

Linking allergy to autoimmune disease

Rudolf Valenta¹, Irene Mittermann¹, Thomas Werfel², Holger Garn³ and Harald Renz³

¹ Division of Immunopathology, Department of Pathophysiology, Center for Physiology and Pathophysiology, Medical University of Vienna, A-1090 Vienna, Austria

² Department of Dermatology, Medical School Hannover, D-30449 Hannover, Germany

³ Department of Clinical Chemistry and Molecular Diagnostics, Philipps University of Marburg, D-35043 Marburg, Germany

Type I allergy is a classical Th2-driven hypersensitivity disease based on IgE recognition of environmental allergens. Exposure of allergic individuals to exogenous allergens leads to immediate type inflammation caused by degranulation of mast cells via IgE-allergen immune complexes and the release of inflammatory mediators, proteases and pro-inflammatory cytokines. However, allergic inflammation can occur and persist in the absence of exposure to exogenous allergens and might paradoxically resemble a Th1-mediated chronic inflammatory reaction. We summarize evidence supporting the view that autoimmune mechanisms might contribute to these processes. IgE recognition of autoantigens might augment allergic inflammation in the absence of exogenous allergen exposure. Moreover, autoantigens that activate Th1-immune responses could contribute to chronic inflammation in allergy, thus linking allergy to autoimmunity.

Allergy and autoimmunity: two mutually exclusive forms of hypersensitivity?

The formation of IgE antibodies against environmental antigens (i.e. allergens) is the hallmark of allergic disease [1–3]. Immune complexes consisting of IgE and allergens induce the release of inflammatory mediators, proteases and cytokines from mast cells and basophils leading to allergic inflammation within a few minutes [4]. The immediate type allergic inflammation is therefore, in principle, a Th2 cell- and IgE-dependent process (Box 1). Allergy is distinct from other hypersensitivity reactions that are mediated by antibody classes other than IgE, that is, Type II and Type III reactions and from the mainly cell-based Type IV immune reactions which are dominated by Th1 cell activation and underlie most autoimmune diseases [1]. According to the underlying T-cell response, IgE-mediated allergy can be regarded as a classical Th2 disease, whereas most other hypersensitivity and autoimmune diseases are dominated by the activation of Th1 cells, cytotoxic cells, complement and the production of inflammatory cytokines such as IFN- γ , IL-12 and IL-17 [5–7].

Epidemiological data indicate that the prevalence of both allergies and autoimmune diseases increase in parallel. Even if one assumes that the parallel increase of these hypersensitivities is caused by a reduction in immune regulatory networks, the parallel increase of Th2- and Th1-mediated diseases is puzzling because, in theory, conditions favouring Th2- or Th1-activation should bal-

ance and even counteract each other as is also proposed according to the hygiene hypothesis [8,9]. In general, conditions of allergy and autoimmunity can co-occur in patients, but it is quite surprising that in many allergic patients chronic allergic inflammation resembles features of a delayed-type, cell-based (Type IV) hypersensitivity which is normally a consequence of a Th1 cell activation [10,11]. Moreover, chronic allergic inflammation can be observed in allergic individuals even when they are not exposed to environmental allergens. Symptoms of chronic allergic inflammation mimicking Th1-like, delayed-type manifestations can be observed in the skin of allergic patients (i.e. atopic dermatitis [AD]), the upper and lower respiratory tract (i.e. chronic allergic rhino-sinusitis, chronic allergic asthma) and even in the gut [12–15]. The immigration of Th1 cells to skin lesions of AD patients seems to follow an initial Th2 activation and might be responsible for the induction of keratinocyte apoptosis leading to eczema [16–18]. Chronic forms of allergic inflammation typically respond better to T-cell targeted forms of therapy such as anti-CD4 treatment, cyclosporine and immunosuppressive drugs than to treatments neutralizing mast cell and basophil mediators or to anti-IgE strategies [14]. It also speaks against the involvement of IgE-dependent mechanisms in these manifestations, that allergen-derived peptides without IgE reactivity can induce chronic allergic inflammation by MHC-dependent T-cell activation [19].

Interestingly, we have found that patients suffering from such manifestations of chronic allergic inflammation, and in particular patients with AD, frequently mount IgE antibody responses against a variety of human proteins that are expressed in various cell types and tissues in addition to exogenous allergens [20]. Furthermore, we found that the magnitude of IgE autoreactivity is associated with disease activity and severity [21]. We have then studied the molecular nature of some of the IgE-reactive autoantigens and investigated the role of autoreactivity in allergy [21–23]. Several of the autoantigens were originally identified with IgE antibodies from allergic patients suffering from chronic allergic inflammation. Interestingly, some of these also turned out to be potent activators of Th1 and cytotoxic T-cell responses [24,25] (Heratizadeh, A. *et al.*, unpublished). Here, we propose that immune recognition of these autoantigens might contribute to allergic inflammation in the absence of exogenous allergen exposure. Moreover, recognition of IgE-reactive autoantigens, which potentially activate Th1 immunity, could explain the unusual Th1-like features of chronic allergic tissue inflammation

Box 1. Definitions: type I, II, III and IV hypersensitivity

Type I: immediate type reactions resulting from soluble antigen (i.e. allergen) interacting with cell-bound IgE.

Type II: antibody reactions with cells or extracellular matrix components leads to destruction by complement lysis or Fc-receptor-bearing cells (opsonisation).

Type III: immune complex reaction involves soluble antigen, IgG and complement.

Type IV: delayed type reactions are mediated by T cells and antigen presenting cells (APCs).

Atopy: a tendency to develop immediate-type hypersensitivity reactions to common allergens.

Allergy: the situation of 'changed reactivity' to antigenic stimulation resulting in immunity or hypersensitivity. Nowadays allergy is used synonymously with IgE-mediated hypersensitivity.

Autosensitization: IgE-mediated sensitization to autoantigens.

and explain the co-occurrence of allergy and autoimmunity in certain allergic manifestations. Allergy and autoimmunity, therefore, do not seem to represent mutually exclusive conditions.

IgE autoreactivity in allergy and autoimmunity

Long before the discovery of IgE antibodies, it was described that patients suffering from severe forms of allergy exhibit immediate type skin inflammation and lymphoproliferative responses to human dander extracts [26,27]. However, studies regarding the biochemical characterization of allergens indicated that reactivity to environmental allergens has a much more important role than recognition of human antigens in allergic disease. Therefore, the concept that autoreactivity could be a possible pathogenetic factor in allergy lost attention until the molecular analysis of environmental allergens revealed surprising sequence and immunological similarities with human proteins [28–32]. Furthermore, it was demonstrated that human proteins with structural similarity to exogenous allergens cross-reacted with allergen-specific IgE antibodies, induced IgE-mediated effector cell degranulation, skin responses and lymphoproliferative responses [28–32]. The occurrence of IgE autoreactivity was most pronounced in patients suffering from severe and chronic allergic inflammation, in particular in patients suffering from AD, a chronic inflammatory skin manifestation with features of a Th1 (i.e. Type IV delayed hypersensitivity reaction) [20,21]. By using IgE antibodies from patients with such chronic allergic manifestations, cDNAs coding for 'autoallergens' could be isolated and their molecular nature revealed [21,22].

Independent studies carried out in the field of autoimmunity showed that several autoantigens, which are involved in classical autoimmune diseases, also reacted with IgE antibodies (Table 1).

The nature and possible importance of IgE-reactive autoantigens

Table 1 provides an overview of IgE-reactive autoantigens, which have been described in the field of allergy and autoimmunity. Certain IgE-reactive autoantigens were

identified as human homologs of environmental allergens [28,30–34] (Table 1, yellow). These allergens represented mainly evolutionarily conserved proteins such as profilin, an actin-binding protein [28,29], serum albumin [32,33], manganese superoxide dismutase and a ribosomal protein [30,31,34]. The homologous autoantigens showed structural similarity with the corresponding exogenous allergens, and IgE-cross reactivity was detected in many cases. Furthermore, certain of these cross-reactive autoantigens induced cell activation and immediate and late phase skin reactions in sensitized individuals, however mostly to a much lower degree than the cross-reactive exogenous allergens [30,31]. According to the cross-reactivity hierarchy (i.e. exogenous allergens reacted stronger than the corresponding autoallergens), one might assume that this type of 'autoreactivity' is based mainly on cross-reactivity with the exogenous allergen. The reactivity to such cross-reactive endogenous antigens would, therefore, be initiated and triggered primarily by the exogenous allergen. Nevertheless, it is quite possible that 'autoreactivity' because of cross-reactivity might contribute to the maintenance of allergen-specific IgE-responses in the absence of exogenous allergen exposure, and it has been shown that IgE recognition of such cross-reactive endogenous antigens can cause inflammation [28,30,31].

Several classical autoantigens which are known as targets in rheumatoid arthritis, systemic lupus erythematosus (SLE), in addition to autoimmune diseases of the skin, gut, eye and endocrine glands, were also reported to react with IgE antibodies (Table 1, green). In the case of bullous pemphigoid, a chronic blistering skin disease, signs of urticaria are often observed and could be due to IgE-recognition of autoantigens. In this context, it has been shown that bullous pemphigoid IgE reproduces the early phase of lesion development in human skin grafted to athymic nude (nu/nu) mice [35]. However, for most of the other IgE-reactive autoantigens belonging to this second group, it has not been demonstrated that IgE reactivity contributes to the pathology of the disease or is associated with certain disease phenotypes or disease severity.

The third group of IgE-reactive autoantigens, which have been termed 'Hom s antigens' according to the international allergen nomenclature [36], was identified in a disease-oriented approach. Sera from patients with various manifestations of allergic disease and control populations were screened for the presence of IgE autoantibodies directed against human cells and tissues [20]. It turned out that the majority of patients (i.e. ~60%) with severe and chronic allergic symptoms, in particular patients suffering from atopic dermatitis (but not patients suffering from mild forms of respiratory allergy or non-allergic individuals) exhibited IgE autoreactivity. The intensity of IgE autoreactivity was associated with the severity of atopic disease and was reduced after successful anti-inflammatory treatment [20,21,37]. Both findings argue for an important role of IgE autoreactivity at least as a sign or marker of severe disease. Interestingly, IgE auto-sensitization could be detected already, early in childhood, and in certain cases IgE antibodies directed towards autoantigens were detected earlier than IgE antibodies towards exogenous allergens, indicating that

Table 1. IgE-reactive autoantigens in allergy and autoimmunity

IgE-reactive autoantigens	Disease association	Biological function other informations	Cellular distribution	Sequence identity	Tissue or organ distribution	Evolutionary conservation	Molecular weight	Refs
Profilin	Allergy	Actin-binding protein, participating in the phosphoinositide pathway and signal transduction	Intracellular	Profilins	All cells	Eukaryotic cells	12–17 kDa	[28]
Albumin	Allergy	Serum protein	Secreted Extracellular	Serum protein	Blood plasma, all tissues	Mammals	60–70 kDa	[32,33]
Manganese superoxide dismutase	Allergy Atopic dermatitis	Enzyme, that catalyzes the dismutation of superoxide radicals	Intracellular	Manganese Superoxide dismutases	All tissues	Eukaryotic cells	26.7 kDa	[30,34]
Acidic ribosomal P2 protein	Allergy	Required for the functional activity of ribosomes	Intracellular	Acidic ribosomal phosphoprotein type 2	All tissues	Eukaryotic cells	13 kDa	[31]
Hom s 1	Atopic dermatitis	Leucine zipper DNA-binding protein, induction of cell cycle arrest and apoptosis	Intracellular Nucleus	SART-1	Mammalian cells, skin, lung, liver, gastrointestinal tract, brain	Mammals	73.4 kDa	[22]
Hom s 2	Atopic dermatitis	Binds to newly synthesized polypeptide chains emerging from the ribosome	Intracellular	Alpha-chain of the nascent polypeptide associated complex	Mammalian cells, skeletal muscle, brain, skin, liver bone, lung	Eukaryotic cells	23.2 kDa	[21,39]
Hom s 3	Atopic dermatitis	Oncogene, upregulated in tumours	Intracellular	BCL7B	Mammalian cells, skeletal muscle, thymus, placenta, liver	Eukaryotic cells	20.1 kDa	[21]
Hom s 4	Atopic dermatitis	Binds calcium	Intracellular	Calcium-binding proteins	Mammalian cells, skin, lung, brain, bone marrow, colon, placenta, liver, heart, breast	Eukaryotic cells	54.2 kDa	[21,24]
Hom s 5	Atopic dermatitis	Formation of intermediate filaments	Intracellular	Cytokeratin type II	Epithelial cells	Mammals	42.6 kDa	[21]
Dense fine speckles 70 kDa, DFS70	Atopic dermatitis	Transcription coactivator, survival factor	Nucleus	Lens epithelium-derived growth factor, P75	Eye, keratinocytes, fibroblasts	Mammals	70 kDa	[52]
30 kDa protein	Atopic dermatitis	Unknown	Unknown	Unknown	Human epidermis	Unknown	30 kDa	[53]
Nuclear antigens	Rheumatoid arthritis, SLE	Unknown	Nucleus	Unknown	Granulocytes, non-organ-specific	Unknown	Unknown	[54,55]
Nucleic acid antigens	SLE	DNA, RNA, tRNA	Nucleus	Nucleic acid	All cells	Eukaryotic cells		[56,57]
Antigenic determinants on the Fc fragment of antibodies	Rheumatoid arthritis, SLE	Immunoglobulin	Extracellular	Immunoglobulins	Blood, body fluids	Vertebrates	120 kDa	[58,59]
Collagen	Rheumatoid arthritis	Extracellular matrix protein	Extracellular	Human collagen type II, bovine collagen types II, IX and XI	Cartilage, Connective tissue	Mammals	Unknown	[60,61]
Ro/SS-A	SLE foetal loss	Ribonucleoprotein	Nucleus and cytoplasm	DNA-binding protein	Most cells and tissues	Eukaryotic cells	52–60 kDa	[62]
Platelet antigens	Asthma	Unknown	Cell surface	Unknown	Platelets	Mammals	55, 68 kDa	[63]
BP180	Bullous pemphigoid	Cell-matrix adhesion molecule, cell surface receptor	Trans-membrane	Collagen type XVII	Skin (hemidesmosome), keratinocytes, brain	Mammals	180 kDa	[64,65]
BP230	Bullous pemphigoid	Adhesion junction plaque protein	Intracellular	Desmoplakin I	Skin (hemidesmosome), keratinocytes	Mammals	230 kDa	[66]
Dsg3 Desmoglein3	Pemphigus vulgaris	Cell adhesion, calcium-binding glycoprotein	Trans-membrane	Cadherin	Skin (desmosomal), epi-dermal keratinocytes	Vertebrates	115 kDa	[67]
Retinal S antigen	Uveitis	Binds to photoactivated-phosphorylated rhodopsin	Intracellular	Arrestin	Photoreceptors of the retina, pineal gland	Eukaryotic cells	48 kDa	[68]
GAD65	Stiffman syndrome Type 1 diabetes mellitus	Catalyses the conversion of glutamate to gamma-aminobutyric acid (GABA)	Intracellular	Glutamic acid decarboxylase	Pancreatic islet β cells, nervous system	Prokaryotic and eukaryotic cells	65.4 kDa	[69,70]
TSH receptor	Graves' disease Thyroid eye disease	Regulates the production of thyroid hormones	Trans-membrane	Thyrotropin receptor	Thyroid gland	Mammals	95–100 kDa	[71]
Thyro-peroxidase	Chronic urticaria Hashimoto's thyroiditis	Liberates iodine for addition onto tyrosine residues on thyroglobulin	Trans-membrane	Thyroperoxidase	Thyroid gland	Mammals	105 kDa	[72,73]
Thyroglobulin	Chronic urticaria	Storage of iodine	Secreted	Thyroglobulin	Thyroid gland	Mammals	660 kDa	[73]
Insulin, Growth-hormone, Erythropoietin, Calcitonin	Allergy	Peptide hormones	Secreted		Endocrine glands	Mammals	58 kDa	[74]
Tissue trans-glutaminase	Coeliac disease	Catalyses the cross linking of proteins, conjugation of polyamines to proteins	Intra- and extracellular	Protein-glutamine gamma-glutamyl transferase 2	Gut, kidney, retina, brain	Eukaryotic cells	24 kDa 34 kDa 34 kDa 75–85 kDa	[75]

Cross-reactive autoantigens comprising human homologs of environmental allergens are indicated in yellow. IgE-reactive autoantigens that have been originally isolated with sera from atopic individuals are coloured in purple. Autoantigens characterized in classical autoimmune diseases that were shown to react also with IgE are indicated in green. Blue and orange colours indicate intracellular and extracellular distribution of the autoantigens, respectively.

Abbreviations: BP, Bullous pemphigoid; GAD65, Glutamic acid decarboxylase isoform 65; Ro/SS-A, Ribonucleoprotein autoantigen Sjögren syndrome type A antigen; TSH, Thyroid-stimulating hormone.

IgE autoreactivity might be a result of a primary auto-sensitization [38].

To identify unambiguously the nature of the autoantigens, we screened a human cDNA library with IgE auto-antibodies from patients with severe atopic dermatitis and isolated cDNA clones coding for IgE-reactive autoantigens. These autoantigens were termed Hom s 1-Hom s 5 (Table 1, purple) and represented intracellular proteins (Table 1: intracellular antigens, blue; extracellular antigens, orange) which are expressed in different cell types and tissues [21]. Hom s 1 was found to be identical to a previously identified tumour antigen which induces strong cytotoxic T-cell responses [22]. Hom s 2 corresponded to the α chain of the nascent polypeptide associated complex, an evolutionarily conserved protein which is involved in ribosomal protein biosynthesis [25,39]. Hom s 3 is identical to the B cell lymphoma 7B protein (BCL7B) oncogene [21], Hom s 4 is a calcium-binding protein [21,24] and Hom s 5 is a cytokeratin type II [21]. The availability of purified recombinant autoantigens allowed us to study the possible role of autoreactivity using *in vitro* and *in vivo* models. When mice were sensitized with alum-adsorbed Hom s 2 or the corresponding murine protein according to a typical protocol used for allergic sensitization, autoimmunity could be induced leading to bronchial airway hyper-reactivity [40]. Furthermore, Hom s 2-sensitized mice developed IgE autoantibodies, IgE-mediated cutaneous hypersensitivity and lung inflammation associated with T-cell reactivity, demonstrating that auto-sensitization can indeed be a cause of inflammation and disease. Interestingly, Hom s 2-sensitized mice developed mixed lung pathology indicative of a Th2 and Th1 activation, and IgG autoantibody formation [40].

The latter finding was in agreement with results obtained from *in vitro* experiments performed with peripheral blood mononuclear cells (PBMC) and T cells from patients containing Hom s 2 or Hom s 4-specific IgE antibodies. In these experiments, Hom s 2 and Hom s 4 favoured the production of the Th1 cytokine interferon (IFN)- γ in PBMC cultures from atopic persons and even stronger in non-atopic persons, whereas exogenous allergens induced mainly the secretion of Th2 cytokines and consistently lower levels of IFN- γ [24,25]. These results were also confirmed at the level of T-cell lines and clones because Hom s 2-specific T cells mainly belonged to the Th1 phenotype and also Hom s 2-specific CD8 cells were identified (Heratizadeh, A. *et al.*, unpublished).

To address the question of whether autoantigen specific T cells might contribute to tissue injury, supernatants from IgE-reactive autoantigen-stimulated human PBMCs were analyzed for the presence of factors capable of damaging epithelial cells. It was found that supernatants from Hom s 2- and from Hom s 4-stimulated PBMCs contained high levels of IFN- γ and that these supernatants induced damage to respiratory epithelial cells *in vitro* in addition to keratinocytes in an IFN- γ -dependent manner [24,25]. Hom s 1, 3 and 5 have not yet been investigated regarding their ability to stimulate T cells or to cause tissue damage. However, Hom s 1 has been earlier identified as an important tumour antigen and as a prominent target for cytotoxic T cells [41]. Likewise, Hom s 3, the *BCL7B* oncogene and

Box 2. Mechanisms triggering auto-sensitization and IgE autoreactivity

Several mechanisms could potentially give rise to auto-sensitization and autoreactivity. Some of the mechanisms listed remain to be proven experimentally.

- Cross-reactivity and mimicry: cross-reactivity with an autoantigen that has structural similarity with an originally sensitizing exogenous allergen, structure or epitope
- Escape from self-tolerance: intracellular autoantigens which have escaped central and peripheral tolerance so that genuine auto-sensitization can occur.
- Altered self: autoantigens that are altered because of denaturation become antigenic and cause auto-sensitization.
- Presentation in a particularly immunogenic fashion by certain types of APCs (e.g. professional dendritic cells).
- Activation of certain T-cell subsets by proteolytic fragments derived from autoantigens.
- Defect in regulatory T-cell function.
- Intrinsic capacity of certain autoantigens to elicit certain cytokine responses.

Hom s 5, a cytokeratin II, have also been speculated to be possible tumour antigens. It is, therefore, conceivable that the Hom s autoantigens induce Th1 and/or cytotoxic T-cell responses leading to tissue damage also by IgE-independent mechanisms.

Immune recognition of autoantigens might, therefore, contribute to the pathology of allergy via IgE-independent in addition to IgE-dependent mechanisms (Box 2).

Autoantigens can trigger IgE-dependent inflammation in allergy

The IgE-reactive autoantigens which are summarized in Table 1 might induce IgE-dependent allergic inflammation in a manner similar to exogenous allergens (i.e. by the activation of mast cells, basophils and eosinophils in addition to Th2 cells) (Figure 1).

One can speculate that auto-sensitization in a manner similar to sensitization to exogenous allergens occurs already, early in childhood, and is directed against a defined set of antigens [42]. Later on, immune responses (i.e. secondary immune responses) might be boosted by antigen contact, or diminish in the absence of antigen exposure [37,43]. Whether or not an atopic person can become sensitized against a certain autoantigen might be determined by the availability of the autoantigen and by conditions favouring or counteracting (e.g. tolerance mechanisms) the sensitization during the critical period (Figure 1). The release of these autoantigens during the course of tissue damage could boost IgE autoantibody production similarly to the exposure to exogenous allergens, which increases allergen-specific IgE antibody levels [43]. In fact, it has been found that IgE autoantibody levels increase after allergic inflammation and tissue damage [21,37].

Furthermore, autoantigens which cross-react with exogenous allergens might maintain or even boost the allergic immune response to the cross-reactive allergen [28] (Figure 1). In fact, it has been demonstrated that the levels of IgE autoreactivity are associated with tissue inflammation and damage [21]. Moreover, IgE auto-reactivity was higher in patients suffering from allergic tissue inflammation occurring during exposure to exogenous

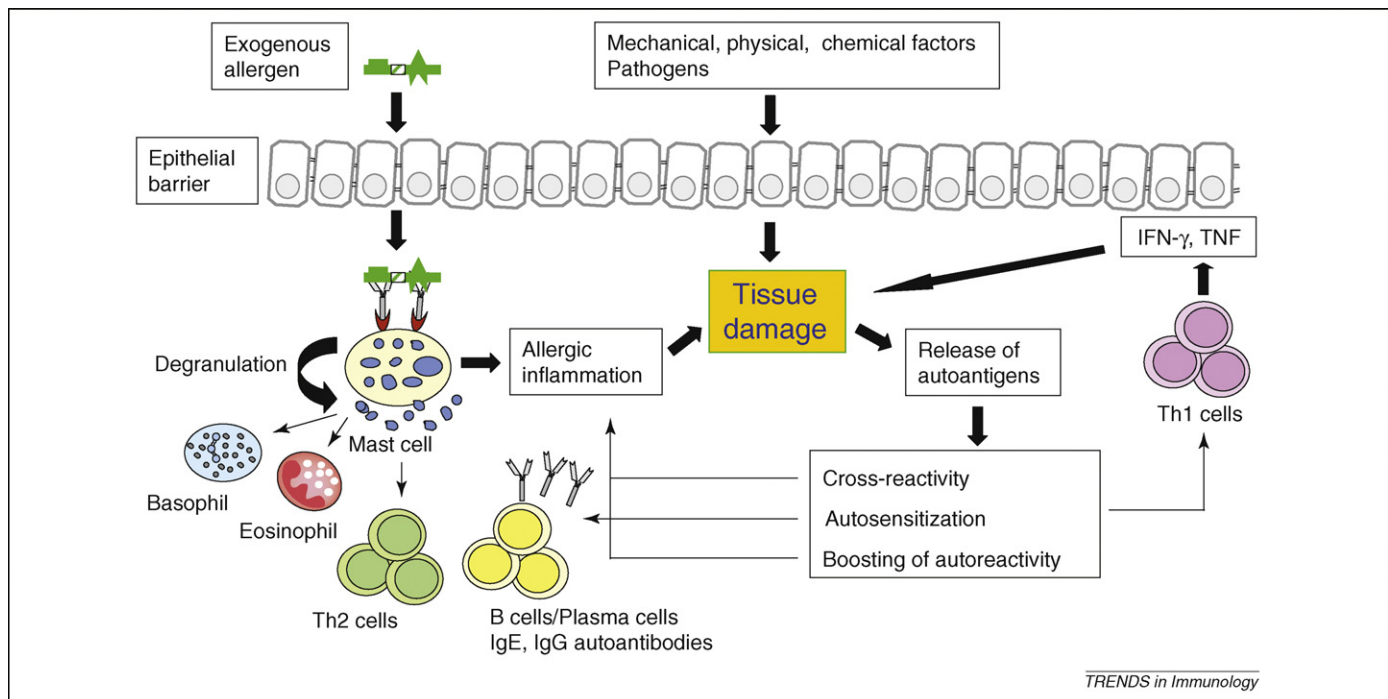


Figure 1. Development of autoreactivity in allergy and its possible pathogenic role. Tissue damage can occur in atopic persons before and after allergic sensitization to exogenous allergens because of mechanical factors, physicochemical factors or pathogens. In sensitized allergic patients, contact with exogenous allergens leads to allergic inflammation, which causes tissue damage. As a result of tissue damage because of exogenous factors, autoantigens are released which can cause auto-sensitization, allergic inflammation via IgE-dependent mechanisms and/or activation of Th1 cells which might lead to IgE-independent tissue damage and perturbation of epithelial integrity. Damage of the epithelial barrier by Th1-mediated mechanisms could then augment exogenous allergen penetration and allergic inflammation and facilitate the transition of pathogens through epithelial barriers promoting infections.

allergens or in the absence of anti-inflammatory treatment [21,37]. IgE auto-reactivity might, thus, also be considered as a sign of tissue inflammation in allergic patients and be useful for diagnostic monitoring.

Support for the assumption that autoantigens can contribute to IgE-dependent allergic inflammation comes from several studies performed in humans and mice. First, it has been demonstrated that IgE-reactive autoantigens can induce IgE-mediated basophil degranulation and immediate type allergic skin reactions in sensitized allergic patients [28,30,31,34]. Second, it has been shown that mice can be sensitized to autoantigens in a similar way to exogenous allergens using sensitization protocols (i.e. aluminium hydroxide-adsorbed antigen) established for murine models of allergy. These autoantigens result in the production of IgE autoantibodies, which cause mast cell degranulation and skin responses when transferred into naïve mice [40]. IgE-reactive autoantigens have also been observed to induce specific lymphoproliferative responses in sensitized patients comparable to those induced by cross-reactive exogenous allergens, and it is possible that T-cell activation can be enhanced by IgE-facilitated antigen presentation as has been shown for exogenous allergens [44,45]. IgE-reactive autoantigens might, therefore, induce IgE- in addition to T-cell-mediated tissue damage.

Non-IgE-mediated inflammation in allergy via autoimmune mechanisms

Exogenous allergens strongly induce Th2 reactivity, which might be partly because of particular intrinsic properties of the antigen [46]. By contrast, certain of the autoantigens

isolated with IgE autoantibodies, for example Hom s 2 and Hom s 4, failed to induce strong basophil and mast cell activation, but much to our surprise induced high levels of IFN-γ from *in vitro* cultured peripheral blood mononuclear cells [24,25]. The strong induction of IFN-γ by certain Hom s autoantigens seemed to be a distinct feature of these proteins because exogenous allergens did not induce such a strong Th1 response (Box 3). Immune recognition of these autoantigens was not confined to the IgE antibodies of atopic individuals, but non-atopic individuals instead raised IgG antibodies against these autoantigens [24]. This finding is similar to the results obtained for exogenous allergens, which are recognized by IgG antibodies from non-allergic persons [47]. The induction of IFN-γ (i.e. Th1-like) in the PBMCs of non-atopic individuals was even higher than in atopics, which might be explained by the dominance of Th2 activation in this group [24].

Box 3. Open questions

- Why is IgE autoreactivity preferentially associated with certain manifestations of allergy (e.g. atopic dermatitis)?
- Is IgE autoreactivity confined to certain target organs in allergy (e.g. skin), and if so, what are the mechanisms behind this (e.g. tissue-specific expression of autoantigens, distribution of circulating IgE-autoantigen immune complexes, homing of autoreactive T cells)?
- Why are some IgE-reactive autoantigens so potent in inducing Th1 responses?
- Can IgE autoreactivity be used as a diagnostic parameter for the monitoring of tissue damage in allergic inflammation?
- Is there a role for the IgE-reactive autoantigens beyond allergic inflammation (e.g. in other autoimmune diseases)?

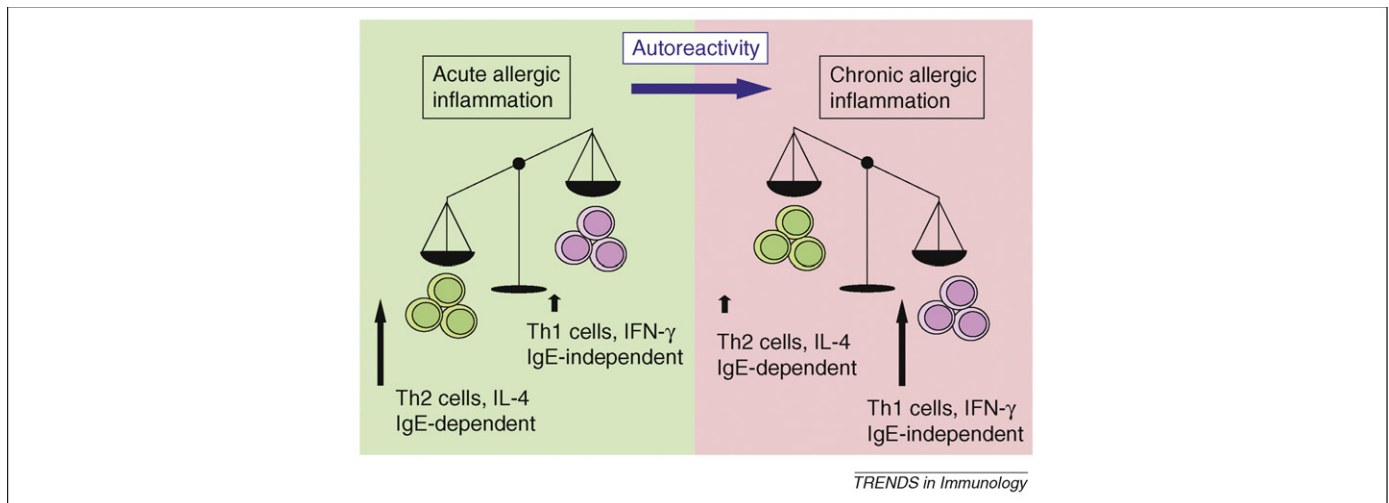


Figure 2. The transition from allergy to autoimmunity. Short-term exposure to exogenous allergens gives rise to acute allergic inflammation characterized by IgE-dependent mast cell and basophil degranulation, in addition to Th2 cell activation with little or no Th1 activity. Chronic exposure to exogenous allergens will initially lead to prolonged allergic inflammation and liberation of autoantigens because of tissue damage (see Figure 1) which then can activate Th1 cells and might, thus, cause IgE-independent tissue damage and inflammation. This autoimmune mechanism could lead to a transition from acute to chronic allergic inflammation dominated by signs of Th1 activation in auto-sensitized persons.

Because the Hom s antigens induced stronger IFN- γ production in the PBMC of non-atopics compared to those of atopics, it is quite possible that they also have a role in other autoimmune diseases (Box 3). Another interesting question is why autoantigens such as Hom s 2 and Hom s 4 induce such strong Th1 activation and if this property is an intrinsic feature of these proteins. At present, our results indicate that most individuals contain Th1 memory cells specific for the Hom s autoantigens. It remains to be studied if these antigens *per se* can initiate strong Th1 responses or whether other factors need to be involved. Among the factors influencing the development of a strong Th1 response might be the site where the autoimmune response is initiated, the dose, condition and structure of the autoantigen, adjuvant factors, type or state of the antigen presenting cells and the targeting of certain T-cell subsets by antigen derived peptides [48]. Interestingly, the Hom s antigens described so far represent intracellular proteins. It is, therefore, possible that they can give rise to autoimmune responses because they have escaped central tolerance mechanisms. It is also possible that epithelial surfaces are exceptionally prone to tissue damage through physicochemical processes facilitating the release of intracellular proteins acting in the context of damage-associated molecular-pattern molecules (DAMPs) and as such become denatured and therefore antigenic [49]. The latter assumption is supported by our observation that certain autoantigens react better with IgE when they are denatured [50]. Finally, it has been shown that AD patients also show Th1 reactivity to exogenous allergens [16,17]. Hence, these patients might be especially prone to mount Th1 responses also to the IgE-reactive autoantigens. As shown in Figure 2, we suggest that tissue damage occurring during acute allergic inflammation, and eventually because of other factors, might lead to the release of autoantigens which can induce strong Th1 cell activation and the release of IFN- γ . This process would explain the appearance of Th1-delayed-type manifestations in chronic allergic inflammation as a transition from allergy to auto-

immunity in auto-sensitized patients (Figure 2). It has also been shown that there is a strong appearance of Th1 cells in lesions of chronic allergic inflammation in atopic dermatitis patients [16,17], which makes it tempting to speculate that lesional Th1 cells might have specificity for autoantigens. The observation that Hom s 2 induced strong induction of IFN- γ was confirmed at the level of T-cell lines and clones showing that most of the T cells specific for Hom s 2 belonged to the Th1 subset and produced high levels of IFN- γ (Heratizadeh, A. *et al.*, unpublished). In addition, CD8⁺ T cells specific for Hom s 2 have been found and an earlier publication has shown that another autoantigen, Hom s 1, is a target for cytotoxic T cells [41]. As yet, we have not found evidence for the recognition of autoantigens, and in particular of Hom s 2, by Th17 cells, which have been reported as potent inducers of autoimmunity and tissue inflammation [51].

In summary, the available data demonstrate that Hom s autoantigens induce the secretion of IFN- γ , which can damage epithelial cells by an IgE-independent mechanism. IFN- γ -dependent epithelial cell damage has indeed been discussed as an important pathomechanism in chronic forms of atopy such as atopic dermatitis and chronic asthma bronchiale [13,18] (Figure 1).

Acknowledgements

This study was supported by grant F1815 of the Austrian Science Fund, FWF.

References

- 1 Kay, A.B. *et al.* (2008) *Allergy and Allergic Disease*. Blackwell Science
- 2 Johansson, S.G. and Bennich, H. (1967) Immunological studies of an atypical (myeloma) immunoglobulin. *Immunology* 13, 381–394
- 3 Ishizaka, K. *et al.* (1966) Physico-chemical properties of human reaginic antibody. IV. Presence of a unique immunoglobulin as a carrier of reaginic activity. *J. Immunol.* 97, 75–85
- 4 Bischoff, S.C. (2007) Role of mast cells in allergic and non-allergic immune responses: comparison of human and murine data. *Nat. Rev. Immunol.* 7, 93–104
- 5 Geha, R.S. *et al.* (2003) The regulation of immunoglobulin E class-switch recombination. *Nat. Rev. Immunol.* 3, 721–732

- 6 Romagnani, S. (2004) Immunologic influences on allergy and the TH1/TH2 balance. *J. Allergy Clin. Immunol.* 113, 395–400
- 7 Romagnani, S. (2008) Human Th17 cells. *Arthritis Res. Ther.* 10, 206
- 8 Black, P. (2001) Why is the prevalence of allergy and autoimmunity increasing? *Trends Immunol.* 22, 354–355
- 9 Rabin, R.L. and Levinson, A.I. (2008) The nexus between atopic disease and autoimmunity: a review of the epidemiological and mechanistic literature. *Clin. Exp. Immunol.* 153, 19–30
- 10 Bartunkova, J. *et al.* (2008) Allergy and autoimmunity: parallels and dissimilarity The Yin and Yang of Immunopathology. *Autoimmun. Rev.* DOI: 10.1016/j.autrev.2008.09.004
- 11 Rottem, M. and Mekori, Y.A. (2005) Mast cells and autoimmunity. *Autoimmun. Rev.* 4, 21–27
- 12 Bieber, T. (2008) Atopic dermatitis. *N. Engl. J. Med.* 358, 1483–1494
- 13 Hansen, G. *et al.* (1999) Allergen-specific Th1 cells fail to counterbalance Th2 cell-induced airway hyperreactivity but cause severe airway inflammation. *J. Clin. Invest.* 103, 175–183
- 14 Larche, M. *et al.* (2003) The role of T lymphocytes in the pathogenesis of asthma. *J. Allergy Clin. Immunol.* 111, 450–463
- 15 Bischoff, S.C. and Sellge, G. (2003) Immune mechanisms in food-induced disease. In *Food Allergy: Adverse Reactions to Foods and Food Additives* (3rd edn), pp. 14–38, Blackwell Science
- 16 Grewe, M. *et al.* (1994) Lesional expression of interferon- γ in atopic eczema. *Lancet* 343, 25–26
- 17 Werfel, T. *et al.* (1996) Allergen specificity of skin-infiltrating T cells is not restricted to a type-2 cytokine pattern in chronic skin lesions of atopic dermatitis. *J. Invest. Dermatol.* 107, 871–876
- 18 Trautmann, A. *et al.* (2000) T cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. *J. Clin. Invest.* 106, 25–35
- 19 Haselden, B.M. *et al.* (1999) Immunoglobulin E-independent major histocompatibility complex-restricted T cell peptide epitope-induced late asthmatic reactions. *J. Exp. Med.* 189, 1885–1894
- 20 Valenta, R. *et al.* (1996) Immunoglobulin E response to human proteins in atopic patients. *J. Invest. Dermatol.* 107, 203–208
- 21 Natter, S. *et al.* (1998) Isolation of cDNA clones coding for IgE autoantigens with serum IgE from atopic dermatitis patients. *FASEB J.* 12, 1559–1569
- 22 Valenta, R. *et al.* (1998) Molecular characterisation of an autoallergen, Hom s 1, identified by serum IgE from atopic dermatitis patients. *J. Invest. Dermatol.* 111, 1178–1183
- 23 Valenta, R. *et al.* (2000) Autoallergy: a pathogenetic factor in atopic dermatitis? *J. Allergy Clin. Immunol.* 105, 432–437
- 24 Aichberger, K.J. *et al.* (2005) Hom s 4, an IgE-reactive autoantigen belonging to a new subfamily of calcium-binding proteins, can induce Th cell type 1-mediated autoreactivity. *J. Immunol.* 175, 1286–1294
- 25 Mittermann, I. *et al.* (2008) The IgE-reactive autoantigen Hom s 2 induces damage of respiratory epithelial cells and keratinocytes via induction of IFN- γ . *J. Invest. Dermatol.* 128, 1451–1459
- 26 Storm van Leeuwen, W. *et al.* (1926) Über die Hautreaktion mit Extrakten menschlicher Kopfhautschuppen bei allergischen Krankheiten. *Klin. Wochenschr.* 5, 1023–1025
- 27 Hashem, N. *et al.* (1963) Infantile eczema: evidence of autoimmunity to human skin. *Lancet* 2, 269–279
- 28 Valenta, R. *et al.* (1991) Identification of profilin as a novel pollen allergen; IgE autoreactivity in sensitized individuals. *Science* 253, 557–560
- 29 Fedorov, A.A. *et al.* (1997) The molecular basis for allergen cross-reactivity: crystal structure and IgE epitope mapping of birch pollen profilin. *Structure* 5, 33–45
- 30 Cramer, R. *et al.* (1996) Humoral and cell-mediated autoimmunity in allergy to *Aspergillus fumigatus*. *J. Exp. Med.* 184, 265–270
- 31 Mayer, C. *et al.* (1999) Humoral and cell-mediated autoimmune reactions to human acidic ribosomal P2 protein in individuals sensitized to *Aspergillus fumigatus* P2 protein. *J. Exp. Med.* 189, 1507–1512
- 32 Patterson, R. *et al.* (1986) Human antibodies against formaldehyde-human serum albumin conjugates or human serum albumin in individuals exposed to formaldehyde. *Int. Arch. Allergy Appl. Immunol.* 79, 53–59
- 33 Spitzauer, S. *et al.* (1994) Molecular characterization of dog albumin as a cross-reactive allergen. *J. Allergy Clin. Immunol.* 93, 614–627
- 34 Schmid-Grendelmeier, P. *et al.* (2005) IgE-mediated and T cell-mediated autoimmunity against manganese superoxide dismutase in atopic dermatitis. *J. Allergy Clin. Immunol.* 115, 1068–1075
- 35 Fairley, J.A. *et al.* (2007) A pathogenic role for IgE in autoimmunity: bullous pemphigoid IgE reproduces the early phase of lesion development in human skin grafted to nu/nu mice. *J. Invest. Dermatol.* 127, 2605–2611
- 36 Chapman, M.D. *et al.* (2007) Nomenclature and structural biology of allergens. *J. Allergy Clin. Immunol.* 119, 414–420
- 37 Kinaciyan, T. *et al.* (2002) IgE autoantibodies monitored in a patient with atopic dermatitis under cyclosporin A treatment reflect tissue damage. *J. Allergy Clin. Immunol.* 109, 717–719
- 38 Mothes, N. *et al.* (2005) The cradle of IgE autoreactivity in atopic eczema lies in early infancy. *J. Allergy Clin. Immunol.* 116, 706–709
- 39 Mossabeh, R. *et al.* (2002) Characterization of a novel isoform of α -nascent polypeptide-associated complex as IgE-defined autoantigen. *J. Invest. Dermatol.* 119, 820–829
- 40 Bänder, R. *et al.* (2004) Induction of auto-allergy with an environmental allergen mimicking a self protein in a murine model of experimental allergic asthma. *J. Allergy Clin. Immunol.* 114, 422–428
- 41 Shichijo, S. *et al.* (1998) A gene encoding antigenic peptides of human squamous cell carcinoma recognized by cytotoxic T lymphocytes. *J. Exp. Med.* 187, 277–288
- 42 Niederberger, V. *et al.* (2002) Evolution of IgM, IgE and IgG(1-4) antibody responses in early childhood monitored with recombinant allergen components: implications for class switch mechanisms. *Eur. J. Immunol.* 32, 576–584
- 43 Niederberger, V. *et al.* (2007) Antigens drive memory IgE responses in human allergy via the nasal mucosa. *Int. Arch. Allergy Immunol.* 142, 133–144
- 44 Stingl, G. and Maurer, D. (1997) IgE-mediated allergen presentation via Fc epsilon RI on antigen-presenting cells. *Int. Arch. Allergy Immunol.* 113, 24–29
- 45 Bieber, T. (1997) Fc epsilon RI on human epidermal Langerhans cells: an old receptor with new structure and functions. *Int. Arch. Allergy Immunol.* 113, 30–34
- 46 Shakib, F. *et al.* (2008) The molecular basis of allergenicity. *Trends Immunol.* 29, 633–642
- 47 Stern, D.A. *et al.* (2007) Exposure to a farming environment has allergen-specific protective effects on TH2-dependent isotype switching in response to common inhalants. *J. Allergy Clin. Immunol.* 119, 351–358
- 48 Pu, Z. *et al.* (2002) Distinct recognition by two subsets of T cells of an MHC class II-peptide complex. *Proc. Natl. Acad. Sci. U. S. A.* 99, 8844–8849
- 49 Rubartelli, A. and Lotze, M.T. (2007) Inside, outside, upside down: damage-associated molecular-pattern molecules (DAMPs) and redox. *Trends Immunol.* 28, 429–436
- 50 Seiberler, S. *et al.* (1999) 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.* 120, 117–125
- 51 Bettelli, E. *et al.* (2008) Induction and effector functions of T(H)17 cells. *Nature* 453, 1051–1057
- 52 Ochs, R.L. *et al.* (2000) Autoantibodies to DFS 70 kDd/transcription coactivator p75 in atopic dermatitis and other conditions. *J. Allergy Clin. Immunol.* 105, 1211–1220
- 53 Altrichter, S. *et al.* (2008) Serum IgE autoantibodies target keratinocytes in patients with atopic dermatitis. *J. Invest. Dermatol.* 128, 2232–2239
- 54 Permin, H. and Wiik, A. (1978) The prevalence of IgE antinuclear antibodies in rheumatoid arthritis and systemic lupus erythematosus. *Acta Pathol. Microbiol. Scand. [C]* 86C, 245–249
- 55 Permin, H. *et al.* (1983) Basophil histamine release induced by leukocyte nuclei in patients with rheumatoid arthritis. *Allergy* 38, 273–281
- 56 Barone, C. *et al.* (1981) Systemic lupus erythematosus with only IgE-class antinuclear antibodies. *Arthritis Rheum.* 24, 1441–1443
- 57 Nagpal, S. *et al.* (1990) Demonstration of IgE antibodies to nucleic acid antigens in patients with SLE. *Autoimmunity* 8, 59–64
- 58 Zuraw, B.L. *et al.* (1981) Immunoglobulin E-rheumatoid factor in the serum of patients with rheumatoid arthritis, asthma, and other diseases. *J. Clin. Invest.* 68, 1610–1613
- 59 Herrmann, D. *et al.* (1991) IgE rheumatoid factor. Occurrence and diagnostic importance in comparison with IgM rheumatoid factor and circulating immune complexes. *J. Invest. Allergol. Clin. Immunol.* 1, 302–307

- 60 Bartholomew, J.S. *et al.* (1991) Serum IgE anti-cartilage collagen antibodies in rheumatoid patients. *Rheumatol. Int.* 11, 37–40
- 61 Cooper, A.L. *et al.* (1993) IgE antibodies specific for cartilage collagens type II, IX and XI in rheumatic diseases. *Scand. J. Rheumatol.* 22, 207–214
- 62 Sekigawa, I. *et al.* (2004) Possible importance of immunoglobulin E in foetal loss by mothers with anti-SSA antibody. *Scand. J. Rheumatol.* 33, 44–46
- 63 Lassalle, P. *et al.* (1990) Plasmapheresis in a patient with severe asthma associated with auto-antibodies to platelets. *Clin. Exp. Allergy* 20, 707–712
- 64 Delaporte, E. *et al.* (1996) IgE autoantibodies directed against the major bullous pemphigoid antigen in patients with a severe form of pemphigoid. *J. Immunol.* 157, 3642–3647
- 65 Christophoridis, S. *et al.* (2000) IgG, IgA and IgE autoantibodies against the ectodomain of BP180 in patients with bullous and cicatricial pemphigoid and linear IgA bullous dermatosis. *Br. J. Dermatol.* 143, 349–355
- 66 Ghohestani, R.F. *et al.* (1998) IgE antibodies in sera from patients with bullous pemphigoid are autoantibodies preferentially directed against the 230-kDa epidermal antigen (BP230). *J. Clin. Immunol.* 18, 202–209
- 67 Spaeth, S. *et al.* (2001) IgG, IgA and IgE autoantibodies against the ectodomain of desmoglein 3 in active pemphigus vulgaris. *Br. J. Dermatol.* 144, 1183–1188
- 68 Muino, J.C. *et al.* (1999) The importance of specific IgG and IgE autoantibodies to retinal S antigen, total serum IgE, and sCD23 levels in autoimmune and infectious uveitis. *J. Clin. Immunol.* 19, 215–222
- 69 Lohmann, T. *et al.* (2000) Immune reactivity to glutamic acid decarboxylase 65 in stiffman syndrome and type 1 diabetes mellitus. *Lancet* 356, 31–35
- 70 Hoppu, S. *et al.* (2004) GAD65 antibody isotypes and epitope recognition during the prediabetic process in siblings of children with type I diabetes. *Clin. Exp. Immunol.* 136, 120–128
- 71 Metcalfe, R. *et al.* (2002) Demonstration of immunoglobulin G, A, and E autoantibodies to the human thyrotropin receptor using flow cytometry. *J. Clin. Endocrinol. Metab.* 87, 1754–1761
- 72 Tedeschi, A. *et al.* (2001) Anti-thyroid peroxidase IgE in patients with chronic urticaria. *J. Allergy Clin. Immunol.* 108, 467–468
- 73 Concha, L.B. *et al.* (2004) IgE antithyroid antibodies in patients with Hashimoto's disease and chronic urticaria. *Allergy Asthma Proc.* 25, 293–296
- 74 Khalaf, A.N. *et al.* (1989) Natural occurrence of IgE antibodies to peptide hormones in man. *Eur. J. Clin. Invest.* 19, 464–465
- 75 Schilling, J. *et al.* (2005) Immunoglobulin isotype profile of tissue transglutaminase autoantibodies is correlated with the clinical presentation of celiac disease. *Scand. J. Immunol.* 61, 207–212