

Autoimmunity and atopic dermatitis

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Purpose of review

It has been demonstrated that a considerable percentage of patients suffering from atopic dermatitis mount IgE autoantibodies against a broad variety of human proteins. This review summarizes evidence for autoimmune mechanisms in atopic dermatitis and suggests novel pathomechanisms that may be involved in this disease.

Recent findings

It has been shown that patients suffering from atopic dermatitis exhibit IgE autoreactivity to human proteins. These autoantigens are expressed in a variety of cell and tissue types.

Complementary DNAs coding for IgE autoantigens have been identified, cloned and characterized at the molecular level.

Using purified recombinant IgE autoantigens, it has been shown in paradigmatic models that IgE autoimmunity may be a pathogenetic mechanism in atopic dermatitis. Moreover, it has been shown that the levels of IgE autoantibodies are associated with severity of disease.

Summary

Patients suffering from severe manifestations of atopy mount IgE autoantibodies against a variety of human proteins. The levels of IgE autoantibodies correspond with disease severity. Several mechanisms of IgE autoimmunity may contribute to the pathogenesis of atopic dermatitis.

Keywords

atopic dermatitis, IgE autoreactivity, autoimmunity

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Abbreviations

α -NAC	α -chain of the human nascent polypeptide-associated complex
DFS70	dense fine speckles of 70 kD
LEDGF	lens epithelium-derived growth factor
MnSOD	manganese superoxide dismutase
Th1	T helper cell type 1
Th2	T helper cell type 2

Introduction

Atopic dermatitis is a chronic relapsing pruritic skin disease, which affects up to 5% of the adult population and up to 10% of children. It often progresses to asthma and allergic rhinitis later in life [1]. Atopic dermatitis is characterized by two phases: an initial phase with acute lesions, predominated by T helper cell type 2 (Th2) cytokines followed by a second Th1-dominated phase that is associated with eczematous chronic atopic dermatitis lesions. In this regard, atopic dermatitis is different from other forms of acute allergic manifestations, as it exhibits a mixture of type I and type IV-like hypersensitivity reactions. The Th1 response is associated with the predominance of interferon- γ and IL-12, whereas the Th2 immune response is associated with the predominance of IL-4, IL-5 and IL-13 [2].

Patients with atopic dermatitis often have elevated serum IgE levels and sensitization against a variety of environmental allergens, but there is also evidence that exacerbation of the disease occurs in the absence of exposure to environmental allergens [3].

The discovery of similarities between exogenous allergens and human proteins and the demonstration of IgE autoreactivity led to the reinvestigation of the earlier described observation that certain allergic patients mount IgE reactivity against human proteins. After the discovery of profilin as an IgE-defined autoantigen [4], other groups searched for IgE cross-reactivity between exogenous and endogenous antigens [5–7]. At the same time it was shown that a high percentage of patients suffering from atopic dermatitis display IgE autoreactivity to a broad spectrum of human proteins, which are expressed in a variety of cell and tissue types [8]. In contrast, atopic persons suffering from mild forms of allergy such as allergic rhinoconjunctivitis as well as healthy individuals failed to display IgE autoreactivity [8]. Moreover it has been demonstrated that the levels of IgE autoantibodies corresponded with severity of chronic atopic disease [9,10]. So far, it has been impossible to identify major IgE-defined autoantigens because patients suffering from severe forms of atopy display IgE autoreactivity against a broad variety of autoantigens. Nevertheless, several IgE autoantigens have been identified by complementary DNA cloning and were expressed as recombinant autoantigens (Table 1) [9]. The timeline in Fig. 1 summarizes the observations regarding autoimmunity in atopy.

Structural similarities between exogenous allergens and human proteins: cross-reactivity between environmental and human proteins

Molecular analysis of environmental allergens has revealed structural and functional similarities between exogenous, environmental allergens and human proteins [4–7,11]. Humoral and cell-mediated autoreactivity to cross-reactive human proteins has been demonstrated for profilin, an ubiquitous actin-binding protein. It was shown that IgE antibodies from allergic individuals bind to human profilin, in addition human profilin induced histamine release from blood basophils of profilin-allergic individuals [4]. Several years later, it was shown that manganese superoxide dismutase (MnSOD), an enzyme that catalyzes the dismutation of superoxide radicals [5], ribosomal P2 protein [6] and cyclophilins [7] were able to bind IgE antibodies from sera of patients

sensitized to the corresponding allergens of the mould, *Aspergillus fumigatus*. Human and *A. fumigatus* MnSOD as well as ribosomal P2 protein induced the proliferation of peripheral blood mononuclear cells in *A. fumigatus*-allergic individuals. Moreover recombinant human MnSOD, P2 protein as well as cyclophilin B elicited immediate type skin reactions in patients sensitized to the homologous mould proteins [5–7]. The latter findings demonstrated that a high degree of sequence homology between exogenous allergens and their homologous human proteins is responsible for cross-reactivity. However, similarity at the structural levels without close sequence similarity (i.e. molecular mimicry) may also be responsible for cross-reactivity [12,13]. Despite the observation of cross-reactivity, it was not clear whether IgE cross-reactivity between environmental allergens and human proteins represents a pure epiphenomenon or is associated with certain diseases or disease manifestations.

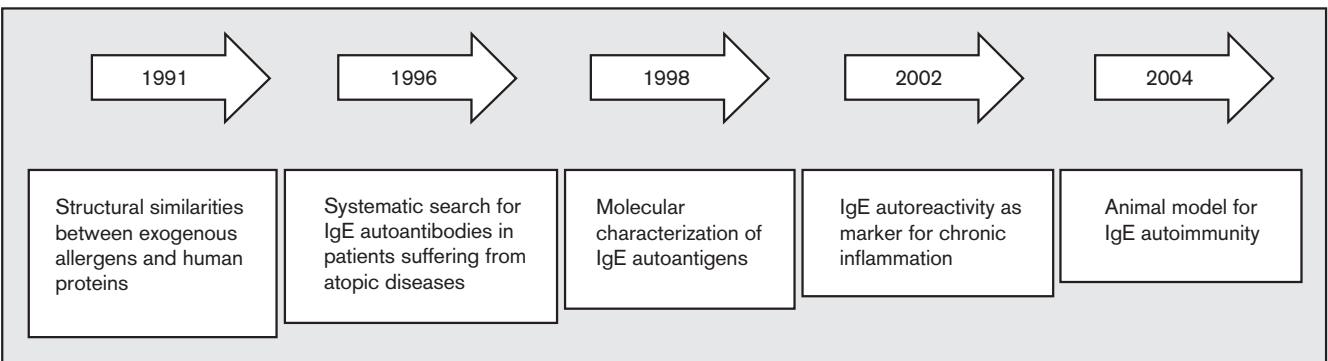
Table 1. Human IgE-reactive autoantigens associated with atopic dermatitis

Autoantigens	Sequence identity, function	References
Hom s 1	Sequence identity with SART-1, an antigen recognized by cytotoxic T cells of carcinoma patients	[15]
Hom s 2	Alpha-chain of the human nascent polypeptide-associated complex, required for signal-specific sorting and translocation of intracellular proteins, phylogenetically well conserved	[9,17,35]
Hom s 3	Sequence identity with the human BCL7B protein, described as putative oncogene	[9]
Hom s 4	Calcium-binding protein, phylogenetically well conserved	[9]
Hom s 5	Cytokeratin type II, a component of the mammalian cytoskeleton	[9]
DFS70/LEDGF	Dense fine speckles protein 70 also described as lens epithelium-derived growth factor and transcriptional coactivator	[20]

Characterization of IgE-reactive autoantigens

To explore the possible relevance of IgE autoreactivity, a systematic search for IgE autoantibodies was carried out for patients suffering from a variety of immunologically-mediated disease manifestations (e.g. atopic dermatitis, allergic rhinoconjunctivitis, urticaria, autoimmune diseases) [8]. The latter study demonstrated that IgE autoreactivity occurs frequently in patients suffering from severe and chronic forms of atopy (e.g. atopic dermatitis). A recent study [14] confirmed these findings. In order to reveal the molecular nature of IgE-defined autoantigens, a systematic approach was taken later on. Using serum IgE autoantibodies from atopic dermatitis patients, complementary DNAs coding for IgE-reactive autoantigens were isolated from human expression complementary DNA libraries and further characterized (Table 1). To date five IgE-autoallergens have been described by cloning: (1) An autoallergen

Figure 1. Timeline



Evidence for autoimmunity in atopic dermatitis.

designated Hom s 1 was highly expressed in epidermis as well as in other target organs of atopy (lung, gastrointestinal tract) [15]. Hom s 1 exhibited almost complete sequence identity with SART-1, an autoantigen recognized by cytotoxic T cells of patients suffering from squamous esophageal cancer [16]. (2) Hom s 2 is the α -chain of the human nascent polypeptide-associated complex (α -NAC). Similar to chaperonins, Hom s 2 is involved in sorting and translocation of intracellular proteins and may also act as a transcriptional coactivator [9,17]. Alpha-NAC is a remarkable thermostable protein that induced specific lymphoproliferative responses in peripheral blood mononuclear cells of a sensitized atopic dermatitis patient [17]. (3) Hom s 3, BCL7B, is a possible oncogene [9]. (4) Hom s 4 is a so far undescribed protein containing calcium-binding domains in its sequence [9]. (5) Hom s 5 forms the central portion of human cytokeratin type II (Table 1) [9].

All these autoallergens represent intracellular proteins that are expressed in a broad variety of tissues and cell types and fulfil important biological functions. The question of whether intracellular autoantigens may contribute to disease was addressed by experiments searching for the presence of IgE–autoallergen immune complexes in sera of atopic dermatitis patients. In fact, some of the IgE–autoantigens (Hom s 1, Hom s 3) were detected in the form of circulating IgE immune complexes in sera of sensitized patients [9,15]. The latter finding indicated that circulating IgE–autoallergen complexes may reach target organs of atopy and bind via Fc ϵ -receptors to effector and inducer cells of atopy and induce allergic reactions in places distant from their release.

Characterization of IgG-reactive autoantigens

Serum antinuclear antibodies in patients with systemic rheumatic diseases such as systemic lupus erythematosus, scleroderma and Sjögren's syndrome are well known and their profile is known to be highly characteristic for each disease [18]. Recently, antibodies against nuclear proteins were also described in patients with atopic dermatitis [19,20]. It was found that about 30% of atopic dermatitis patients contained antinuclear antibodies, but there was no correlation between positive antinuclear antibodies and high IgE levels, eosinophilia, disease duration, or the presence of respiratory atopy. Moreover, antinuclear antibodies were also found in 20% of sera from healthy individuals [21].

IgG as well as IgE antibodies against a 70 kD antigen (DFS70) were found in atopic dermatitis patients, particularly in patients with facial dermatitis [20]. DFS70 was originally characterized as a nuclear antigen in patients with interstitial cystitis, an inflammatory

disease of the bladder [22]. But DFS70 was also recognized by autoantibodies in other atopic or inflammatory diseases, such as asthma [20], age-related cataracts [23], and Vogt-Koyanagi-Harada disease [24]. DFS70 is also described as transcriptional coactivator p75 [25] and as lens epithelium-derived growth factor (LEDGF). DFS70/LEDGF is present predominantly in the nucleus of actively dividing cells and it is expressed in various human tissues [23–25]. It was shown that LEDGF stimulates growth and survival of many cell types and that anti-LEDGF antibodies induce apoptosis of fibroblasts, keratinocytes and lens epithelial cells [23,26]. Moreover LEDGF is overexpressed after heat and oxidative stress and is able to activate the expression of stress-related genes [27].

Furthermore, it has been shown that LEDGF undergoes caspase-mediated cleavage during apoptotic cell-death and that this cleavage abrogates its pro-survival function [28]. This cleavage alters the function of LEDGF and enhances its immunogenicity by creating newly accessible epitopes [28]. The latter has also been previously suggested for IgE-reactive autoantigens [29,30].

IgE autoimmunity and exacerbation of atopic dermatitis: IgE autoreactivity, a marker for chronic inflammation

Atopic dermatitis patients with IgE autoantibodies tended to suffer from more severe cutaneous manifestations than those patients without detectable IgE autoantibodies, and IgE autoreactivity increased when skin symptoms were aggravated in response to contact with environmental allergens [9,30]. During exacerbation of skin manifestations, IgE autoantibody levels increased strongly [9,10]. A remarkable reduction of IgE antibody reactivity to human proteins was observed in an atopic dermatitis patient during systemic cyclosporin A treatment [10]. The improvement of skin lesions was associated with a reduction of IgE autoreactivity. When skin symptoms worsened during exogenous allergen contact, IgE autoreactivity increased [10]. All of the latter findings indicated that IgE autoreactivity can serve as a diagnostic parameter for chronic atopic inflammation.

How IgE autoreactivity may contribute to disease

At least two possible pathomechanisms depending on IgE autoreactivity may be considered. First, it is possible that autoallergens may cross-link effector cell bound IgE autoantibodies and lead to immediate type allergy symptoms by the release of inflammatory, anaphylactogenic mediators. Support for this idea comes from the finding that IgE autoantigens caused histamine release from basophils and induced immediate type skin reactions [4–7]. In this context it has also been studied

whether IgE autoantigens may be related to IgE-dependent histamine releasing factors. IgE-dependent histamine release activity has been defined as the property of sera from atopic patients to activate basophils without addition of allergens [31,32]; it was therefore tempting to speculate that this could be caused by immune complexes found between IgE and autoallergens. However, the outcome of a recently performed study was that IgE autoreactivity and IgE-dependent histamine release activity seemed to represent rather distinct phenomena that are not related with each other [33].

The second possibility of how IgE autoreactivity and IgE autoantigens may contribute to disease is activation of autoreactive T cells. On the one hand, autoreactive T cells may be activated via IgE antibody-mediated presentation of autoallergens by dendritic cells or monocytes. Alternatively, it is possible that IgE autoantigens activate T cells via non-IgE dependent mechanisms. The presence of T cells recognizing IgE autoantigens has indeed been demonstrated in atopic patients [17]. Another possibility to study the pathological relevance of autoreactivity is the use of animal experiments. The criteria of Rose state that autoreactivity is of pathogenic relevance if the following conditions can be fulfilled: evidence for transfer of pathogenetic antibodies or pathogenetic T cells; reproduction of the autoimmune disease in experimental animal models by immunization with autoantigens and diagnosis of autoimmune disease from clinical clues [34].

Very recently it was shown that sensitization of mice with the highly conserved IgE autoantigen α -NAC induced immediate as well as chronic manifestations of atopy in a murine model [35]. Mice immunized with human or murine α -NAC exhibited IgE autoreactivity, IgE-dependent immediate type skin reactions and symptoms of asthma. Interestingly, autosensitized mice developed a mixed pattern of Th2 and Th1 autoreactivity as observed in patients containing IgE autoantibodies and who suffer from severe and chronic forms of atopy. The latter study was therefore the first to demonstrate that IgE autosensitization can cause disease in an experimental animal model [35].

Conclusion

There is increasing evidence that IgE autoreactivity, as well as other autoimmune phenomena, frequently occur in atopic dermatitis and may be associated with severity of disease. Moreover it has been shown that autosensitization can induce a mixed Th2/Th1 autoimmunity in mice similar to that observed in atopic dermatitis. All these findings point to a possible role for IgE autoreactivity in the pathogenesis of atopic dermatitis.

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References

- 1 Leung DY. Atopic dermatitis: new insights and opportunities for therapeutic intervention. *J Allergy Clin Immunol* 2000; 105:860–876.
- 2 Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003; 36:151–160.
- 3 Leung DY. Role of IgE in atopic dermatitis. *Curr Opin Immunol* 1993; 5:956–962.
- 4 Valenta R, Duchene M, Pettenburger C, et al. Identification of profilin as a novel pollen allergen: IgE autoreactivity in sensitized individuals. *Science* 1991; 253:557–560.
- 5 Cramer R, Faith A, Hemmann S, et al. Humoral and cell-mediated autoimmunity in allergy to *Aspergillus fumigatus*. *J Exp Med* 1996; 184:265–270.
- 6 Meyer C, Appenzeller U, Seelbach H, et al. Humoral and cell-mediated autoimmune reactions to human acidic ribosomal P2 protein in individuals sensitized to *Aspergillus fumigatus*. *J Exp Med* 1999; 189:1507–1512.
- 7 Appenzeller U, Meyer C, Menz G, et al. IgE-mediated reactions to autoantigens in allergic diseases. *Int Arch Allergy Clin Immunol* 1999; 118:193–196.
- 8 Valenta R, Maurer D, Steiner R, et al. Immunoglobulin E responses to human proteins in atopic patients. *J Invest Dermatol* 1996; 107:203–207.
- 9 Natter S, Seiberler S, Hufnagl P, et al. Isolation of cDNA clones coding for IgE autoantigens with serum IgE from atopic dermatitis patients. *FASEB J* 1998; 12:1559–1569.
- 10 Kinaciyan T, Natter S, Kraft D, et al. IgE autoantibodies monitored in a patient with atopic dermatitis under cyclosporin A treatment reflect tissue damage. *J Allergy Clin Immunol* 2002; 109:717–719.
- 11 Spitzauer S, Schweiger C, Sperr WR, et al. Molecular characterization of dog albumin as a cross-reactive allergen. *J Allergy Clin Immunol* 1994; 93:614–627.
- 12 Fedorov AA, Ball T, Mahoney NM, et al. The molecular basis for allergen cross-reactivity: crystal structure and IgE epitope mapping of birch pollen profilin. *Structure* 1997; 5:33–45.
- 13 De Marino S, Morelli MAC, Fraternali F, et al. An immunoglobulin fold in a major plant allergen: the solution structure of Phl p 2 from timothy grass pollen. *Structure* 1999; 7:943–952.
- 14 Kortekangas-Savolainen O, Peltonen S, Pummi K, et al. IgE-binding components of cultured human keratinocytes in atopic eczema/dermatitis syndrome and their crossreactivity with *Malassezia furfur*. *Allergy* 2004; 59:168–173.
- 15 Valenta R, Natter S, Seiberler S, et al. Molecular characterization of an autoallergen, Hom s 1, identified by serum IgE from atopic dermatitis patients. *J Invest Dermatol* 1998; 111:1178–1183.
- 16 Shichijo S, Nakao M, Imai Y, et al. A gene encoding antigenic peptide of human squamous cell carcinoma recognized by cytotoxic T lymphocytes. *J Exp Med* 1998; 187:277–288.
- 17 Mossabeh R, Seiberler S, Mittermann I, et al. Characterization of a novel isoform of α -nascent polypeptide-associated complex as IgE-defined autoantigen. *J Invest Dermatol* 2002; 119:820–829.
- 18 von Muhlen CA, Tan EM. Autoantibodies in the diagnosis of systemic rheumatic diseases. *Semin Arthritis Rheum* 1995; 24:323–358.
- 19 Ohkouchi K, Mizutani H, Tanaka M, et al. Anti-elongation factor-1 α autoantibody in adult atopic dermatitis patients. *Int Immunol* 1999; 11:1635–1640.
- 20 Ochs RL, Muro Y, Si Y, et al. Autoantibodies to DFS 70 kD/transcription coactivator p 75 in atopic dermatitis and other conditions. *J Allergy Clin Immunol* 2000; 105:1211–1220.
- 21 Watanabe A, Kodera M, Sugiura K, et al. Anti-DFS70 antibodies in 597 healthy hospital workers. *Arthritis & Rheumatism* 2004; 50:892–900.
- 22 Ochs RL, Stein TW, Peebles CL, et al. Autoantibodies in interstitial cystitis. *J Urol* 1994; 151:587–592.
- 23 Singh DP, Ohguro N, Kikuchi T, et al. Lens epithelium-derived growth factor: effects on growth and survival of lens epithelial cells, keratinocytes, and fibroblasts. *Biochem Biophys Res Commun* 2000; 267:373–381.

- 24 Yamada K, Senju S, Shinohara T, *et al.* Humoral immune response directed against LEDGF in patients with VKH. *Immunology Lett* 2001; 78:161–168.
- 25 Ge H, Si Y, Roeder RG. Isolation of cDNAs encoding novel transcriptional coactivators p52 and p75 reveals an alternate regulatory mechanism of transcriptional activation. *EMBO J* 1998; 17:6734–6729.
- 26 Ayaki M, Sueno T, Singh DP, *et al.* Antibodies to lens epithelium-derived growth factor (LDGF) kill epithelial cells of whole lenses in organ culture. *Exp Eye Res* 1999; 69:139–142.
- 27 Singh DP, Fatma N, Kimura A, *et al.* LEDGF binds to heat shock and stress-related element to activate the expression of stress-related genes. *Biochem Biophys Res Comm* 2001; 283:943–955.
- 28 Wu X, Daniels T, Molinaro C, *et al.* Caspase cleavage of the nuclear autoantigen LEDGF/p75 abrogates its pro-survival function: implications for autoimmunity in atopic disorders. *Cell Death Differ* 2002; 9:915–925.
- 29 Seiberler S, Bugajska-Schretter A, Hufnagl P, *et al.* Characterization of IgE-reactive autoantigens in atopic dermatitis. 1. Subcellular distribution and tissue-specific expression. *Int Arch Allergy Immunol* 1999; 120:108–116.
- 30 Seiberler S, Natter S, Hufnagl P, *et al.* Characterization of IgE-reactive autoantigens in atopic dermatitis. 2. A pilot study on IgE versus IgG subclass response and seasonal variation of IgE autoreactivity. *Int Arch Allergy Immunol* 1999; 120:117–125.
- 31 MacDonald SM, Rafner T, Langdon J, Lichtenstein LM. Molecular identification of an IgE-dependent histamine-releasing factor. *Science* 1995; 269:688–690.
- 32 Schroeder JT, Lichtenstein LM, MacDonald SM. An immunoglobulin E-dependent recombinant histamine-releasing factor induces interleukin-4 secretion from human basophils. *J Exp Med* 1996; 183:1265–1270.
- 33 Budde IK, de-Heer PG, Natter S, *et al.* Studies on the association between immunoglobulin E autoreactivity and immunoglobulin E-dependent histamine-releasing factors. *Immunology* 2002; 107:243–251.
- 34 Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). *Immunol Today* 1993; 14:426–430.
- 35 Buender R, Mittermann I, Herz U, *et al.* Induction of auto-allergy with an environmental allergen mimicking a self protein in a murine model of experimental allergic asthma. *J Allergy Clin Immunol* (in press).