?

Thirty-one of 1408 studies were deemed suitable for inclusion in this systematic review, as shown in the study flow chart in Fig 1 and listed in the supplemental reference list (see references E1-E31 in this article's Online Repository at www.jacionline.org). Fourteen of these 31 articles^{E1-E14} reported on the frequency of autoreactivity in patients with AD and are described more fully in Table I. These 14 articles involving 1253 patients with AD and 1391 control participants reported autoreactivity in 18% to 91.4% of patients with AD compared with 0% to 11.7% in control subjects.

In 8 studies^{E1-E8} that concentrated on IgE autoantibodies, 242 of a total of 634 patients with AD showed serum IgE autoantibodies with capacity to bind to human proteins compared with 11 of 173 control subjects who showed similar autoreactivity (38.2% vs 6.36%; weighted risk ratio using a random-effects model, 13.2; 95% CI, 1.75-99.4; Fig 2). Studies with a sample size of greater than 100 patients with AD^{E5,E7} produce more conservative estimates of autoreactivity, ranging from 23% to 28%. Quality of the studies, such as diagnostic criteria and study design, did not seem to explain the variation in the prevalence of autoreactivity.

No difference in the prevalence of autoreactivity was noted in the 2 studies that distinguished between patients with intrinsic (total serum IgE, <100-200 kU/L and no known sensitization

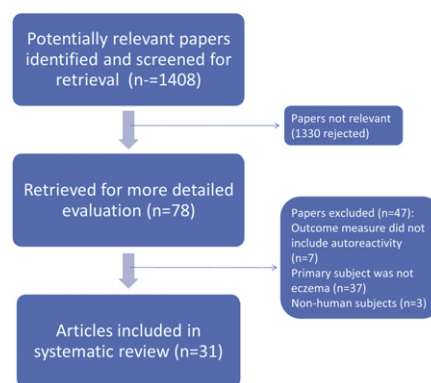


FIG 1. Study flow diagram.

against common inhalant or food allergens)^{E6,E8} and extrinsic AD. Total IgE levels have also been found to be strongly correlated with the prevalence of IgE autoreactivity in 3 studies.^{E6-E8} In those shown to have IgE autoreactive capacity, the total IgE level has been found to be significantly greater than that seen in patients without autoreactivity.^{E6-E8} There was no clear association between autoreactivity and age, sex, or duration of disease.

Positive antinuclear antibody (ANA) results were reported in 19% to 41% of patients with AD.^{E9,E13,E28} Severe facial eczema has previously been described to be present more often in patients with eczema with positive ANA results (titer >1:40).⁹ However, no consistent facial predilection was noted in the 3 studies that we identified that contained information on locations of lesions (Table I).^{E13,E28,E30}

Is autoreactivity a marker of AD severity?

Ten studies summarized in Table II^{E2,E5,E6,E8,E10-E13,E19,E20} recorded disease severity, only 5 of which^{E5,E6,E8,E11,E13} analyzed the possible association between autoreactivity and AD severity. Two reported a statistically significant correlation between autoreactivity and severity,^{E6,E11} whereas the other 3^{E5,E8,E13} found an association between autoreactivity and a higher total severity score, although these did not achieve statistical significance. Another study contained sufficient data to permit a contingency χ^2 test.^{E2} Eighty-two percent (18/22; 95% CI, 62% to 94%) of patients with demonstrable IgE autoreactivity had moderate-to-severe eczema compared with 55% (16/29; 95% CI, 37% to 72%) among those who had no detectable IgE autoantibodies ($P = .052$). One report^{E19} documented a close relationship between the intensity of IgE autoreactivity on immunoblotting band with disease severity (Scoring Atopic Dermatitis [SCORAD] score) in an individual patient with severe AD. Immunoblotting band intensity and SCORAD scores both reduced after initiation of a systemic anti-inflammatory treatment (cyclosporin), and both increased again when AD worsened during exogenous allergen contact. Details of the relevant regression analysis or validation/standardization of immunoblotting intensity were not reported.

Evidence for or against a causative role of autoreactivity in AD pathogenesis

Strength and specificity of association. The most striking observation in our 14 included studies is the strong

TABLE I. Prevalence of autoreactivity in patients with eczema

Reference	Study design and size	Diagnostic criteria for eczema	Methods	Prevalence of autoreactivity in control subjects	Prevalence of autoreactivity in patients with eczema (no. [95% CI])
IgE					
Valenta et al, 1996 ^{E1}	Case-control; 20 patients with eczema, 28 control subjects (2 healthy subjects, 5 with urticaria, 4 with GVHD, 7 with allergic rhinoconjunctivitis, 10 with SLE)	Clear	Western blot, whole serum IgE against endothelial cells, epithelial cells (A431), platelets, and fibroblasts	0%	60% (12/20 [38% to 79%])
Natter et al, 1998 ^{E2}	Case series, 51 patients with eczema	Clear	Western blot, whole serum IgE against endothelial cells and A431	NA	43% (22/51 [30% to 57%])
Kortekangas-Savolainen et al, 2004 ^{E3}	Case-control; 27 patients with IgE-mediated AEDS, 6 control subjects	Unclear	Western blot, serum IgE against keratinocytes	0%	37% (10/27 [21% to 56%])
Aichberger et al, 2005 ^{E4}	Case-control; 12 patients with eczema, 11 patients with rhinoconjunctivitis, 6 healthy control subjects, 6 control subjects with chronic dermatoses (3 with contact dermatitis and 3 with psoriasis)	Clear	Western blot, serum IgE against epithelial cell line A431 and rHom s 4	0%	91% (11/12) to epithelial cells (A341) 16.7% to Hom s 4
Mothes et al, 2005 ^{E5}	Case-control; 174 patients with eczema, 10 patients with psoriasis, 26 healthy control subjects	Clear	Western blot, whole serum IgE against epithelial cell-derived antigens	0%	23% (40/174 [17% to 30%])
Schmid-Grendelmeier et al, 2005 ^{E6}	Case-control; 69 patients with eczema, 5 healthy subjects, 13 patients with psoriasis, 13 patients with ABPA, 13 patients with allergy to <i>A fumigatus</i>	Clear	Allergen-specific ELISA against rhMnSOD, SPT against rhMnSOD	0% in other control subjects 100% in patients with ABPA (11/11 [76% to 100%])	42% (29/69 [31% to 54%])
Altrichter et al, 2008 ^{E7}	Case series, 192 patients with eczema	Clear	Western blot, serum IgE against epithelial cell line A431	NA	28% (54/192 [22% to 35%])
Zeller et al, 2009 ^{E8}	Case-control; 71 patients with atopic eczema, 18 patients with nonatopic eczema, 12 patients with psoriasis, 24 healthy control subjects	Clear	Western blot, serum IgE against recombinant human proteins	0%	71.8% (51/71 [61% to 81%]) in patients with atopic eczema 72.2% (13/18 [49% to 89%]) in patients with nonatopic eczema
ANA					
Ohkouchi et al, 1999 ^{E9}	Case-control; 256 patients with eczema, 60 control subjects	Clear	Indirect immunofluorescent ANA	11.7% (7/60 [5.2% to 22%])	ANA 36% (93/256 [31% to 42%])
Ochs et al, 2000 ^{E14}	Case-control; 64 patients with eczema, 39 control subjects	Clear	Indirect immunofluorescent ANA; Western blot of serum IgE against anti-DFS70 IgG	ANA not reported WB-DFS70 0% (0/39) in healthy control subjects 16% (8/50 [7.7% to 28%]) in asthmatic patients 8.7% (9/103 [4.3% to 15%]) in patients with interstitial cystitis	ANA 41% (26/64 [29% to 53%]) WB-DFS70 30% (19/64 [19% to 42%])
Higashi et al, 2009 ^{E13}	Case-control; 100 patients with eczema, 1004 healthy control subjects	Clear	Indirect immunofluorescent ANA	6.8% (68/1004 [5.3% to 8.5%])	19% (19/100 [12% to 28%])

(Continued)

TABLE I. (Continued)

Reference	Study design and size	Diagnostic criteria for eczema	Methods	Prevalence of autoreactivity in control subjects	Prevalence of autoreactivity in patients with eczema (no. [95% CI])
Other experiments					
Szakos et al, 2004 ^{E11}	Case-control; 72 patients with AEDS, 22 healthy subjects	Unclear	ELISA for antiphospholipid antibodies (ACL and anti- β_2 -glycoprotein)	4.5% (1/22 [0.2% to 20.4%]) in healthy control subjects	18% (13/72 [10% to 28%]) ACL level increased
Tanaka et al, 2006 ^{E12}	Case-control; 61 patients with eczema, 13 patients with psoriasis, 46 healthy control subjects	Clear	Histamine release from basophils by semipurified sweat antigen	8.7% (4/46 [2.8% to 19.7%]) in healthy control subjects 0 (0/13 [0% to 21%]) in patients with psoriasis	77% (47/61 [65% to 86%])
Hide et al, 2002 ^{E10}	Case-control; 66 patients with eczema, 7 patients with allergic rhinitis, 27 healthy control subjects	Clear	Skin test: intradermal injection of autologous sweat	11.1% (3/27 [2.9% to 27%]) in healthy control subjects 71.4% (5/7 [33% to 95%]) in patients with allergic rhinitis	85% (56/66 [75% to 92%])

ABPA, Allergic bronchopulmonary aspergillosis; ACL, anticardiolipin; AEDS, atopic eczema/dermatitis syndrome; GVHD, graft-versus-host disease; NA, not applicable; rhMnSOD, recombinant human manganese superoxide dismutase; SLE, systemic lupus erythematosus; SPT, skin prick test.

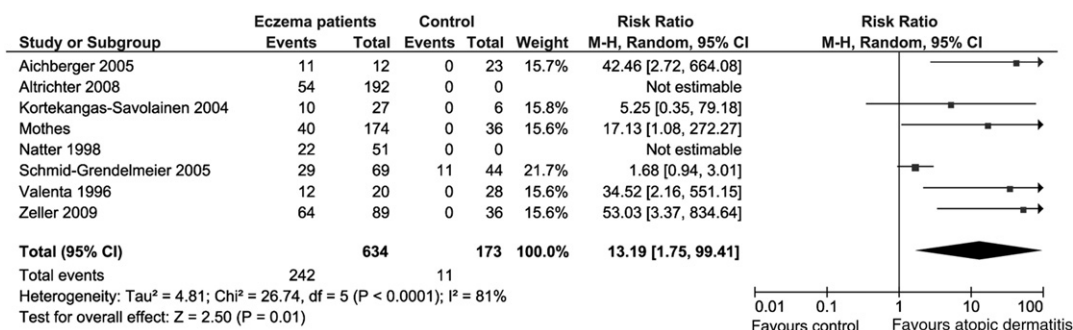


FIG 2. Forest plot showing pooled analysis of the prevalence of IgE autoantibodies (Events) in subjects with eczema and control subjects. The weighted risk ratio was calculated by using the Mantel-Haenszel (M-H) statistical method and a random-effects model.

and highly specific association between autoreactivity and AD. Autoantigens were absent in all of the control populations apart from 1 case-control study,^{E1-E14} whereas IgE autoreactivity was commonly observed in the serum samples of patients with AD (Table I). Control participants not only consist of healthy subjects but also other atopic patients with allergic rhinoconjunctivitis and patients with other forms of chronic skin inflammation, including psoriasis, contact dermatitis, and graft-versus-host disease. The only other factors to exhibit IgE autoantibodies found in our searches were patients with allergic bronchopulmonary aspergillosis who had autoreactive IgE against both recombinant human manganese superoxide dismutase and fungal manganese superoxide dismutase secreted by *Aspergillus fumigatus*, both of which were identified previously as a specific marker for this condition.^{E17} In 2 case-control studies patients with AD were found to have a higher risk of an ANA titer of greater than 1:40 than control subjects (relative risks, 2.79 and 3.07, respectively).^{E9,E13}

Two further reports showed that the relative risks of reacting with autologous semipurified sweat and demonstrating a positive skin patch test result were 7.6 and 8.9 in patients with AD compared with control subjects by using a basophil histamine release assay.^{E10,E12}

Biological gradient in autoreactivity. Some correlation between global severity and the presence of autoreactivity was evident, as shown in Table II. Surprisingly, few studies commented on the strength of autoreactivity and the severity at the individual participant level.

Biological plausibility and concordance. We present our findings for IgE autoantibodies, atopy-related autoallergen, IgG autoantibodies, and cellular immunity in turn. In the context of IgE autoantibodies, homologous environmental allergens refer to self-proteins that share sequence and structural similarity with known external allergens. Twenty studies* identified and characterized homologous autoantigens in patients with AD in both *in vitro* and direct *in vivo* experiments. Recombinant self-antigens, such as manganese superoxide dismutase,^{E6} ribosomal P2 protein,¹⁰ cyclophilin,¹² or thioredoxin,¹¹ have also been shown to have the ability to bind serum IgE and to elicit strong skin test reactions exclusively in patients with serum IgE against the corresponding homologous environmental allergens. Competitive inhibition ELISAs have also shown that recombinant human autoantigens and homologous environmental allergen compete

*References 10-13, E1-E4, E6-E8, E14-E18, E21, E22, E25, and E26.

TABLE II. Association between eczema severity and autoreactivity

Reference	Study design and size	Diagnostic criteria for eczema	Severity measure	Autoreactivity measurement methods	Results
Natter et al, 1998 ^{E2}	Case series, 51 patients with eczema	Clear	Own score	Western blot, whole serum IgE against endothelial cells and A431	No formal analysis
Hide et al, 2002 ^{E10}	Case-control; 66 patients with eczema, 7 patients with rhinitis, 27 healthy control subjects	Clear	Rajka and Langeland	Skin patch test against autologous sweat	No formal analysis
Kinaciyan et al, 2002 ^{E19}	Case report, 1 patient with eczema	Unclear	SCORAD	Western blot, whole serum IgE against human epithelial cell extracts	No formal analysis; association reported in graphs
Szakos et al, 2004 ^{E11}	Case-control; 72 patients with AEDS, 22 healthy subjects	Unclear	SCORAD	ELISA for antiphospholipid antibodies (ACL and anti- β_2 -glycoprotein)	Increased prevalence of high ACL level in severe eczema (SCORAD score >75; $P = .0185$)
Mothes et al, 2005 ^{E5}	Case-control; 174 patients with eczema, 10 patients with psoriasis, 26 healthy control subjects	Clear	SCORAD, Diepgen score	Western blot, whole serum IgE against epithelial cell-derived antigens	Insignificant result but higher total Diepgen score in autoreactive patients ($P = .36$); SCORAD results not reported
Schmid-Grendelmeier et al, 2005 ^{E6}	Case-control; 69 patients with eczema, 5 healthy subjects, 13 patients with psoriasis, 13 patients with ABPA, 13 patients with allergy to <i>A fumigatus</i>	Clear	SCORAD	Allergen-specific ELISA against rhMnSOD, SPT against rhMnSOD	Correlation of SCORAD score with serum anti-human MnSOD IgE level ($R = 0.756$, $P < .0001$)
Tanaka et al, 2006 ^{E12}	Case-control; 61 patients with eczema, 13 patients with psoriasis, 46 healthy control subjects	Clear	Own score	Histamine release from basophils by semipurified sweat antigen	No formal analysis reported
Higashi et al, 2009 ^{E13}	Case-control; 100 patients with eczema, 1004 healthy control subjects	Clear	Rajka and Langeland	Indirect immunofluorescent ANA	No significant association between autoreactivity and total eczema severity or facial eczema severity (P value not reported)
Lind et al, 2009 ^{E20}	Case-control; 78 patients with eczema, 45 healthy subjects	Clear	SCORAD	iNKT autoreactivity	Analysis not performed
Zeller et al, 2009 ^{E8}	Case-control; 71 patients with atopic eczema, 18 patients with nonatopic eczema, 12 patients with psoriasis, 24 healthy control subjects	Clear	SCORAD	Western blot, serum IgE against recombinant human proteins	Insignificant result but higher total SCORAD score in autoreactive patients (47.4 vs 44.1, $P < .76$)

ABPA, Allergic bronchopulmonary aspergillosis; ACL, anticardiolipin; AEDS, atopic eczema/dermatitis syndrome; iNKT, invariant CD1D-restricted natural killer T cells; rhMnSOD, recombinant human manganese superoxide dismutase; SPT, skin prick test.

for some common IgE-binding epitopes.^{11,12,E6} Atopy-related autoallergens, such as Hom s 1 to Hom s 4, are human intracellular proteins expressed by keratinocytes and identified by using cDNA cloning from serum samples of patients with AD. They are thought to be released by tissue damage induced by activities, such as scratching, during the chronic inflammation phase of eczema, which allows these proteins to be in contact with immune-active cells and thereby potentially induce autoallergy. For a postulated mechanism of the development of autoallergy, please refer to Fig 3. The full character and details of these autoantigens are summarized in recent reviews.^{6,14} Zeller et al^{E8}

assessed the repertoire of IgE-binding self-antigens in patients with AD by screening phage surface-displayed human cDNA libraries for clones binding to serum IgE using high-throughput technology and identified 141 sequences encoding potential IgE-binding self-antigens associated with AD. Sixteen cDNA sequences encoded previously described autoantigens. Three new sequences showed homology with environmental allergens, 86 encoded known human proteins, 7 predicted proteins, and 28 showed sequence identity with genomic contigs. These data demonstrate a broad spectrum of at least 140 IgE-binding self-antigens associated with AD.

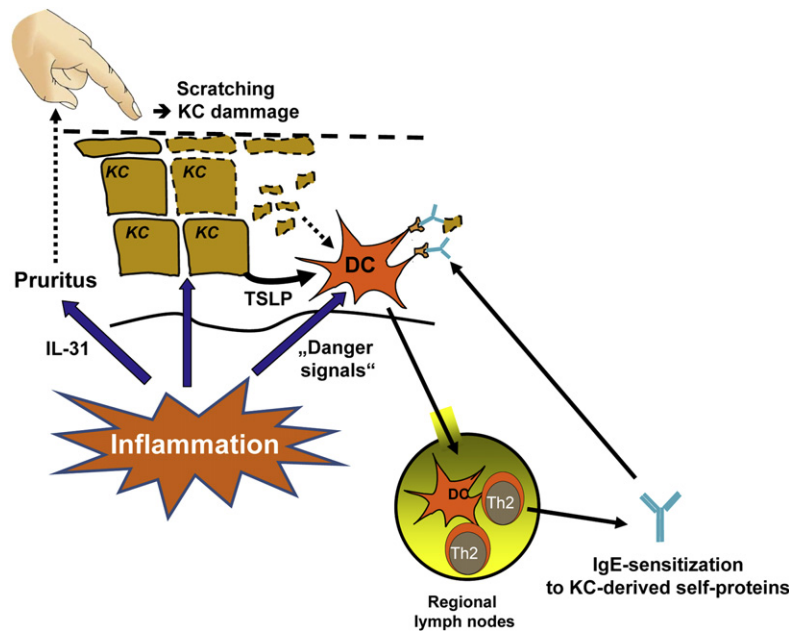


FIG 3. Mechanisms of IgE sensitization to epidermal self-proteins in patients with AD. Inflammation induces pruritus through IL-31 production. Scratching results in cellular damage and release of membranous and intracellular compounds from keratinocytes (KC) and possibly other skin cells. The local dendritic cells (DC) subjected to thymic stromal lymphopoietin (TSLP) will induce a T_H2 response and the generation of specific IgE directed against these self-proteins. IgE will bind to $Fc\epsilon R1$ on dendritic cells in the skin and thereby amplify the immune response and inflammatory reaction in the skin.

Both IgG and IgE antibodies against a 70-kDa antigen showing a characteristic pattern of dense fine speckles (DFS-70) were found in patients with AD, particularly in patients with facial involvement.^{E14} The presence of anti-DFS70 autoantibodies has been associated with AD, asthma, age-related cataracts, and interstitial cystitis.^{E14}

Hom s 1 has been previously identified as a tumor antigen and a potent target for cytotoxic T cells,^{15,16} yet no such autoreactivity has been demonstrated in patients with AD. Both Hom s 2 and Hom s 4 have been found to induce strong release of IFN- γ in both atopic and healthy persons.^{E4,E22} IFN- γ -containing culture supernatant from Hom s 2-stimulated PBMCs have been observed to cause disintegration of apoptosis of skin keratinocytes, which could be inhibited with a neutralizing anti-IFN- γ antibody. In a study by Heratizadeh et al,^{E16} autoallergen-specific T lymphocytes (both $CD4^+$ and $CD8^+$ cells) against rHom s 2 were found in serum and skin biopsy specimens from patients with AD. The authors found that Hom s 2, also known as α -nascent polypeptide-associated complex, was able to induce an antigen-presenting cell-dependent preferential proliferation in cutaneous-homing ($CCR4^+$ or cutaneous lymphocyte-associated antigen-positive) T cells when compared with $CCR4^-$ cutaneous lymphocyte-associated antigen-negative T cells. The same study also presented a T_H1 predilection in $CD4^+$ α -nascent polypeptide-associated complex-specific T-cell clones in lesional skin biopsy specimens.^{E16} No other reports on autoallergen-specific T cells were found.

Direct clinical experiment. Four clinical experiments were identified in our search. Natter et al^{E2} performed skin prick tests on 2 patients with AD and 3 nonatopic subjects with purified recombinant IgE autoantigens. Immediate-type reactions were observed in both patients with AD but not in the control subjects.

In another study intradermal skin tests with *A fumigatus* P2 protein and human P2 protein^{E22} showed specific skin reactions to both only in the 4 patients with severe AD or allergic bronchopulmonary aspergillosis. A study by Hide et al^{E10} showed that 85% of patients with AD (56/66; 95% CI, 75% to 92%; relative risk, 7.6 compared with 3/27, 11.1% in healthy control subjects) had positive reactions to autologous sweat. The fourth study, by Schmid-Grendelmeier et al,^{E6} investigated skin prick test responses to recombinant human manganese superoxide dismutase, rAsp f 6, and crude extracts of *A fumigatus* and *Malassezia sympodialis* in 69 patients with AD and 42 control subjects and found that only the subjects with high serum allergen-specific IgE levels (ImmunoCAP positive), which included 29 patients with AD and 11 patients with allergic bronchopulmonary aspergillosis but none of the healthy control subjects, had *in vivo* skin reactions to corresponding fungal extracts. Collectively, the above 4 studies provide some direct evidence that a self-antigen was sufficient to elicit eczematous reactions in patients with AD sensitized to antigens.

Consistency of evidence across several studies. We have identified at least 31 articles that describe autoreactivity in patients with AD. Regardless of study design, all included studies have reported some degree of autoreactivity in patients with AD by using a variety of techniques.

Temporal relationship between autoreactivity and eczema progression. One study^{E5} of 20 children with AD aged between 2 and 6 years evaluated repeat serum samples 1 year apart and found that 5 subjects had IgE autoreactivity during this period. The authors concluded that the occurrence of autoreactivity is likely to develop in early childhood. We did not identify any other longitudinal studies that elucidated a possible temporal relationship between autoreactivity and AD persistence.

DISCUSSION

Main findings

Our review has systematically identified and appraised a significant body of evidence that suggests a potential role for autoreactivity in AD pathogenesis. The phenomenon of IgE autoreactivity in patients with AD suggests that it is a relatively specific phenomenon because no such association can be shown in healthy control subjects, atopic patients with mild respiratory diseases, or patients with other chronic inflammatory skin conditions. A significant proportion of patients with AD demonstrated autoreactivity in various *in vitro* and direct clinical experiments across distinct study populations. We also identified some limited evidence of a correlation and temporal relationship between the strength of autoreactivity and the global AD severity score.

Strengths and limitations

Despite our systematic approach, it is still possible that we might have missed some key published studies. Our definition of autoreactivity was deliberately broad to be as comprehensive as possible, which in turn resulted in wide methodological variations between included studies. Study heterogeneity in terms of design, diagnostic criteria, participant selection, disease severity scoring, and laboratory methods of determining autoreactivity hampered direct comparison across studies. Overestimation of intrinsic eczema can occur by not including a sensitive list of allergens for investigation, and underestimation of systemic autoimmunity can occur because sensitive autoimmune assays were not always performed. Most studies were hospital based and might not be generalizable to populations with milder disease in the community. Publication bias (ie, the tendency to only publish those studies that have shown a positive association) might also have occurred.

Clinical and research implications

As exemplified by the observation that high titers of ANA (>1:40) are detected in approximately 26% of healthy subjects,¹⁷ immunologic evidence of autoreactivity does not automatically translate into a clinically relevant autoimmune process. Also, intradermal injections and skin prick tests have high false-positive rates in patients with AD, and a positive dermal challenge test result does not necessarily correlate with clinical symptoms because up to 40% of the subjects sensitized to environmental allergens are asymptomatic.¹⁸ The exact role of autoreactivity in the development of AD is still unclear, especially whether it is simply an epiphenomenon as a result of chronic inflammation or a contributor to the spread and perpetuation of the disease. Longitudinal studies are needed to separate cause from effect, but such studies are lacking. Increased total serum IgE levels have been observed to correlate with increased prevalence of IgE autoreactivity in patients with eczema.^{E5-E8} Although some argue that autoreactivity might be a natural phenomenon as a result of chronic, persistent increased IgE levels, the presence of patients with high IgE titers with no autoreactivity contradicts this hypothesis and suggests there might be a distinct subset of patients with eczema who have autoreactivity.⁶ Many atopy-related autoallergens are intracellular proteins and as such would not normally be available for antigen-antibody interactions.⁶ Constant

scratching secondary to intractable pruritus caused by AD has been proposed to inflict cellular injury, which releases intracellular autoantigens and in turn can lead to disease progression through autoimmunity.^{E16}

Recent research has opened up many dimensions of possible pathogenic or perpetuating mechanisms of AD.^{19,20} However, what remains largely unknown is what has gone wrong and in what sequence it went wrong. New longitudinal research is needed to determine whether an autoreactive subgroup of AD exists and whether the onset and extent of such autoreactivity can predict prognosis. If autoreactive AD subgroups do exist, then it might be worth treating the development of such autoimmunity aggressively and at an early stage in the hope of disrupting disease progression, which might be mediated through epitope spread.

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1. exp Dermatitis, Atopic/
2. atopic dermatitis.mp.
3. dermatitis atopic.mp.
4. exp Eczema/
5. childhood eczema.mp.
6. infantile eczema.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Autoimmunity/
9. exp Autoantigens/
10. autoallerg\$.mp.
11. autoreactivity.mp.
12. Profilins/
13. ribosomal P2.mp.
14. exp Thioredoxins/
15. exp Immunoglobulin G/
16. exp Immunoglobulin E/
17. Superoxide Dismutase/
18. autoantibod\$.mp.
19. self-antigen.mp.
20. self-react\$.mp.
21. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 7 and 21
23. limit 22 to (male and female and humans and humans)

FIG E1. Search strategy.