

Review article

Autoantibodies in atopic dermatitis

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Abstract

Recent progress in the autoimmune aspects of atopic dermatitis has clarified that patients with atopic dermatitis develop IgE-class autoantibodies mainly against intracellular proteins. The cloning of cDNAs encoding autoallergens with human expression cDNA libraries and serum IgE from atopic dermatitis patients has unraveled the molecular characteristics of IgE-binding autoantigens. Some patients with atopic dermatitis also have IgG-class autoantibodies, especially anti-nuclear antibodies. One of the nuclear autoantigens was identified as DFS70/transcription coactivator p75. In addition, p80-coilin in nuclear coiled bodies is also targetted. Several lines of evidence suggest that a subset of atopic dermatitis may be associated with an autoimmune response. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Atopy is an immune disorder of hypersensitivity to common, rather innocuous environmental antigens derived from agents such as pollen and house dust mites. It is the leading cause of asthma, rhinitis, and atopic dermatitis (AD). However, allergic mechanisms do not play a central pathogenic role in AD [1,2]. For example, elevated total serum IgE or antigen-specific sensitivities are not essential for the development of

dermatitis and are frequently absent in those without coexisting respiratory atopy. Hanifin summarized four current hypotheses concerning the cause of AD in his review [3]: (1) cyclic nucleotide dysfunction; (2) the role of superantigen; (3) IgE-mediated allergy to airborne and food allergens; and (4) autoimmunity to self-antigens.

During the past 10 years, several IgE-binding autoantigens have been characterized using biochemical and molecular biological methods and there is increasing evidence that IgE-mediated reactivity against autoantigens could play a role in the pathology of severe atopic conditions [4,5]. Recent progress in the autoimmune and autoallergic aspects of AD are reviewed in this article.

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2. Anti-IgE autoantibodies

Circulating anti-IgE autoantibodies have been demonstrated in the sera of a large portion of individuals with atopic disease [6–8] and to a lesser extent in normal individuals [9,10]. According to previous reports, the proportion of the anti-IgE autoantibodies in AD patients was > 50% [8] or > 80% [7,11]. However, one of the major problems in determining anti-IgE antibodies is the fact that the antigen (IgE) coexists with the autoantibody in approximately equimolar concentrations, forming immune complexes in vivo [12] or in vitro [13].

Although anti-IgE antibodies have been considered anaphylactogenic, the histamine releasing activity of the antibodies are controversial [11,14]. Because of the difficulty in purifying anti-IgE autoantibodies, which exist mostly in the form of immune complexes with IgE in serum and only in very small quantities [12,15], estimations of the biological activities of the antibodies have not been established. Anti-IgE antibodies have been also shown to vary greatly in their capacity to inhibit IgE synthesis [16]. An epitope mapping study by Czech et al. [17] demonstrated that anti-IgE antibodies from AD patients recognize mainly the CH3 domain.

3. IgE-class autoantigens

More than 50 years ago, it was reported that human dander extract can elicit immediate-type skin reactions in AD patients and that human skin extracts can induce the proliferation of leukocytes in AD patients [5]. After 1990, cloning and sequencing of environmental allergen-encoding cDNAs revealed that some environmental allergens shared structural and functional similarities with human proteins. Many investigators have been using an isolating system of cDNA encoding an allergenic protein with serum IgE from sensitized individuals and a cDNA library derived from the antigenic species. And various novel allergens were reported, such as white birch and human profilin which induce histamine release from blood basophils of profilin-allergic individuals [18].

Cramer et al. isolated cDNAs encoding manganese superoxide dismutase (MnSOD) and ribosomal phosphoprotein type 2 (P2 protein) using serum IgE from *Aspergillus fumigatus*-sensitized individuals [19,20]. Both human and *Aspergillus fumigatus*-MnSOD and P2 protein induced the proliferation of peripheral blood mononuclear cells in *Aspergillus fumigatus*-allergic subjects. Moreover, recombinant human MnSOD and P2 protein elicited strong type 1-specific skin reactions in these individuals. They demonstrated humoral and cell-mediated autoreactivity to the corresponding human proteins in vitro and in vivo. Inhibition studies showed that patients' IgE-class autoserum recognized common epitopes between human and other species. Actually, sera of MnSOD-sensitized individuals recognized various species of MnSOD including the *Drosophila* enzyme [21] which is rarely exposed to the human immune system. Although this indicates molecular mimicry as a mechanism for the cross-reactivity, in the case of albumin which has very high sequence identity (> 70%) between animals and human, mammalian serum albumin-sensitized human sera did not recognize human serum albumin [22,23]. Sequence identities between human and birch profilin, human and *Aspergillus fumigatus*-MnSOD, and human and *Aspergillus fumigatus*-P2 are 34, 52 and 62%, respectively [4]. Interestingly, sensitization to P2 protein was found only in individuals with severe AD [20]. Ribosomal proteins including P2 are well known to be IgG-class autoantigens recognized by lupus sera and the major epitope resides in the C-terminus [24], while the IgE-class epitope has not been determined. For the above two fungal and human antigens, the serum IgE antibodies bind to human antigen with lower affinity than in the case of fungal antigens [22,23]. So far, it has not been clearly shown whether these autoantigens described above maintain hypersensitivity as actual boosters or whether they can be released at the site of inflammation and cause tissue damage.

Valenta's group has succeeded in directly obtaining cDNAs coding for 'autoallergens' using IgE antibodies from an AD and human cDNA library [5] using a methodology that was established when Chambers and Keene cloned the

cDNA of nuclear autoantigen (SS-B/La) in 1985 [25]. Their published IgE-class autoallergens are summarized in Table 1. These autoantigens are intracellular proteins, mostly cytoplasmic proteins. In immunohistochemistry, the protein expression of Hom s 1 was strong in skin and weaker in other tissues [26]. Anti-Hom s 1 stained skin sections prominently in the epidermis from lesional skin biopsies of AD patients as well as those from normal skin of healthy controls. Since circulating immune complexes (Hom s 1-IgE or Hom s 3-IgE) were detected in sera of AD patients [26,27], intracellular IgE autoantigen appears to be released into the circulation and to occur as IgE immune complexes, which may reach target organs of AD and lead to the release of biological mediators through the binding to effector cells (e.g. mast cells, basophiles, eosinophils). Actually, purified recombinant proteins of these IgE autoantigens induced immediate type skin reactions in AD patients [27]. In longitudinal studies [27,28], IgE responses to autoallergens increased during periods of disease exacerbation in some patients, possibly due to boosting by seasonal exposure to exogenous allergens. Although these autoantigens shared no significant sequence homology with known exogenous antigens, AD patients with strong IgE autoreactivity frequently showed IgE antibodies against many different environmental allergens [27]. This might suggest that the formation of IgE autoantibodies occurs by the tissue damage that is probably induced by exoge-

nous allergens. The expression of IgE autoantigens in a variety of tissues [27,29] means that AD is not an organ-specific autoimmune disease. However, AD patients with IgE-class autoantibodies against human proteins frequently suffer from severe cutaneous manifestations [27,30].

4. Antinuclear antibodies

In systemic rheumatic diseases such as systemic lupus erythematosus, Sjogren syndrome, and scleroderma, the profile of serum antinuclear antibodies (ANA) in the patients is well known to be highly characteristic for each disease [31]. Recently, several laboratories in Japan have reported the presence of ANA in some patients with AD [32–35]. According to their reports, the characteristics of ANA in patients with AD can be summarized as follows: (1) The positivity is 25–35%. (2) The positive presence of ANA is more often seen in females than in males. (3) ANA titers in AD patients are not always low (1:40–1:80). Nearly half the patients have ANA at a titer of more than 1:160. (4) The patterns of their ANA are mostly speckled, homogeneous or homogeneous and speckled. More detailed descriptions of their patterns have not been reported. (5) There are no correlations between positive ANA and a high IgE level, eosinophilia, disease duration, or the presence of respiratory atopy. (6) AD patients with severe facial lesions tend to have positive ANA.

Table 1
Human IgE-defined autoantigens cloned by Valenta et al.

Autoallergen	Molecule	MW (kDa)	Localization	Function
Hom s 1 ^a	SART-1	125	nuclei?	Recognized by cytotoxic T cells of a patient with squamous esophageal cancer
Hom s 2	α -NAC ^b	10	Cytoplasm	Sequence-specific sorting and translocation of intracellular proteins
Hom s 3	BCL7B	20	Cytoplasm?	A putative oncogene
Hom s 4	CALC	36 ^c	?	Possessing calcium-binding motif
Hom s 5	Cytokeratin II	43	Cytoplasm	Formation of intermediate filaments in epithelial tissues

^a Cloned DNA encodes a 73 kDa protein and anti-Hom s 1 antibody reacted to ~55kDa polypeptide in the tissue extracts. The antibody showed that Hom s 1 antigen resides in the cytoplasm [26].

^b α chain of the nascent polypeptide-associated complex.

^c Partial clone encodes 36 kDa polypeptide.

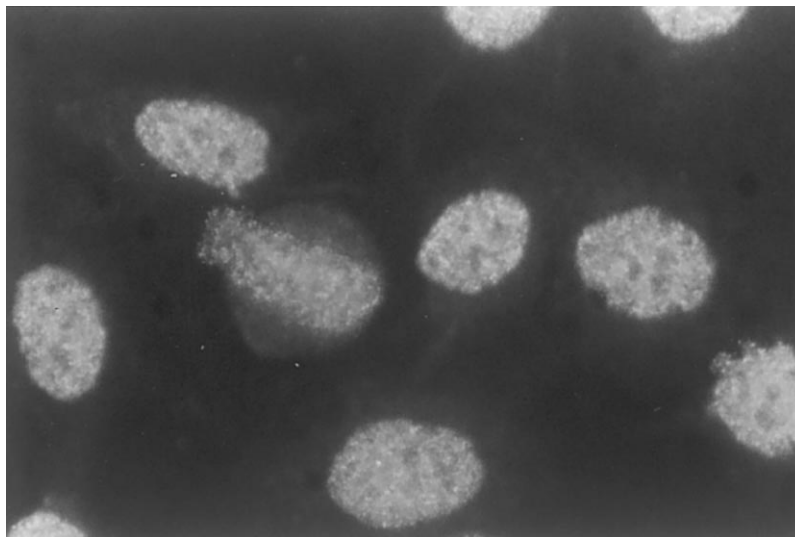


Fig. 1. Immunofluorescence on HEp-2 cells with anti-DFS70 antibodies from an atopic dermatitis patient.

5. Anti-DFS70 antibodies and DFS70 antigen

DFS70 is a major IgG-class autoantibody/autoantigen system in AD that we recently reported [36]. In immunohistochemistry, sera from AD patients displayed a characteristic pattern showing a nuclear distribution of dense, fine speckles as the most common ANA pattern (Fig. 1). The sera also recognized a 70-kDa protein on immunoblots (Fig. 2), and therefore the antigen was termed dense fine speckles 70 (DFS70).

Initially, the cDNA encoding DFS70 was cloned with ANA from an interstitial cystitis (IC) patient. IC is a chronic inflammatory disease of the bladder characterized by bladder pain and urinary frequency and urgency [37]. Although the cause of IC is currently unknown, allergic disorders are known to be a major complaint in IC and the pathology is characterized by a predominantly mononuclear cell infiltration with increased numbers of mast cells. We compared the prevalence of the antibody in various disease conditions including AD and IC using the recombinant protein on immunoblotting [36]. Nearly 30% of Japanese AD patients, 16% of American patients with asthma and 9% of American patients with IC had anti-

DFS70 antibodies, while patients with classical systemic autoimmune disease, psoriasis or normal controls rarely had the antibodies. Although anti-DFS70 antibody was found significantly more often in females (14/34) than in males (5/30), there was no significant relationship between the presence of the antibody and parameters of age, disease duration, IgE levels, eosinophilia, and respiratory atopy. Notably, 16/18 AD patients with DFS70 autoantibodies had facial dermatitis. Also, very interestingly, IgE-class anti-DFS70 autoantibody was also found in some AD patients.

When the DFS70 cDNA which we cloned was deposited in GenBank (No. U94319) in 1997, there were no identical sequences reported. However, in 1998, two groups independently published identical clones to DFS70. One is called 'transcription coactivator p75' [38] and another is lens epithelium-derived growth factor (LEDGF) [39]. Ge et al. isolated cDNAs encoding two transcriptional coactivators (p52 and p75) which are derived from alternatively spliced products of a single gene [38]. p52 (333 amino acids) and p75 (530 amino acids) have 325 common amino-terminal amino acids. Although both these proteins possess functions as transcriptional coactivators

in an *in vitro* transcription system dependent on RNA polymerase II and general transcription factors, p75 was less active for most activation domains [38]. p52 also has an interaction with the essential splicing factor ASF/SF2 to modulate ASF/SF2-mediated pre-mRNA splicing, while p75 has no such activities [40]. Interestingly, anti-DFS70 autoantibodies recognized exclusively the cellular p75 isoform [36], suggesting that the autoepitope was located in the C-terminal region of p75, which is defective in p52. Singh et al. obtained cDNA of LEDGF using the serum of a patient with age-related cataracts [39]. They have shown interesting experimental data [41,42]: (1) LEDGF was secreted to the extracellular space in lens epithelial cells, then bound to the cell surface and transferred to the cytoplasm, nucleus and nucleolus; (2) the addition of LEDGF to lens epithelial cell cultures stimulated cell growth; (3) the addition of rabbit antibodies to LEDGF induced the cell death of

fibroblasts and lens epithelial cells in culture; and (4) overexpression of LEDGF in cultured lens epithelial cells stimulated the expression of heat shock protein 27 and α B-crystallin, and conferred resistance to thermal and oxidative stress. As it is well-known that cataracts and other ocular symptoms sometimes complicate with AD [43], it is necessary to clarify the pathological relationships among the anti-DFS70 antibody, LEDGF (DFS70) and the development of cataracts in AD patients.

6. Anti-p80-coilin antibodies

In this review, I would like to describe another autoantibody specificity, p80-coilin, that was characterized recently in our laboratory [44]. Although the autoantibodies are also recognized in other diseases [45,46], our current data suggest that a number of AD patients have the antibodies. p80-coilin is the major autoantigen in the nuclear coiled body which is a round structure found in most eukaryotic cells [47]. Autoantibodies to p80-coilin recognize mostly one or two nuclear bodies with a maximum of eight bodies per interphase cell in immunofluorescent studies (Fig. 3) and an 80-kDa nuclear protein on immunoblotting (Fig. 2). p80-coilin is thought to play a role in RNA processing and cellular trafficking, especially in relation to coiled bodies and nucleoli [47]. According to our published data, three of 64 AD patients had anti-p80-coilin antibodies [44]. Of an additional 67 AD patients studied, three had the same antibody specificities (unpublished data). These six patients with anti-p80-coilin antibodies, who had typical symptoms of AD, were female except for one, but hyper IgE did not always exist in them. Previous surveys of various diseases showed that anti-p80-coilin antibodies were present in 3–4% of Sjogren syndrome, primary biliary cirrhosis or localized scleroderma [45,46]. Although further work is needed to identify the relationship between anti-coiled body antibodies and AD, the presence of anti-p80-coilin antibodies in AD patients (~5%) is not rare compared to other diseases.

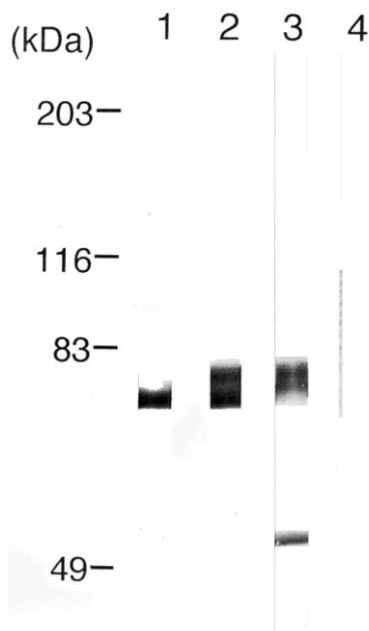


Fig. 2. Immunoblotting of three selected sera from atopic dermatitis patients with HeLa cell extracts as the antigen. A 7.5% polyacrylamide gel was used. Lane 1, anti-DFS70 antibody; lane 2, anti-p80-coilin antibody (see section 6); lane 3, coexisting anti-DFS70 antibody and anti-p80-coilin antibody; lane 4, normal control.

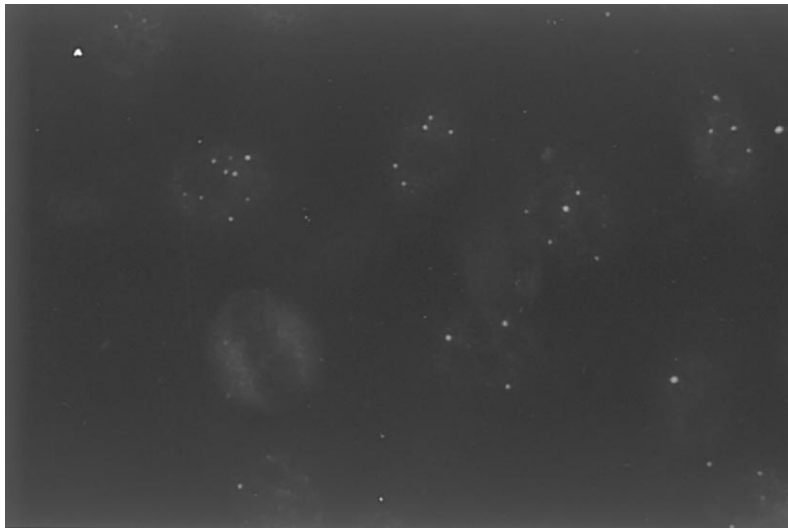


Fig. 3. Immunofluorescence on HEp-2 cells with anti-p80 coilin antibodies from an atopic dermatitis patient.

7. Pathological significance of autoantibodies in AD

Recent studies on autoimmunity in AD suggest that a subset of AD may be associated with an autoimmune response. Valenta et al. noted in their review [5] two possible pathomechanisms of auto allergy. One is that autoallergens may cross-link effector cell-bound IgE autoantibodies and lead to immediate-type symptoms by the release of inflammatory mediators. Second is that IgE-mediated presentation of autoallergens may activate autoreactive T cells to release proinflammatory cytokines, inducing delayed-type reactions. IgE autoimmunity could contribute to chronicity or exacerbation in AD even in the absence of environmental allergens. For some autoantibodies, the structural similarity of conserved proteins might be responsible for maintaining IgE antibody titers in type I allergy. Although most autoantigens are intracellular components, the damaged tissue of AD skin might induce the release of autoantigens which then become available to IgE antibodies. As for DFS70, the secretory form could be also considered according to studies on LEDGF [41,42].

In Japan, AD is a major health problem and adult AD patients with persistent and treatment-

resistant eczematous lesions of the face are increasing [48]. The pathomechanisms by which the recalcitrant facial erythema is produced remain obscure. Multiple exacerbating factors, such as topical corticosteroids, environmental irritants, allergens, sunlight, and stress, may have a relationship with the severity of this symptom. Considering reports on ANA in Japanese AD patients and the possible association between facial dermatitis and ANA, autoimmunity might be involved in the exacerbation of the inflammatory reactions. Further investigation is needed to determine how the factors described above influence autoantigens including DFS70.

The abnormal skin physiology with increased transepidermal water loss, xerosis of the skin and increased scaling forms a setting for the accumulation of *Staphylococcus aureus* on the skin which leads to mitogen-like or superantigen stimulation. In addition, chronic skin inflammation may cause some trouble in the impaired lymphocyte surveillance, which may make the patient especially liable to develop autoantibodies. The autoantibodies might not directly play a pathogenic role but the AD autoantigens could be disregulated in their function or localization, leading to the provocation of an immune response [49].

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