

REVIEW ARTICLE

Autoimmunity in atopic dermatitis: Biomarker or simply epiphenomenon?

Francesca CIPRIANI,¹ Giampaolo RICCI,¹ Maria Chiara LEONI,² Lucetta CAPRA,³ Giuseppe BAVIERA,⁴ Giorgio LONGO,⁵ Nunzia MAIELLO,⁶ Elena GALLI⁷

¹Pediatric Unit, Department of Medical and Surgical Sciences, University of Bologna, Bologna, ²Pediatric Unit, Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, ³Department of Reproduction and Pediatrics, University Hospital S. Anna, Ferrara, ⁴National Health System Pediatrician ASL RMC-D6, Rome, ⁵University of Trieste, Trieste, ⁶Department of Woman, Child and General and Specialized Surgery, Second University of Naples, Naples, and ⁷Pediatric Allergy Unit, Research Center, San Pietro Hospital – Fatebenefratelli, Rome, Italy

ABSTRACT

The idea that a mechanism of autoimmunity could play a role in the pathogenesis of atopic dermatitis gained support from the observation that patients with atopic dermatitis display IgE reactivity to a variety of human protein antigens, several of which have been characterized at molecular level. A broad spectrum of at least 140 IgE-binding self-antigens associated with atopic dermatitis has been demonstrated; they might promote, perpetuate, or both, skin inflammation by binding IgE antibodies or activating specific T cells. Even if the presence of autoreactivity seems to be associated with the severity of the disease and may be used as a parameter reflecting chronic tissue damage, at the state of art the role of autoimmunity in atopic dermatitis is far from clear. Data from the literature show that the use of autoantibodies as *biomarkers* of atopic dermatitis are still limited by the evidence that the *epiphenomenon* of autoreactivity is detectable only in a percentage of patients and that the involved self-allergens often are not the same; further longitudinal case-control studies are needed to investigate and to clarify the pathogenetic role of autoimmunity in the course of atopic dermatitis.

Key words: atopic dermatitis, autoantibodies, autoantigens, autoimmunity, self antigen.

INTRODUCTION

Traditionally immunological aberrations are thought to be a primary event in the initial development of atopic dermatitis (AD), according to the so called “inside-to-outside hypothesis”. The existence of a genetically determined barrier defect at the basis of AD, as in other skin disorders, is now well known; alterations of the filaggrin gene and of other genes that encode proteins of the epidermal differentiation complex have been supported by numerous studies.¹

When the skin barrier is impaired, the skin is inevitably more sensitive to external aggression, allergens or many irritant stimuli that can easily penetrate the epidermal barrier, and induce a secondary immunologic reaction (“outside-to-inside hypothesis”).²

Anyway, in the early stage of AD, so-called Th2 immunity predominates leading to increased IL-4, IL-5, IL-13, and IgE levels; with the progression of disease, the Th2-predominant reactions of acute phase transit to a mixture of type I and IV hypersensitivity reactions with a prevalence of Th1 related

cytokines (IFN- γ and IL-12). These abnormal immunological reactions induce a condition of epidermal inflammation that subsequently lead to secondary epidermal barrier defects.

In the progression of disease the discharge from the acute to the chronic phase is a crucial step; in recent years more interest has focused on highlighting the mechanisms at the basis of this immunological change. The possible involvement of autoimmune mechanisms has been the content of several studies and reviews,^{3–6} but at the present time the role of autoimmunity in AD is far from clear.

In contrast to the traditional concept of an inverse association between atopy and autoimmunity, some recent evidences support the possibility of a co-existence in the same subject of TH1 autoimmune diseases (thyroiditis, IDDM, celiac disease, psoriasis, rheumatoid arthritis) with TH2 mediated disorders both in adults and in the pediatric population, suggesting an excessive simplicity of the TH1/TH2 paradigm.⁷

The aims of this review are to investigate the prevalence of skin autoreactivity defined as an *in vitro* or *in vivo* evidence of immune response to autologous human, generic human, or

Correspondence: Giampaolo Ricci, M.D., Pediatric Unit, Department of Medical and Surgical Sciences, University of Bologna, S.Orsola-Malpighi Hospital, Pad 16, via Massarenti 11, 40138 – Bologna, Italy. Email: giampaolo.ricci@unibo.it
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recombinant human proteins or other tissue/cellular components⁶ and to clarify its role as a possible *biomarker* in the progression, extension and localization of AD or as a *simple epiphenomenon* of the disease.

To systematically review the literature addressing this issue, we searched PubMed for publications from 1970 to 2013, using multiple strings with the term “atopic dermatitis” in combination with “autoimmunity” or “autoreactivity” or “autoallergy” or “autoantigen” or “antinuclear antibodies”. We extracted a total of 199 relevant papers and among these we selected only the original articles written in English, performed on human subjects. We rejected review articles, papers with irrelevant outcomes and some articles describing data reported subsequently about the same population study (Fig. 1). The online search was supplemented by adding relevant articles found in the references of the selected papers.

PATHOGENETIC MECHANISMS OF SKIN AUTOREACTIVITY

The evidence of an immune mechanism against self-antigens in AD is supported by two main considerations: the first is the chronic relapsing course of the disease, as observed also in autoimmune diseases; the second is the ability of some autologous human components to elicit immediate hypersensitivity skin reactions in patients with severe AD. In fact, the presence of antibodies (Abs) of class IgG and IgE directed towards self-antigens has been demonstrated in both allergic and autoimmune diseases. In the context of atopy, they have been highlighted especially in chronic diseases with severe presentation, mainly in AD, while they are not found in association with the mild forms of AD and with allergic respiratory diseases. At the same time, many autoimmune pathologies are associated with the clear demonstration of autoreactive autoantibodies (aAbs),

namely rheumatoid arthritis, lupus erythematosus systemicus, Hashimoto's thyroiditis, Graves disease, and others.

The skin represents an important interface between organism and environment, since it is at the forefront of environmental insults. The barrier function of the skin is carried out thanks to the particular epidermal structure in layers and thanks to all the substances produced by the skin appendages (sebaceous and sweat glands). Keratinocytes also provide for preservation of this structure by regulating the epidermal loss of water (transepidermal water loss, TEWL) and electrolytes, and by contributing to defense against various mechanical and chemical environmental agents. Meanwhile, the main protagonists of the immune response in the skin are represented by antigen-presenting cells (APC). The so called Langerhans cells are a subgroup of APC steadily allocated in the deeper layers of the epidermis where they exert their function. Another subgroup of APC includes cells with the capacity to migrate to lymphatic organs and induce a specific antibody response, as well as a development of the immunological memory.

Langerhans cells are specialized cells of the immune system of the skin and are an integral part of the global body's defense mechanism. They play a basic role in the recognition of pathogens and initiation of the innate immune response, thanks to the ability to express Toll-like receptors (TLRs). TLRs share with the IL-1 receptor the same signaling cascade that involves the activation of NFκB, a key transcription factor in promoting the expression of genes encoding inflammatory cytokines. Therefore, activation of TLRs helps to activate inflammatory responses, but also phagocytosis and the release of both antibacterial molecules and non-specific antimicrobial peptides. The expression of IgG-Fc receptors by mast cells themselves is important for the immune response against pathogens; the cross-linking with the IgG results in the activation of these cells both in autoimmune diseases as in allergy.⁸ The simultaneous discovery of the important role in these diseases of TH17 and Treg cells supported the hypothesis of a link between these conditions.⁹ T helper cells 17 (TH17) have the characteristic ability to secrete IL-17, a proinflammatory cytokine. They represent a recently discovered subpopulation of distinct T cell lines compared to TH1 and TH2 with a pleiotropic activity on fibroblasts, keratinocytes, endothelial cells, neutrophils and memory T cells; they are thought to play a crucial role as mediators of inflammation and autoimmunity.¹⁰

It is well known that the early acute phase of AD switches to a later chronic phase with a mixture of type I and IV hypersensitivity reactions: from a predominantly TH2- to a predominantly TH1-cytokine pattern (INF-γ and IL-12), that can perpetuate the inflammatory response.⁵ During this step, the phenomenon of *autoreactivity* can be induced. As a consequence of inflammation and scratching, some human and never before recognized epitopes could be released and exhibited⁴; throughout the recognition of these self-antigens the development of autoreactive T cells would take place. Another possible mechanism able to induce the development of a skin autoreactivity has been specifically described in AD during a concomitant infection by *Malassezia sympodialis*; in this condition T cells differentiate into CD4⁺ T lymphocyte clones

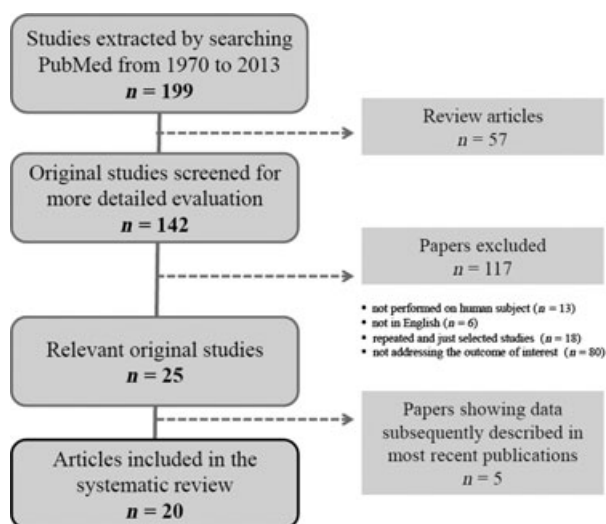


Figure 1. Selection of original studies included in the review by searching PubMed.

directed against the fungal enzyme thioredoxin (Mala s 13); Mala s 13 is able to cross-react with the human homologous anti-inflammatory protein (hTrx) and to contribute to the perpetuation of the inflammation through the inhibition of this enzyme.^{11,12}

SELF-ANTIGENS

As result of several different mechanisms, the self-antigens associated with atopy derive from different cells and tissutal components, but they have in common the ability to be recognized as autoallergens by the immune system. In the past few decades, various self-proteins have been identified as target antigens in AD through the recognition of a link with specific IgE aAbs. Zeller *et al.*¹³ demonstrated a broad spectrum of at least 140 IgE-binding self-antigens associated with AD; binding IgE Abs or activating specific T cells, they might promote, perpetuate, or both, existing skin inflammation. Some autoallergens are intracellular proteins expressed by human keratinocytes, such as Hom s antigens, and they are released mainly as a consequence of scratching; in the chronic phase of eczema the tissue damage allows these self-antigens to interact with the APC and potentially to induce *autoallergy*.

The autoallergen Hom s 2 is the human transcriptional coactivator α -nascent polypeptide-associated complex (α -NAC). Hom s 2 would be able to induce an immune response dependent from APC: α -NAC-specific T-cell clones (TCC) can be generated from the blood and lesional skin of patients with AD.¹⁴ These TCC produce not only Th2, but also Th1 cytokines which may explain the Th1 phenotype of inflammation in AD.

The complete Hom s 4 cDNA codes for a 54-kDa basic protein containing two typical calcium-binding domains separated by an unusually long-helical domain and with its homologous proteins constitutes a novel subfamily of calcium binding proteins. The protein is strongly expressed within epidermal keratinocytes and dermal endothelial cells, as detected by using Hom s 4-specific Abs. Purified Hom s 4 showed IgE cross-reactivity with exogenous calcium-binding allergens from plants and fish but, in contrast to the exogenous allergens, induced only a weak histamine release from basophils.¹⁵ However, the analysis of Hom s 4-specific cytokine and humoral immune responses indicated that Hom s 4 strongly induces Th1 responses which are accompanied by the release of IFN- γ , a cytokine implicated in epithelial cell damage. A production of Hom s 4-induced IFN- γ was found in normal individuals, in patients with chronic inflammatory skin diseases and in Th2-prone atopic subjects, suggesting that Hom s 4 represents a protein with an intrinsic property to induce Th1-mediated auto-reactivity.¹⁵

Specific IgE Abs against the human protein manganese superoxide dismutase (MnSOD) were also found in AD patients. MnSOD was earlier identified as an allergen in patients with allergic bronchopulmonary aspergillosis (ABPA), but not in *Aspergillus fumigatus*-sensitized individuals without clinical signs of ABPA or in healthy controls. MnSOD is an essential enzyme upregulated under many stress conditions like UV radiations, mechanical trauma, and any form of acute

or chronic inflammation, including AD. MnSOD was able to induce *in vitro* T-cell reactivity and eczematous reactions to atopy patch test (ATP) in sensitized patients with AD. Co-sensitization to structurally related and cross-reacting fungal MnSOD and skin-colonizing yeast *Malassezia sympodialis* was observed in all patients sensitized against human MnSOD.¹⁶

Lens epithelium-derived growth factor/dense fine speckles 70 kDa protein (LEDGF/DFS70) is another target antigen identified in AD patients. LEDGF/DFS70 is a known survival factor, growth factor, and HIV-1 transporter. LEDGF/DFS70 is predominantly located in the nucleus of the basal epidermal cells and translocates into the cytoplasm during differentiation; once in the cytoplasm, LEDGF/DFS70 accumulates in the keratohyalin granules in the granular layer. In some studies, serum IgE-anti-DFS70 aAbs and IgG(4)-anti-DFS70 aAbs may be related to higher chemokine concentrations and to the severity of AD¹⁷; in addition, Watanabe *et al.*¹⁸ recently provided evidence that AD patients have significantly high-avidity IgG-anti-DFS70 autoantibodies, proposed as a potential novel serological marker for AD.

Also the human anti-inflammatory protein thioredoxin (hTrx) can represent a target antigen of the autoantibody immune response, as a consequence of a cross-reacting mechanism with the homologous fungal enzyme of *Malassezia sympodialis*.^{11,12}

Several other proteins have been identified as immunologic targets in the contest of the IgE-autoreactive response observed in allergic diseases and in AD¹⁹; some of these (Table 1) are cross-reacting proteins homologous to plant and fungal antigens (<http://allergome.org/script/about.php>).

EVIDENCE OF A LINK FROM THE LITERATURE

The widely debated link between AD and autoimmunity aims to establish, in the most recent studies, if the autoreactivity can represent a simple epiphenomenon of the chronic inflammation or whether it is the key element in the recurrence and chronicity of AD.

Several aAbs that have been categorized as IgE class or IgG class have been detected in patients with AD; Zeller *et al.*¹³ examined sera of patients with AD in a case-control study to investigate the presence of self-antigens binding-IgE and finding a spectrum of more than 140 different types of self-antigens binding-IgE. Both CD4⁺ and CD8⁺ auto-allergen specific T lymphocytes against Hom s 2, also known as complex bound to the polypeptide α -nascent, were found in serum and in samples of skin biopsies of patients with AD. Valenta *et al.* tested sera from patients with atopic diseases and, for control purposes, from persons with immunologically mediated disorders for serum IgE reactivity with nitrocellulose-blotted human proteins; Western blot (WB)-detectable IgE Abs were found in 12 of 20 sera from atopic patient with pronounced skin lesions and the molecular weights of the IgE-defined autoantigens ranged predominantly from 10 to 100 kDa. Surprisingly, patients suffering predominantly from allergic rhinoconjunctivitis as well as the other control individuals failed to display serum IgE autoreactivity.²⁹

Table 1. Auto allergens confirmed *in vitro* and/or *in vivo* in atopic dermatitis and allergic diseases

Auto allergen		Biological function	MW	Allergenicity tests		Cross reactivity	References
Name	Common names			<i>In vivo</i>	<i>In vitro</i>		
Hom s 1	SART-1	Squamous cell carcinoma antigens, cell cycle arrest and apoptosis	55		Yes		20
Hom s 2	Alpha NAC	NAC-alpha proteins, activator of transcription	10.3	Yes	Yes		21 22 23
Hom s 3	BCL7B	B-cell CLL/lymphoma 7 proteins, oncogene	20.1	Yes	Yes		22
Hom s 4	CALC	Calcium uptake proteins	54	Yes	Yes	Cyp c1 Phl p 7	20 15
Hom s 5	Cytokeratin	Intermediate filament proteins	42.6	Yes	Yes		22
Hom s Profilin	Profilin	Actin-binding proteins	15		Yes	Bet v 2	24
Hom s P2	Ribosomal Protein P2	Ribosomal proteins (part of the 60S subunit)	12.6	Yes	Yes	Asp f 8	25
Hom s MnSOD	Fe/Mn-SOD, SOD	Mn superoxide dismutases	25	Yes	Yes	Asp f 6 Hev b 10 Mala s 11	26
Hom s Cyp B	Cyclophilin, Cyp	Rotamases, peptidyl-prolyl cis-trans isomerase	21		Yes		27
Hom s Trx	Thioredoxin, Trx	Oxidoreductases	12	Yes	Yes	Mala s 13	28
DFS70		Survival factor, growth factor	70		Yes		17 18

MW, Molecular weight.

A correlation between severity of skin lesions and prevalence of autoreactivity was reported in a case series study performed by Natter *et al.*²² They showed an intensive IgE autoreactivity in AD patients with moderate to severe skin manifestations, while no detectable intensive autoreactivity was observed in patients with mild AD. This study also revealed for the first time the molecular nature of four IgE autoantigens. An expression cDNA library constructed from a human epithelial cell line (A 431) was screened with serum IgE from two AD patients. DNA sequence analysis of three IgE-reactive clones identified the α -chain of the nascent polypeptide-associated complex (ara-NAC, also known as Hom s 2), cytokeratin type II (ara KER, also known as Hom s 5), and the BCL7B oncogene (also known as Hom s 3) as atopy-related IgE autoantigens (ara). The fourth cDNA coded for an IgE autoantigen containing a typical calcium binding motif (ara CALC) that occurred in histogenetically different cells and tissues (keratinocytes, muscle, brain). An interesting finding was that in serum samples collected from an AD patient over a period of 5 years, IgE anti-ara NAC antibody levels peaked during disease exacerbation.

In a Swedish study group it was demonstrated that patients with severe AD have a high rate of specific sensitization to human MnSOD (hMnSOD); specific IgE Abs against human MnSOD correlating with the disease activity were found in 29 of 67 patients (43.3%) with AD.¹⁶ These observations exclude *Aspergillus fumigatus* as primary sensitizing agent, even if a strong cross-reacting between MnSOD and *Aspergillus fumigatus* has been detected, maybe, for the high incidence of autoreactivity to hMnSOD observed in patients with AD. Interestingly, all patients with AD showing serum IgE against hMnSOD were concomitantly sensitized to the skin-colonizing

yeast *Malassezia sympodialis*, and IgE raised against hMnSOD and fungal extract correlated fairly well.¹⁶

In a Turkish study, the IgE autoreactivity of AD patients to cultured keratinocytes and the potential cross-reacting epitopes in cultured keratinocytes and *Malassezia furfur* were investigated. Serum samples of 27 AD patients and 14 control subjects were analyzed; among AD patients 13 were *Malassezia furfur* radioallergosorbent test (RAST) positive and 14 negative. Ten IgE-binding protein bands were detected in cultured human keratinocytes by IgE immunoblotting using sera from adult AD patients: antikeratinocyte IgE Abs were mostly associated with elevated S-IgE level rather than *Malassezia furfur* RAST, so a clear cross-reactivity with *Malassezia furfur* could not be shown.³⁰

A percentage of 28% of IgE autoreactivity was reported for AD patients, but not for healthy individuals, in a study performed by Altrichter *et al.* by WB analysis; immunostainings identified cytoplasmic and, occasionally, also cell membrane-associated moieties as targets for autoreactive IgE Abs. In this study interestingly, in certain autoreactive patients, the surface-staining pattern was accentuated at cellular contact sites.³¹ Zeller *et al.* reported a percentage of 71.8% of IgE-autoreactivity assessed by WB against recombinant human proteins in 71 adult patients with AD, without differences between atopic and non-atopic eczema.¹³

To address the question at which age of life IgE reactivity to endogenous antigens starts and what factors may influence the development of IgE autoreactivity, Mothes *et al.* performed a retrospective analysis of clinical and serological parameters in 174 well-documented adult patients with AD with and without IgE autoreactivity and a serological survey for IgE autoreactivity

in 102 children with AD during their first years of life.³² Among the adult population they found that 23% of the patients with AD showed IgE reactivity to a variety of human epithelial antigens. Sera from 26 control individuals without any atopic disorders and 10 patients with psoriasis showed no IgE autoreactivity. In the autoantibody-positive group they observed a more pronounced xerosis, dyshidrosis and ichthyosis of the skin ($P < 0.01$); in addition, these patients had much more frequent recurrent bacterial and viral infections of the skin such as impetigo contagiosa or eczema herpeticum during the course of atopic eczema. Among the child population, autoreactivity occurred in 15% of patients, but if children with moderate to severe AD were analyzed independently this percentage amounts to 80%. These autoantibody-positive children had significantly higher total IgE serum levels than autoantibody-negative children, and most of them had already developed sensitizations against food allergens. The authors identify the early infancy (2nd–6th years of life) as the critical period for IgE autosensitization in AD patients and emphasize the importance of this period for the development of atopic diseases as well as for preventive measures against allergy.³² The prevalence of IgE autoreactivity in AD patients against several autoantigens is shown in Table 2.

Tang *et al.* in a recent systematic review on the prevalence of *autoreactivity* in patients with AD showed the interesting evidence of a strong and highly specific association between autoreactivity and AD. From the results of 14 studies performed on a total of 1253 patients and 1391 controls, a clear higher prevalence of autoreactivity in subjects with AD (18–91.4%) than in control subjects (0–11.7%) was shown.⁶ In all studies, except one, the absence of autoantigens in control subjects was documented, while an IgE autoreactivity of serum samples of patients with AD was widely confirmed.

The positivity of anti-nuclear Abs (ANA, with titre >1:40) in patients with AD seems to be about 19–41%^{34,35} and not related to peculiar findings of localization, even if previous studies correlate this positivity with a higher tendency to develop a strict localization to the face.³⁶ As exemplified by the fact that approximately 26% of healthy subjects shows a positivity of ANA,³⁷ the evidence of an immunological autoreactivity is not automatically deemed to be a clinically relevant autoimmune process. In a study performed on 256 adult patients with AD, a high titre of serum antinuclear antibody (ANA) was found in 31.3% of patients and 65% of ANA-positive sera reacted to a 52 kDa protein (p52) in HeLa cell immunoblots; its cDNA sequence was identical to human elongation factor-1 alpha (hEF-1 α). The anti-hEF-1 α antibody-positive AD patients were characterized by higher facial involvement and lower white blood cell counts compared with antibody-negative patients.³⁴

The rates of both severe AD and severe facial AD were slightly but not significantly higher among ANA-positive patients than among ANA-negative patients (disease severity: 28% vs 17.8%; facial disease severity: 18.2% vs 12.3%). Furthermore, titre of ANA were not significantly higher in patients with severe AD or severe facial AD than in other patients. The prevalence of ANAs generally increases with age.³⁵

Controversial data on the role of non-allergen-specific Abs in atopic dermatitis aimed also some authors to investigate the occurrence of the antiphospholipid Abs (anticardiolipin, and anti-b2-glycoprotein I) in children with AD.

Szakos *et al.*, in a study performed on 72 children with AD, showed that 13 of 72 children with AD (mean age 8.3 years) had elevated serum levels of anticardiolipin (ACL), and eight of 72 anti-b2-glycoprotein I Abs. The ratio of patients with highly increased severity scoring of AD (SCORAD index >75) was significantly higher in the group with elevated ACL levels (4/13) than in the group with normal ACL levels (2/59) and there was a significant association between the appearance of mite (*D. pteronyssinus*, *D. farinae*) specific IgE and ACL IgM Abs (6/13).³⁸

In the same year, another description of a link between AD and anticardiolipin Abs was provided from an Italian study performed by Ricci *et al.*³⁹ They studied 51 children with different subtypes of AD (intrinsic or extrinsic type) compared with 12 children without allergy: an increase in serum levels of ACL was observed in 13 children (25.5%): one child (9%) from intrinsic type AD patients, 12 children (30%) from extrinsic type AD with statistically significant difference; in this study the presence of ACL-IgG in extrinsic AD was shown, but no association was found between high levels of ACL and an increased severity score of AD.

Pedulla *et al.* in a recent study examined the prevalence of autoimmune thyroiditis in 566 children with AD, urticaria, rhinitis, chronic cough and asthma looking for an epidemiological link between these two clinical entities.⁴⁰

CONCLUSIONS

The description of “autoreactivity” goes back to early last century when the sensitivity of individuals to human skin dander was demonstrated.^{41,42} The observation that aAbs might play a role in the pathogenesis of AD was not further followed until progress in molecular biology allowed isolation of cDNAs encoding IgE-binding proteins.^{43,44}

The idea that mechanisms of autoimmunity could also play a role in the pathogenesis of AD gained support by the observation that patients with AD display IgE reactivity to a variety of human protein antigens, several of which have been characterized at a molecular level. The spectrum of IgE-reactive autoantigens seems to be very broad and includes proteins with structural similarities to exogenous allergens such as plant profilins, dog serum albumin, mold-derived manganese, superoxide dismutase, and genuine autoantigens.^{22,24,29} The characteristic clinical features of the autoantibody-positive subgroup of patients with AD (xerosis, dyshidrosis, ichthyosis, bacterial and viral infections, pruritus) may contribute to mechanical damage of the skin and perpetuate the release of autoallergens from skin keratinocytes as a primary phenomenon. On the other hand, autoreactivity may be responsible for the development of these manifestations. The survey for IgE autoreactivity performed in several studies^{6,32} confirmed earlier observations that IgE autoreactivity specifically occurs only in a subgroup of patients with AD, but not in healthy individuals or persons with other inflammatory skin diseases.

Table 2. Prevalence of IgE autoreactivity against several different autoantigens in patients with AD

References	Study design and population	Age of AD patients (mean and/or range - years)	Diagnostic criteria for AD	Methods	Autoantibodies	Autoantigens	Prevalence of autoreactivity	
							Patients with AD	Control subjects
Valenta <i>et al.</i> ²⁹	Case-control. 20 atopic pts with AD, 28 control subject (7 with RC, 19 with immunologically mediated disorders, 2 healthy subjects) Case series. 51 pts with AD	1-63	H&R	WB	IgE	Endothelial cells, epithelial cells (A431), platelets, and fibroblasts	60%	0%
Natter <i>et al.</i> ²²		26.8 (1-63)	H&R	WB	IgE	ara NAC, ara BCL7B, ara CALC, ara KER DFS70	43%	NA
Ochs <i>et al.</i> ³³	Case-control. 64 AD pts, 409 control subject (39 healthy subjects, 50 with asthma, 320 with immunologically mediated disorders)	24.4 (4-43)	H&R	WB	IgG and less frequently IgE		30%	0% in healthy subjects, 16% in pts with asthma, 4.7% in other control subject
Kortekangas- Savolainen <i>et al.</i> ³⁰	Case-control. 27 atopic pts with AD, 13 control subjects (3 psoriasis, 4 urticaria, 6 healthy subjects)	33	Unspecified	WB	IgE	Keratinocytes	37%	0%
Aichberger <i>et al.</i> ¹⁵	Case-control. 12 pts with AD, 23 control subject (11 pts with RC, 6 healthy control subjects, 6 with chronic dermatoses)	38.4 (20-72)	H&R	WB	IgE	Epithelial cell line A431 and rHom s 4	91% to epithelial cells (A341) 16.7% to Hom s 4	0%
Mothes <i>et al.</i> ³²	Case-control. 174 adult pts with AD, 10 patients with psoriasis, 26 healthy control subjects	35.4	H&R	WB	IgE	Epithelial cell- derived antigens	23%	0%
Schmid- Grendelmeir <i>et al.</i> ¹⁶	Case-control. 69 pts with AD, 5 healthy subjects, 13 pts with psoriasis, 13 pts with ABPA, 13 pts with allergy to A. fumigatus	29.3	H&R	ELISA	IgE	rhMnSOD	42%	100% in ABPA pts 0% in other control subjects
Altrichter <i>et al.</i> ³¹	Case-control. 192 pts with AD, 26 healthy control subjects	38 (18-80)	H&R	WB	IgE	Epithelial cell line A431 and keratinocytes	28%	0%
Zeller <i>et al.</i> ¹³	Case-control. 71 atopic pts with AD, 18 non atopic pts with AD, 12 pts with psoriasis, 24 healthy	33.3 in atopic AD pts; 39.3 in non atopic AD pts	H&R	WB	IgE	Recombinant human proteins	71.8% in atopic pts 72.2% in non atopic pts	0%

Table 2. (continued)

References	Study design and population	Age of AD patients (mean and/or range - years)	Diagnostic criteria for AD	Methods	Autoantibodies	Autoantigens	Prevalence of autoreactivity	
							Patients with AD	Control subjects
Watanabe <i>et al.</i> ¹⁷	control subjects Case-control. 61 pts with AD, 20 healthy controls subjects	26.2 (13-59)	H&R	ELISA	IgE, IgG4	LEDGF/DFS70	15%	0%

H&R, Hanifin and Rajka's diagnostic criteria for AD; NA, not assessed.

The presence of IgE autoreactivity appears to be a phenomenon related to the severity and chronicity of AD, in fact in retrospective studies performed on adult patients with AD and IgE autoreactivity the frequency of early-onset forms is higher and in the pediatric population with moderate to severe forms of AD the prevalence of autoreactivity increases with increasing age and duration of the disease.³²

The presence of atopy seems to be an independent unrelated condition for the development of autoreactivity, as demonstrated by the fact that patients with allergic rhinitis or asthma do not exhibit this phenomenon^{15,29,33} and by the fact that there are many differences in the autoreactivity prevalence between extrinsic and intrinsic forms of AD.¹³ Clear evidence showing that autoreactivity could be a pathogenic factor for severe chronic allergic diseases is still lacking, and the only observation supporting this hypothesis is that the levels of IgE autoantibodies in AD patients correlate to the severity of the disease.

To define the exact role of autoreactivity in AD and to establish a cause-effect relationship between these two, however, further longitudinal case-control studies are needed. Demonstrating that autoreactivity plays a role in AD progression is important because such a finding might open up new therapies to inhibit the development and progression of autoimmunity.

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