



# Immunoglobulin E-Mediated Autoimmunity

Marcus Maurer, Sabine Altrichter, Oliver Schmetzer, Jörg Scheffel, Martin K. Church\* and Martin Metz

Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Berlin, Germany

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### \*Correspondence:

Martin K. Church  
mkc@soton.ac.uk

### Specialty section:

This article was submitted to  
Immunological Tolerance and  
Regulation,  
a section of the journal  
Frontiers in Immunology

**Received:** 02 February 2018

**Accepted:** 20 March 2018

**Published:** 09 April 2018

### Citation:

Maurer M, Altrichter S, Schmetzer O,  
Scheffel J, Church MK and Metz M  
(2018) Immunoglobulin E-Mediated  
Autoimmunity.  
*Front. Immunol.* 9:689.  
doi: 10.3389/fimmu.2018.00689

The study of autoimmunity mediated by immunoglobulin E (IgE) autoantibodies, which may be termed autoallergy, is in its infancy. It is now recognized that systemic lupus erythematosus, bullous pemphigoid (BP), and chronic urticaria, both spontaneous and inducible, are most likely to be mediated, at least in part, by IgE autoantibodies. The situation in other conditions, such as autoimmune uveitis, rheumatoid arthritis, hyperthyroid Graves' disease, autoimmune pancreatitis, and even asthma, is far less clear but evidence for autoallergy is accumulating. To be certain of an autoallergic mechanism, it is necessary to identify both IgE autoantibodies and their targets as has been done with the transmembrane protein BP180 and the intracellular protein BP230 in BP and IL-24 in chronic spontaneous urticaria. Also, IgE-targeted therapies, such as anti-IgE, must have been shown to be of benefit to patients as has been done with both of these conditions. This comprehensive review of the literature on IgE-mediated autoallergy focuses on three related questions. What do we know about the prevalence of IgE autoantibodies and their targets in different diseases? What do we know about the relevance of IgE autoantibodies in different diseases? What do we know about the cellular and molecular effects of IgE autoantibodies? In addition to providing answers to these questions, based on a broad review of the literature, we outline the current gaps of knowledge in our understanding of IgE autoantibodies and describe approaches to address them.

**Keywords:** immunoglobulin E-mediated autoimmunity, autoallergy, urticaria, bullous pemphigoid, immunoglobulin E-mechanisms

## INTRODUCTION

Friend or Foe? This is the major question that the immune system must address in every individual from the time of conception, through the development of the fetus and the child, right into adulthood. But sometimes it gets this wrong and raises an inappropriate immunological response against self. Although there are several types of autoimmunity this review will address solely immunoglobulin E (IgE)-mediated autoimmunity. Because its mechanisms have much in common with classical allergy involving exogenous allergens, such as grass pollen or house dust mites, IgE-mediated autoimmunity is generally termed “autoallergy” and the target molecules of the response are called “autoallergens.”

Although the presence of an allergic antibody has been postulated since the innovative serum transfer experiment of Prausnitz and Kustner in 1921 (1), it was not until 1967 that this antibody was characterized as IgE (2–4). IgE, which is the least abundant immunoglobulin isotype and found only in mammals, signals through 2 types of Fcε receptor, the high-affinity receptor, FcεRI, which is found primarily on mast cells and basophils, and the low-affinity receptor, FcεRII or CD23, a C-type

lectin, which is found on mature B cells, activated macrophages, eosinophils, follicular dendritic cells, and platelets. The primary role of IgE is held to be host defense, particularly initiating the expulsion of parasitic worms (helminths) and environmental substances, such as toxins, venoms, irritants, and xenobiotics.

Although IgE has a well-documented role in classical allergy to exogenous allergens, this review will address only IgE-mediated autoimmunity. It will focus on three related questions: what do we know about the prevalence of IgE autoantibodies and their targets in different diseases? What do we know about the relevance of IgE autoantibodies in different diseases? What do we know about the cellular and molecular effects of IgE autoantibodies? In addition to providing answers to these three questions, based on a comprehensive review of the literature, we outline the current gaps of knowledge in our understanding of IgE autoantibodies and describe approaches to address them.

## WHAT DO WE KNOW ABOUT THE PREVALENCE OF IgE AUTOANTIBODIES AND THEIR TARGETS IN DIFFERENT CONDITIONS?

Within a decade of its discovery, reports began to incriminate IgE as a possible contributor to the pathogenesis of several chronic inflammatory disorders, such as rheumatoid arthritis (RA) (5–7), bullous pemphigoid (BP) (8, 9), atopic dermatitis (AD) (10), and systemic lupus erythematosus (SLE) (11, 12). More recently, IgE-mediated autoallergy has been suggested for other disorders including chronic spontaneous urticaria (CSU) (13, 14) and chronic inducible urticaria (CindU) (15). The conditions in which IgE autoantibodies have been detected, which are summarized in **Table 1**, will now be considered in more detail.

### Atopic Dermatitis

Decades before the discovery of IgE, it was reported that human dander extract can elicit immediate-type skin reactions in patients with severe atopy and that this skin sensitivity could be passively transferred with serum (30–35). Many years later, the analysis of the presence of IgE autoantibodies in sera from patients with various manifestations of atopy and other autoimmune disorders indicated that IgE reactivity against a variety of autoantigens occurred most frequently in AD patients. IgE autoreactivity has first been found and described in AD (36), where IgE autoantibodies are very frequent (23–91%) (19) and especially present in severely affected patients (37–39). IgE autoantibodies had been identified directed against Keratinocytes (40) and a broad variety of autoantigens (41), including, e.g., human protein manganese superoxide dismutase (38), thioredoxin (42), DFS70/LEDGF (43), and Hom s 1–5 (44, 45).

Interestingly, this phenomenon has already been seen in very young infants of less than 1 year where 15% of the children with atopic eczema mounted IgE autoreactivity and raised in the age group of 2–13 years with moderate to severe AE and total IgE serum levels higher 1,000 kU/L up to 80% (46).

**TABLE 1** | Percentage of patients in which immunoglobulin E (IgE) autoantibodies have been detected in various diseases.

Disease	IgE against	Prevalence	Reference
Allergic rhinoconjunctivitis	Profilin		(16)
Asthma	n.a.	n.a.	(17, 18)
Atopic dermatitis	>140 IgE-binding self-antigens	23–91%	(19, 20)
Autoimmune pancreatitis	n.a.	n.a.	(21)
Bullous pemphigoid	BP 180 or 230	22–100%	(22)
Chronic spontaneous urticaria	Thyroidperoxidase (TPO), double stranded DNA (dsDNA), IL-24	0–80%	(23)
Graves disease	TPO, muscle autoantigens	67%	(24, 25)
Multiple sclerosis (MS)	Small myelin protein-derived peptides	n.a.	(26)
Pemphigus	Desmoglein1, Desmoglein 3, Lamininin-332 und LJM11	11–81%	(22)
Rheumatoid arthritis	ANA, anti-citrullinated protein?	60%	(27)
Systemic lupus erythematosus and lupus nephritis	dsDNA, Sm, SS-A/Ro, SS-B/La, APEX, MPG, CLIP4, ANA, RNP, nucleosome, specific IgE, acidic ribosomal P <sub>2</sub> protein	3.6–82%	(28)
Uveitis	Retinal S antigen	69%	(29)

*n.a.*, not assessed.

### Systemic Lupus Erythematosus

In SLE, several IgE autoantigens have been described (28, 47), and their occurrence is frequent. In a study of 92 SLE patients (48), 29 (32%) had antinuclear-IgE antibodies. No such antibodies were found in a parallel healthy control group. Sub-analysis of the IgE autoantibodies in the 29 positive patients showed reactions with nucleosomes (79.3%), double stranded DNA (dsDNA) (48.3%), SS-A/Ro (48.3%), SS-B/La (18.7%), Sm (48.3%), and RNP (62.1%). In a multicentre study of 196 SLE patients (49), more than 50% showed autoreactive IgE to one or more of the four common SLE nuclear autoantigens, dsDNA, SS-A/Ro, SS-B/La, and Sm. This figure rose to around 74% in patients with active disease where autoreactive IgE to dsDNA was most prevalent with an incidence of 63%. From these findings, Dema and colleagues (49) suggest that the presence of autoreactive IgE, and in particular dsDNA-specific IgE, in SLE, may be a reasonable clinical indicator of increased disease activity. This conclusion is supported by a study that showed that disease flares rates were higher in SLE patients with demonstrable circulating IgE-anti-dsDNA antibodies than in those without (50).

Because approximately half of SLE patients do not have demonstrable IgE antibodies to the common nuclear autoantigens, the prevalence of IgE autoantibodies to other autoallergens has been explored. One study showed high levels of IgE autoantibodies to APEX nuclease 1, *N*-methylpurine-DNA glycosylase and CAP-Gly domain-containing linker protein family member 4 in some SLE patients but not healthy controls. These autoantigens were unique in that they seemed specific targets of IgE autoantibodies but not autoantibodies of the IgG class (49). In another study, 31% of 90 SLE patients displayed IgE antibodies against human P 2 proteins, an antigen that has also been described to be

cross-reactive with other members of the ribosomal P 2 protein family, which are minor allergens in fungal allergy (51).

Finally and importantly, IgE to Ro/SSA, a ribonucleoprotein autoantigen has been suggested to be relevant for fetal loss by mothers with SLE (52). This is of special interest as IgG-anti-Ro/SSA antibodies are known to be associated with neonatal lupus (congenital heart block, neonatal transient skin rash, hematological and hepatic abnormalities). However, they are suggested not to negatively affect other gestational outcomes, and the general outcome of these pregnancies is good when managed by experienced multidisciplinary teams (53).

## Bullous Pemphigoid

Bullous pemphigoid is an autoimmune blistering disease that mainly affects elderly patients. It is the most common pemphigoid disorder accounting for around 80% of all pemphigoid cases (28). IgG, IgA, and IgE autoantibodies are directed against two hemidesmosomal proteins, the transmembrane protein BP antigen 2 (BP180, type XVII collagen) and the intracellular BP antigen 1 (BP230) (22, 54, 55). Binding of autoantibodies leads to a complex inflammatory response involving complement activation, the infiltration of inflammatory cells, and the subsequent release of reactive oxygen species and distinct proteases that finally mediate subepidermal splitting (56).

Immunoglobulin E autoantibodies against BP180 target mainly the 16th non-collagenous domain (BP180 NC16A) (54, 57) although BP180 epitopes outside the NC16A domain have also been described to be recognized by IgE (58). That IgE-anti-BP180 is functional was demonstrated by the ability of serum from BP patients to sensitize mast cells and basophils for BP180-induced histamine release (59). The percentage of BP patients with IgE-anti-BP180 autoantibodies, shown in **Table 2**, varied substantially in the different reports. The reason in this variation is likely to be due to the different test systems used, i.e., ELISA or immunoblotting, and the use of diluted or undiluted patient sera.

Several studies were able to detect IgE autoantibodies against the intracellular BP230 autoantigen. Engineer et al. reported IgE-anti-BP230 without detection of BP180-specific IgE autoantibodies in 100% of six BP patients (67). In contrast, other studies revealed IgE-anti-BP230 and IgE-anti-BP180 autoantibodies in 67% of 67 sera (61) and 50% of 32 sera (68). IgE-anti-BP230 reactivity was associated with local eosinophil accumulation (61),

with disease activity (69) and correlated with total IgE serum levels (68, 70).

## Other Autoimmune Blistering Disorders

Pemphigus vulgaris (PV) is another severe autoimmune bullous skin disease and is primarily associated with IgG against desmoglein 3 (dsg3), a desmosomal adhesion protein. However, raised IgE in these patients has also been reported (71). Intercellular IgE deposits were detected in the epidermis of 37 patients with acute onset of the disease, and IgE-anti-dsg3 was detected more frequently in the sera of patients with acute onset, compared to chronic-active PV (72). Spaeth and colleagues reported dsg3-reactive IgE in the serum of 13% of 15 patients with acute onset, 11% of 18 patients with chronic-active, and none of 8 patients with remittent PV patients (73).

In mucus membrane pemphigoid, one of four patients showed IgE reactivity to the gamma2 subunit of laminin-332 (74). In endemic pemphigus foliaceus, IgE-anti-desmoglein 1 was found in 81% of 143 patients with fogo selvagem (75), and serum levels of IgE against LJM11, a major immunogenic component of sand fly salivary gland antigens, were significantly higher compared to controls (76).

In summary, reports in pemphigus are limited, but IgE reactivity seems to be more prevalent in the endemic form of pemphigus foliaceus than in PV.

## Chronic Urticaria

An important role of IgE and FcεRI reactions was postulated in both CSU and CindU for several decades (77) before it was finally confirmed by the successful treatment of the disease with anti-IgE (omalizumab) (14, 15, 78). Although specific IgE against classical common allergens, i.e., aeroallergens and food allergens (79–82), or to less common allergens such as fungi (83, 84) can be detected in some patients with CSU, they are not regarded as pathophysiologically relevant for the development of the signs and symptoms of CSU (81, 85–87).

Perhaps the first evidence of autoreactivity in CSU came with the clinical observation that CSU patients have high rates of thyroid diseases (88). Detailed analysis of CSU patients with thyroid pathology led to the detection of IgE anti-thyroidperoxidase (TPO) autoantibodies. Almost 20 years ago, Bar-Sela and coworkers reported the detection of IgE-anti-TPO in a female CSU patient who also had Hashimoto's thyroiditis (89). More recently, elevated levels of IgE-anti-TPO were reported in 61% of 478 CSU patients (13). However, other studies found only 13–17% of 23 patients (90) and 10% of 20 patients (91) to have IgE-anti-TPO, while a further study failed to find IgE-anti-TPO in 23 CU patients (92). The most likely explanation for these differences is the use of different assay systems, for example direct ELISA vs capture ELISA, and the interference of IgG autoantibodies against TPO (93). Functional relevance was suggested as flow cytometry analysis showed CD203c induction in a dose-dependent manner in basophils sensitized with serial additions of TPO in CU patients having high specific IgE to TPO (94).

Beside thyroid diseases, the prevalence of individual autoimmune diseases in chronic urticaria is increased in general ( $\geq 1\%$  in most studies vs  $\leq 1\%$  in the general population). In a review,

**TABLE 2** | Percentage of patients with bullous pemphigoid showing immunoglobulin E (IgE) reactivity to BP180.

Number of patients	Percentage with IgE-anti-BP180	Reference
37	22	(60)
67	30	(61)
117	40	(56)
44	41	(62)
18	55	(63)
31	61	(64)
56	71	(65)
43	77	(58)
18	83	(66)
10	100	(54)

the rates of comorbidity were  $\geq 1\%$  for insulin-dependent diabetes mellitus, RA, psoriasis, and celiac disease,  $\geq 2\%$  for Graves' disease,  $\geq 3\%$  for vitiligo, and  $\geq 5\%$  for pernicious anemia and Hashimoto's thyroiditis. Interestingly,  $> 15\%$  of CSU patients have a positive family history for autoimmune disease (95).

A recent review investigated also the correlation of chronic urticaria with other autoimmune diseases such as SLE. The prevalence of CSU and CSU-like rash in SLE was investigated from 42 independent studies. Comorbidity in adult patients reportedly ranged from 0 to 22% and 0.4 to 28%, respectively (urticarial vasculitis: 0–20%). In children with SLE, CSU was reported in 0–1.2% and CSU-like rash in 4.5–12% (urticarial vasculitis: 0–2.2%) (96). Specifically, significantly higher levels of IgE-anti-dsDNA, but not corresponding IgG levels, have also been found in a study of 85 chronic urticaria patients (97). Furthermore, basophils from 2 out of 9 of these patients exhibited degranulation in response to dsDNA, indicating functional relevance of these autoantibodies.

Beside these IgE antibodies that target antigens known in autoimmune diseases, patients with CSU can also develop IgE autoantibodies against probably disease-specific antigens. Schmetzer et al. found more than 200 IgE autoantigens in patients with CSU that were not found in healthy controls (98). Of the 31 IgE autoantigens detected in more than 70% of patients, 8 were soluble or membrane-bound and expressed in the skin and IgE autoantibodies to IL-24 were found in all patients with CSU. *In vitro* studies showed functional relevance, and clinically IgE-anti-IL-24 levels showed an association with disease activity. Detailed analysis of the remaining identified IgE targets had not been provided yet.

## Other Diseases

In many diseases, single or few reports have indicated a presence or potential role of autoreactive IgE.

### Autoimmune Uveitis

Beside IgG autoantibodies, in autoimmune uveitis specific IgE to retinal S antigen was positive in 69% of 32 patients. In contrast, patients suffering from bacterial uveitis, as well as the healthy controls were negative for autoantibodies to retinal S antigen (29). Furthermore, IgE, IgG, and IgA anti-Galectin-1 (Gal-1) antibodies were increased in sera from patients with autoimmune uveitis and toxoplasmic retinochoroiditis compared to healthy controls (99). Both, anti-Gal-1 IgE and IgG antibodies were associated with progressive disease and poor disease outcome.

### Rheumatoid Arthritis

A role of IgE antibodies in RA was first suggested several decades ago (27, 100). Antinuclear antibodies of the IgE class were found in 60% of 20 RA patients with neutropenia, whereas only 16% of RA patients without neutropenia had IgE antibodies of similar specificity (27). Anti-citrullinated protein antibodies are suggested to be highly specific and predictive for RA. In a study from Schuerwegh and colleagues, evidence for IgE directed against citrullinated protein was proposed (101), but later the paper was retracted (102). In recent times, no valid studies regarding this topic have been published.

## Multiple Sclerosis

A role of IgE antibodies in the disease was suggested, despite the fact that there was no association between MS and allergies (103). In a study from Mikol and colleagues in 26 MS patients, a total of 128 peptides showed some IgE reactivity (mean 4.9 per subject), compared to 59 among the 15 controls (mean 3.9 per subject) (26). A detailed analysis of short, unique myelin protein-derived peptides (SUMPPs) revealed that for several SUMPPs, MS patients had significantly more reactive IgE, whereas for other SUMPPs, there was no significant difference between MS subjects and controls. The authors speculated that IgE reactive against CNS target antigens may have diagnostic and pathogenic significance.

## Hyperthyroid Graves' Disease

The presence of IgE autoantibodies in Graves' disease was first proposed 40 years ago (104). Elevation of serum IgE  $\geq 170$  U/mL was found in up to 36% of the patients (105–108), but not in another study (109). Furthermore, there was immunohistochemical evidence for IgE involvement in Graves' orbitopathy (110). Studies regarding specific IgE autoantibodies in thyroid disease showed IgE class TPO autoantibodies in 13 of 18 Graves' and in 12 of 17 Hashimoto patients (24) and muscle autoantigens in thyroid associated ophthalmopathy (25). Evidence for a functional relevance of these IgE autoantibodies was shown by Raikow and colleagues, who showed that serum IgE is elevated in connection with certain stages of rapid dysthyroid orbitopathy progression (111).

## Autoimmune Pancreatitis

Elevated total IgE levels are frequent in patients with autoimmune pancreatitis (21, 112), and it was recently suggested that analysis of total IgE in serum might be useful in the differentiation between autoimmune pancreatitis and pancreatic carcinoma (113). Nevertheless, IgE specific targets remain currently unknown, although there may be cross-reactivity with environmental antigens, as patients with higher IgE levels and with allergic diseases were more likely to have onset in March, April, May, August, September, or October (21).

## Asthma

Autoallergic mechanisms have been proposed in murine models of asthma (17, 114). In human asthma, approximately 50% of patients with non-allergic asthma react to intradermal injection of autologous serum, indicating the presence of circulating vasoactive factors and suggesting the possibility of an autoreactive mechanism (18). In one patient with corticosteroid-dependent asthma associated with aspirin sensitivity, the presence of circulating IgE antibodies against 55 and 68 kDa platelet antigens has been described (115). Overall, autoallergy in asthma has not been studied in detail in humans so far.

## Allergic Rhinoconjunctivitis

There is very limited evidence for IgE autoreactivity in allergic rhinoconjunctivitis. IgE antibodies from allergic individuals that bind to natural and recombinant birch profilin also bind

to human profilin (16). Similar cross-reactivity was shown for human acidic ribosomal P2 protein in individuals sensitized to *Aspergillus fumigatus* P2 protein (116).

## Diseases in Which IgE Autoantibodies Were Looked for but Not Found

In chronic rhinosinusitis with nasal polyps no IgE autoreactivity to epithelial antigens, or anti-IgE IgG, has been detected, despite extensive tests (117).

## WHAT DO WE KNOW ABOUT THE RELEVANCE OF IgE AUTOANTIBODIES IN DIFFERENT DISEASES?

IgG-mediated autoimmune diseases occur in up to 9% of the population (118). Whether or not other immunoglobulin subtypes, including IgE, are critically involved in the pathogenesis of autoimmune diseases is largely unknown for most diseases. In contrast, polyreactive natural antibodies, which are not antigen-specific, can often detect self-antigens with low affinity. Most of these natural antibodies belong to the isotypes IgM, IgG<sub>3</sub>, and IgA, and these unspecific antibodies, even if they can bind to self-antigens, are thought to be protective, rather than harmful (119, 120). There is also some published evidence for the existence of natural IgE antibodies against pancreatic cancer cells (121) and conserved biotinylated-enzyme molecules present in many organisms, such as *Anisakis simplex*, *Toxocara canis*, *Ascaris suum*, and *Culex quinquefasciatus* (122, 123). While there are currently no data available on the role and relevance of natural IgE antibodies and how they could affect disease activity, there is some published evidence for a role of antigen-specific IgE against self in different diseases. For some diseases, there is only a single report on the potential role for auto-IgE. As reviewed above, in PV, high concentrations of serum IgE autoantibodies have been detected, and a strong correlation between dsG3-reactive IgE has been observed in patients with acute disease onset, indicating a role for auto-IgE in pemphigus (72). In patients with MS, there are some data indicating that IgE against CNS target antigens may have a pathogenic significance, particularly if other peptide-specific, potentially blocking immunoglobulins are absent (26). In other autoimmune diseases or diseases in which autoimmunity is thought to play a role, some more information on the potential role of auto-IgE has been published.

### Atopic Dermatitis

Although the pathogenesis of AD is still not completely understood, it is generally accepted that the underlying etiology is multifactorial, including environmental factors, impaired skin barrier function, and a hyper-immune activation (124). The role and relevance of autoimmunity in AD is as of yet unclear. In AD patients, many autoantigens can be detected, and IgE against self is highly prevalent (125, 126). Whether these auto-IgE antibodies indeed contribute to disease activity and severity or are merely bystanders cannot be concluded at present (125, 126). There is some evidence, however, that is suggestive of a pathogenic role for IgE against self in AD. Tang and colleagues have summarized this

evidence and conclude that IgE autoreactivity is of importance in the pathogenesis of AD, especially because autoreactivity has been identified in various *in vitro* and direct clinical experiments across distinct study populations (19). Furthermore, significant associations between auto-IgE levels in AD patients and disease severity have been reported (37, 38), while a further two reports show a trend, but no significance for such a correlation (41, 46). In contrast, one investigation did not identify a correlation (39).

If auto-IgE is importantly involved in AD pathogenesis, treatment with anti-IgE antibodies should be able to improve symptoms. Because of the above mentioned investigations, omalizumab has been widely used in treatment refractory AD patients and many case reports and case series have been published. Two recent systematic reviews on the use of omalizumab in AD both come to the conclusion that anti-IgE treatment can be beneficial in the treatment of AD, but that larger clinical trials are missing to fully support this statement (127, 128).

### Systemic Lupus Erythematosus

Autoreactive IgE against a number of different antigens has been reported in SLE (see respective section above). In many investigations, a close correlation between levels of auto-IgG and auto-IgE in the same patients has been shown, making it difficult to estimate the contribution of auto-IgE to the pathology of SLE (49, 51, 129, 130). However, Henault and colleagues reported that the concentration of IgE anti-dsDNA correlates with disease severity and is likely to contribute to disease pathology independent from IgG anti-dsDNA (129). Dema and colleagues similarly show an association of the levels of IgE against different autoantibodies with SLE, comparable to autoreactive IgG levels (49). The best prediction of disease activity was found to be the presence of both, dsDNA-specific IgE and IgG, possibly indicating a role for auto-IgE in SLE (49).

In a recent publication, Pan and colleagues have shown that SLE patients not only have high levels of IgE directed against various autoantigens but also strongly decreased numbers of circulating basophils, suggesting auto-IgE-dependent basophil activation in the blood (131). These authors also stated that basophils from SLE patients showed high rates of activation that closely correlated with SLE activity. How this correlates with disease mechanisms is not clear. Anti-IgE treatment has not been reported in SLE patients as of yet.

### Bullous Pemphigoid

The largest body of evidence for a pathological role of autoreactive IgE in the literature can be found for BP. In those patients presenting with specific IgE directed against the autoantigen BP180, a correlation of auto-IgE and disease severity has been reported (56, 60, 63). Moreover, Freire and colleagues have shown that IgE-anti-BP180 cannot only be found in the serum of BP patients, but also in the skin, bound to the surface of tissue-resident mast cells (132). Furthermore, they show that patient-derived IgE-anti-BP180 complexes can activate basophils, indicating the functionality of these antibodies (132).

In a number of case reports and case series, excellent efficacy of treatment with omalizumab has been shown in BP patients (133–140). While these findings are highly suggestive of a

pathogenic role for auto-IgE in BP, controlled clinical trials with omalizumab in BP are necessary to prove the efficacy of anti-IgE treatment and thus of the relevance of auto-IgE in BP.

## Chronic Urticaria

The evidence for a pathogenetic role of auto-IgE in chronic urticaria has been extensively discussed in a recent review (141). This paper concluded that there are still many aspects of the pathologic mechanisms of CSU that need to be resolved, but that it is becoming increasingly clear that there are at least two distinct pathways, type I (IgE-mediated) and type II (IgG-mediated) autoimmunity, both of which contribute to the pathogenesis of this complex disease.

Since then, further evidence for a role for auto-IgE in CSU has been presented by Schmetzer and colleagues. Overall, more than 200 autoantigens that are recognized by IgE have been detected in CSU patients, and in 80% of more than 1,000 CSU patients, IgE-anti-IL-24 was present (98). Furthermore, levels of IgE-anti-IL-24 in the serum correlated with CSU disease activity, and *ex vivo*, IL-24 was able to activate mast cells after pre-incubation with serum from IgE-anti-IL-24 positive patients, indicating a biological relevance for IgE-anti-IL-24 in CSU patients (98).

The clinical relevance of IgE in both CSU and CindU has been proven in numerous case reports and case series and in a number of randomized-controlled trials using the anti-IgE antibody omalizumab (142–145). In fact, the first multi-center placebo-controlled study of omalizumab in CSU, the XCUISITE trial, was done in CSU patients who had IgE-anti-TPO (146). In this trial, 70% of patients of omalizumab-treated patients, but only 5% of placebo-treated patients experienced complete protection from wheal development, and the onset of omalizumab effects was early after the initiation of treatment. This strongly argues that the rapid and profound neutralization of auto-IgE by omalizumab contributed to its effects and that these IgE autoantibodies play a role in the pathogenesis of CSU. Further support for this comes from a recent study that showed that serum reactivity predicts the time to response to omalizumab therapy in CSU patients (147), suggesting that patients with IgG autoantibody-mediated CSU show delayed responses, whereas patients with IgE-autoantibody-mediated CSU have fast onset of improvement. The exact mechanisms by which anti-IgE treatment leads to the resolution of symptoms in most CSU patients are, as of yet, unclear. Nonetheless, at least in a proportion of CSU patients, the massive reduction of autoantigen-specific IgE is likely to be the most relevant mechanism.

In CindU, there is also a strong indication for an important role of IgE against self. For example, anti-IgE treatment has been shown to be highly effective in CindU in numerous case reports and case series, as well as in two randomized-controlled trials (Table 3). Furthermore, a direct involvement of IgE in some patients with CindU has been shown by passive transfer experiments. In cold urticaria (148, 149) as well as in symptomatic dermographism (150) disease activity was, in some patients, transferable from patients to healthy subjects by intradermal injection of patient sera. In these investigations, IgE was identified to be the relevant serum factor (148–150).

**TABLE 3** | Summary of chronic inducible urticaria patients showing a complete or partial response to omalizumab reported in case reports, case series, and clinical trials.

Condition	Total patients	No. of responders	Percentage responders
Symptomatic dermographism	58	43	74
Cold urticaria	51	39	76
Solar urticaria	47	34	72
Delayed pressure urticaria	32	29	91
Cholinergic urticaria	21	17	81
Heat urticaria	5	3	60
Vibratory angioedema	1	0	0
Aquagenic urticaria	1	1	100
Total	216	166	77

Data contained in this table were obtained from Ref. (145, 151–153).

## WHAT DO WE KNOW ABOUT THE GENETIC BASIS OF IgE-MEDIATED AUTOALLERGY

In an effort to understand the genetic influence on autoallergic diseases, it is best to look first at well-analyzed diseases such as SLE, where autoreactive IgE has been known for four decades (27). The prevalence of SLE and the presence of new autoreactive IgE are remarkably dependent on sex and race being 2.3-fold higher in Black persons than in White persons and 10-fold higher in females than in males (154). The greater incidence in females may be partially explained by the observation that women treated with estrogen and progesterone have a 1.34 times higher risk of developing SLE flares as compared to placebo treated.

Autoreactive IgE has been assessed in two SLE patient cohorts, IgE targeting classical SLE antigens being found in 63.3% of patients of French origin but only 52.9% of the patients from the United States (49). Most prominent in this study was IgE-anti-dsDNA but also auto-IgE against other SLE antigens (Sm, SSA/Ro, SSB/La). Non-SLE IgE only antigens (APEX, MPG, CLIP4) were also found. This autoreactive IgE correlated highly significantly with disease activity (SLEDAI score) and reduced C3 or C4 levels suggesting that IgE facilitates the amplification of autoimmune inflammation (155).

Chronic spontaneous urticaria is another example of an auto-IgE-mediated disease, where a strong and complex genetic bias *via* multiple alleles exists. These include *C5AR1* (156), *FPRL1* (157), *FcγR2B1* (158), *TGFβ1* (159, 160), IgE (161), IL-13 (162), histamine *N*-methyltransferase (163), *PTPN-22* (164, 165), *CTLA-4* (166), and *ACE* (167).

In addition to the well-known loci linked to hypersensitivity and atopy, such as *PLA2G7*, *MS4A2*, *IL4R* (168), *IL-10* (169), *IL12RB1* (170), *STAT4/6*, *CTLA-4* (171), and *GATA3* (172), recent studies identified many new alleles which regulate IgE production independent of external stimuli. However, these are often single findings, and only a genome-wide screening could weigh these findings and determine their relation to atopy, IgE and auto-IgE. One genome-wide screening on alleles influencing total IgE level identified *FCERIA* polymorphisms as having most impact, followed by *RAD50* and *STAT6* as the lowest relation (173).

One genetic variant has been studied in detail which links elevated IgE concentrations to a polymorphism in the *IL21R* gene promoter (174). This –83T–C promoter polymorphism in the *IL21R* gene is linked to a changed response of IgE synthesis to IFN-gamma stimulation (175). If *IL-21* is knocked-out in murine models, IgE production after immunization is increased, while IgG subtypes are decreased in otherwise normal animals (176). In contrast, loss-of-function of the *IL-21R* gene in humans leads to a severe primary immune defect (177). The difference to the murine model is not surprising, given the low degree of homology of the IgE system between man and rodent.

In addition to this *IL-21* gene variant, environmental receptor encoding genes, such as *NOD1* have been linked to asthma (178). This opens a crucial new viewpoint on genetics where environmental stimuli are related to selected genotypes to explain the phenotype. Another example is the  $\beta$ 2-adrenoreceptor gene promoter polymorphism that determines modulation of IgE production as a response to xenobiotics ( $\beta$ 2-agonists and glucocorticoids) (179).

These examples demonstrate the vast complexity of the genetic regulation of IgE synthesis (180). With modern deep sequencing strategies there are more and more variants found which change the risk for asthma and atopy, and influence IgE level. Sequencing of the *IL4* gene alone lead to 14 new, previously unrecognized polymorphisms in addition to only two known previously (181). There are no studies on auto-IgE and *HLA* polymorphisms. However, IgE is involved in antigen uptake *via* immune complexes and presentation *via* MHC class II to CD4 cells (44, 182, 183). Therefore, there is a high likelihood that *HLA* genotypes will be linked to auto-IgE, but the studies need to be done.

## WHAT DO WE KNOW ABOUT THE CELLULAR AND MOLECULAR EFFECTS OF IgE AUTOANTIBODIES?

When looking on the effects of IgE autoantibodies, mast cells and basophils are usually the focus of attention as they express high levels of the high-affinity receptor for IgE (Fc $\epsilon$ RI). Antigen-dependent activation of mast cells and basophils *via* Fc $\epsilon$ RI is the cause of acute allergic reactions induced by the rapid release of preformed mediators from granules and subsequent liberation of *de novo* synthesized lipids, cytokines, and chemokines. Yet, mast cells and basophils are not the only cells that express Fc $\epsilon$ RI and, importantly, other receptors such as CD23 (Fc $\epsilon$ RII) and galectin-3 are capable of binding IgE and inducing cellular responses. Thus, mast cell and basophil activation may be only the tip of the iceberg when considering the biology of IgE autoantibodies and their contribution to diseases. In particular, the function of CD23 in IgE-dependent sensitization of the host to autoallergens, which in turn may further strengthen the production of autoreactive IgE might be of great importance in the development of autoallergies.

In general, all IgE, whether it is autoreactive or whether it recognizes exogenous antigens, can trigger the same cellular responses as there is no evidence yet that autoreactive IgE have special molecular characteristics that drive certain functions/

responses such as, for instance, cytokinergic activity. However, certain activities are not necessarily triggered by autoreactive IgE such as the CD23-mediated transepithelial transport of IgE. Here, we will focus on IgE-binding receptors with regards to their contribution in autoallergy.

## Effects of IgE/Autoantigen on Fc $\epsilon$ RI Signaling

The high-affinity receptor for IgE (Fc $\epsilon$ RI) consists of one IgE-binding  $\alpha$  chain, which binds IgE with a very high affinity ( $10^{10}$  M $^{-1}$ ), but does not contain intracellular signaling motives, one transmembrane-spanning  $\beta$  chain, which crosses the plasma membrane four times and contains an immunoreceptor tyrosine-based activation motive (ITAM), and two identical  $\gamma$  chains each containing an ITAM (184). This  $\alpha\beta\gamma\gamma$  motive is mainly expressed by mast cells and basophils although expression has also been shown in airway smooth muscle cells and bronchial epithelial cells of asthmatic patients (185, 186). A  $\alpha\gamma\gamma$  version of this receptor can be expressed by a variety of other cells including subsets of dendritic cells and monocytes/macrophages (187–189), eosinophils (190), neutrophils (191), and platelets (192, 193). Because of its high affinity for IgE, the receptor is occupied by monomeric IgE. When cross-linked by a multivalent antigen, it triggers signaling cascades leading to the immediate degranulation in mast cells and basophils, i.e., the release of preformed mediators from intracellular granules and *de novo* synthesis of lipid mediators such as prostaglandins and leukotrienes as well as the production of cytokines and chemokines and the expression of various surface markers. These include chemokine receptors such as CCR7 on plasmacytoid dendritic cells (pDCs) (129) or the selectin CD62L on basophils (194) that facilitate the migration of activated cells to local lymph nodes, but also co-stimulatory molecules like CD83 and CD86 on pDCs. Moreover, autoreactive IgE activates pDCs more efficiently and further synergizes with IgG through co-engagement of activating Fc $\gamma$ RIIa, even in concentrations several orders of magnitude below IgG concentrations and drive B cell expansion and plasma cell differentiation (129, 130). Fc $\epsilon$ RI engagement by IgE and allergen also induces IL-16 in Langerhans cells, a chemoattractant for CD4+ T cells, dendritic cells, and eosinophils (195). Thus, autoreactive IgE may have the capacity to augment disease activity in autoimmunity.

Surface bound IgE has been shown to stabilize and enhance the surface expression of Fc $\epsilon$ RI on mast cells and basophils, thereby allowing cells to bind more IgE, which in turn may lower the threshold for antigen-induced cell activation (196). This amplification loop might be of particular importance in autoallergic patients who present with increased serum and tissue IgE levels. Consistently, treatment with antibodies directed against IgE does not only lower serum IgE levels but also Fc $\epsilon$ RI surface expression on dendritic cells, basophils, and mast cells (197–199). Moreover, Fc $\epsilon$ RI-bound IgE promotes mast cell survival and migration (200). Interestingly, certain IgEs even induce mast cell and basophil degranulation and cytokine release in an antigen-independent manner (201). Although the *in vivo* relevance of this “cytokinergic” activity

has not been demonstrated yet, it may have an impact in autoallergy. Cytokinergic IgE molecules associate with themselves and show an enhanced propensity to be polyreactive to various autoantigens (202, 203).

FcεRI-bound and antigen cross-linked IgE becomes internalized rapidly (129, 204). Thus, on the one hand, free serum IgE is cleared by dendritic cells and monocytes. On the other hand, when cross-linked, autoantigens become internalized and are capable of stimulating intracellular pattern recognition receptors such as TLRs. In pDCs, IgE autoantibodies directed against dsDNA become internalized and directed to phagolysosomes where TLR9 becomes activated to trigger the generation of inflammatory cytokines, such as INF-α, IL-6, IL-8, and TNF-α (129). Alternatively, internalized IgE/autoantigen is presented *via* MHC class-II by basophils, cutaneous Langerhans cells, or other dendritic cells in regional lymph nodes or local submucosal sites to naïve T cells to induce T<sub>H</sub>2 cells (194, 196, 205, 206). In systemic lupus erythematosus (SLE), activation of basophils by autoreactive IgE can induce the upregulation of CD62L, MHC-II and the B cell-activating factor BAFF. Activated basophils then migrate into the secondary lymphoid organs, where they produce IL-4 and IL-6, thereby promoting a T<sub>H</sub>2 environment with more IL-4 producing activated T cells and enhanced B cell proliferation with increased IgG<sub>1</sub> and IgE production (194). In addition, CD1c+ dendritic cells may have the capacity for cross-presentation of internalized antigen to induce cytotoxic CD8+ cells. However, this is strongly inhibited by IL-4-producing T<sub>H</sub>2 cells (207). On monocytes, the engagement of FcεRI induces antibody-dependent cell-mediated cytotoxic activities of the cells rather than antibody-dependent cell-mediated phagocytic activities (ADCP), which are linked to the engagement of the low-affinity IgE receptor, CD23 (see below).

In BP, CSU and AD, the degranulation of mast cells and basophils contributes to disease manifestations. This, however, does not occur in systemic lupus erythematosus patients, who lack classical allergic manifestations. A possible mechanism for this is the co-engagement of inhibitory receptors such as FcγRIIb by autoreactive IgG in SLE (208). Moreover, cross-linking of FcεRI in monocytes and dendritic cells induces “late” anti-inflammatory IL-10, which can attenuate basophil and dendritic cell activation and suppresses monocyte phagocytic activity (209–211). Additionally, in monocytes, FcεRI engagement induces the upregulation of indoleamine 2,3-dioxygenase (IDO), which inhibits T cell proliferation and activates FOXP3+ regulatory T cells through the depletion of tryptophan (212).

A soluble version of FcεRI consisting of a single α-chain has been described (213). How sFcεRI is generated *in vivo* is not known so far. *In vitro* experiments suggest that it is generated during cellular FcεRI engagement. sFcεRI may bind to IgE with similar affinity as membrane-bound FcεRI and, therefore, might serve as a soluble regulator of free IgE and IgE-mediated cellular activation. Binding in a 1:1 ratio to IgE, it has the potential to prevent IgE from binding to the cellular receptor, and could negatively affect FcεRI expression levels. *In vitro* and *in vivo* studies with sFcεRI show inhibitory properties on mast cell and basophil

degranulation (214). Its impact in autoallergy, however, needs to be determined.

## Effects of IgE/Autoantigen on CD23 (FcεRII) Signaling

Most studies on the effects of IgE-mediated responses focus on mast cells or basophils and FcεRI signaling, as they are responsible for the immediate allergic response. However, the so-called “low affinity” receptor for IgE, CD23, has important functions in positively or negatively regulating IgE synthesis as well as antigen presentation to T cells (215). It is expressed on various cells including epithelial cells, activated B and T cells, Langerhans cells, plasma cells, monocytes, and eosinophils (196). CD23 belongs to the family of C-type lectins, which are calcium-dependent carbohydrate binding structures and contain three lectin domains located on the C-terminal extracellular head of the molecule. Interestingly, binding of IgE to the head domains seems not to involve carbohydrate structures (216). Although the affinity of a single CD23 head for the IgE-Fc is comparably low, the combined interaction of all three heads with IgE results in an strong binding with an affinity ( $10^8$ – $10^9$  M<sup>-1</sup>) that is comparable to that of FcεRI (215). Interestingly, CD23 is prone to shedding by disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) resulting in various soluble forms (monomeric or trimeric with varying sizes), all of which are capable to bind IgE (214, 217) and are found in autoimmune diseases like SLE where auto-IgE has been described (218). Multiple ligands/interaction partners other than IgE have been described to interact with CD23 and are important for its function including the complement receptor 2, 3, and 4 (CD21; CD18/CD11b; CD18/CD11c), MHC-II, the receptor for vitronectin (αVβ3-integrin) and the αVβ5-integrin (215, 219). One important function of CD23 with regards to autoallergy is probably associated with the regulation of IgE production by B cells committed to IgE secretion. IgE-induced engagement of membrane CD23 induces a negative feedback while sCD23 (trimeric) through co-ligation of CD21 enhances IgE production (215). Moreover, CD23 bound IgE-antigen complexes can be presented to T cells *via* a process called facilitated antigen presentation (FAP). In FAP, the antigen-loaded IgE-CD23 gets internalized and loaded onto MHC-II molecules for presentation on the B-cells surface (219). A Th2 environment, as derived by activation of mast cells and basophils *via* FcεRII activation, may support this by increasing the expression of CD23 on B cells. Importantly, any activated B cell that expresses CD23, can present allergens to T cells independently of the specificity of the B cell receptor (BCR). By this, CD23-FAP can lead to epitope spreading, a process where the response to one epitope encountered by the BCR induces epitope-specific immunoglobulin production against the allergen internalized by CD23 (215). Epitope spreading can occur intra- or intermolecularly and is thought to be the driving cause for the development of polyspecific allergies to unrelated antigens. It is, therefore, of particular importance for the development of autoallergies. Antigen presentation via the CD23–MHC-II axis is as efficient as presentation of antigens by dendritic cells mediated by FcγRs and by far more efficient than BCR internalization (220). This is particularly dangerous when epitopes of an autoantigen and a pathogen are very similar



in sequence and/or conformation (molecular mimicry) and IgE against the pathogen (IgE<sub>PATH</sub>) also binds to the autoantigen (221). Low-affinity IgE<sub>PATH</sub>-autoantigen interactions can lead *via* FAP dependent epitope spreading to high affinity auto-IgE. For many autoimmune diseases, such as SLE and BP, where IgE autoantibodies have been identified, B cell epitope spreading has been recognized as an important contributor for disease development.

On monocytes and macrophages, engagement of CD23 induces nitric oxide synthase and proinflammatory cytokines and importantly mediates IgE-dependent phagocytosis of targeted cells suggesting a use for immunotherapy, for instance in cancer (188, 222). Interestingly, auto-IgE to tumor antigens can be found in tumor tissue as well as systematically, suggesting a tumor suppressive function of these IgE autoantibodies.

## Effects of IgE/(Auto)Antigen on Galectin-3 Signaling

Galectin-3 is a secretory lectin containing a carbohydrate recognition domain connected to a non-lectin linker domain that associate to form a pentameric structure like IgM molecules. Galectin-3 is expressed by various immune cells including mast cells, basophils, neutrophils, monocytes, Langerhans cells, as well as T and B cells (196). It can be found in the nucleus, intracellular vesicles, or exosomes of expressing cells or gets secreted by a yet not fully characterized mechanism (223). Following secretion, it interacts with a large variety of cell surface and extracellular matrix proteins including IgE and FcεRI. Interestingly though, galectin-3 appears to have distinct binding capacities for IgE isoforms that are differentially glycosylated, although the consequence of this phenomenon in allergy and autoallergy is not clear (224). Because it is capable of binding to IgE and FcεRI, it can activate mast cells and other FcεRI-expressing and/or IgE-loaded cells in an IgE-dependent or independent manner and boost mast cell and basophil activation. In autoimmune diseases, galectin-3 is often increased in the serum and in tissues and may support auto-IgE-induced inflammation. However, most effects of galectin-3 on the immune system are independent of its ability to crosslink IgE and FcεRI. Its effects and relevance in autoallergy, therefore, need to be determined carefully (214, 225).

## GAPS OF KNOWLEDGE, UNMET NEEDS, AND UNANSWERED QUESTIONS

### Need for Improved Detection Methods

There are two different major drawbacks of the tests currently used to assess autoreactive IgE. First, different methods show a high variability and low reproducibility of IgE reactivity (226). This has been best demonstrated using the well characterized BP autoantigen BP180-NC16A. An improved ELISA method showed a significantly higher frequency of NC16A-specific IgE autoantibodies in the sera of BP patients than previously described (66). This study also demonstrated that most BP sera contain both, IgE and IgG class autoantibodies specific for NC16A and that IgG reactive to the same autoantigen as IgE can mask the detection of autoreactive IgE. This is the second major drawback of direct ELISA methods. This problem can be addressed by the use of

indirect ELISA methods, where total IgE is first captured on the plate by anti-IgE and labeled autoantigen is used for detection (98). This approach, however, also has limitations. Saturation of the anti-IgE with non-autoreactive IgE in sera with very high total IgE concentrations can lead to the underestimation of autoallergen-specific IgE. Also, this method requires recombinant IgE to be able to calculate the specific IgE concentration in international units.

Yet unaddressed questions are the relevance of different conformational states of IgE, such as the bent-form, that may not be detectable by ELISA depending on which anti-IgE is used (227). Relevant cross-autoreactive IgE might also be prone to oligomerization due to stacking, which may hinder binding to capture antibodies.

Finally, autoreactive IgE may be preferentially captured in the tissue in patients with high FcεRI expression due to high IgE levels. Increased levels of IgE are frequently seen in patients with chronic urticaria and in atopic individuals (228, 229). *Vice versa*, as antigen reactivity encoded by the Fab-domain can change also the Fc part and, therefore, influence Fc receptor binding, some autoreactive IgEs might be over- or underrepresented in the non-cell bound IgE fraction due to changed FcεRI binding (230). Even assays detecting non-autoreactive IgE often fail to show a clinical relevance (231). The questions above need to be addressed for IgE in general, not only autoreactive IgE, in further studies, and improved methods need to be developed.

## What Leads to the Development of Autoantibodies of the IgE Isotype?

There are several possible mechanisms that might lead to a preference of IgE isotype for autoantibodies. Most IgE autoantigens are phosphorylated molecules (97, 232, 233). It has been demonstrated that IgG autoantibodies in BP preferably recognize a phosphorylated epitope (232, 234). The importance of phosphorylation for the development of autoantibodies in general has been shown for myeloperoxidase-anti-neutrophil cytoplasmic IgG autoantibodies in a mouse model (235). However, further studies are needed to assess whether this is a general rule preferably for IgE autoantigens, or for all autoantigens.

## IgE Cross-Reactivity Remains Largely Unexplained

In contrast to IgG and IgA, IgE has, in general, a much higher degree of cross-reactivity. This makes the determination of antigen-specific IgE difficult. As of now, very little is known about cross-reactivity of IgE autoantibodies. One study that performed site-directed mutagenesis of an allergenic peptide found that even after the mutation of all of the four residues that are mainly involved in IgE binding, the IgE still bound, albeit with a 100-fold reduced affinity (236). Furthermore, many studies have shown IgE cross-reactivity to structurally similar allergens, e.g., sensitization to the fungus *F. proliferatum* may lead to allergy to penicillin (237).

Usually, IgE cross-reactivity is explained by the recognition of carbohydrate-containing epitopes such as in cross-reactive IgEs against wheat/pollen or latex/hymenoptera proteins (238–241)

or between different pollen allergens (242–244). Hierarchies of cross-reactivity toward different pollen allergens have been established (245).

In latex–pollen–food allergy, a good example of non-carbohydrate based cross-reactivity, cross-reactive IgE binds to latex and maize (246) or other food allergens (247). The antigenic epitopes of these allergens are well characterized and show only a low degree of sequence homology. The cross-reactivity can only be explained by a similar charge distribution, which, in the case of IgG, does usually not lead to cross-reactive antibodies (248).

Other examples of IgE cross-reactivity include pollen–food allergy, such as apple–birch allergy or pollen–fruit allergy (249–253), dog–cat allergy (254, 255), poultry–meat allergy (256), fish–chicken allergy (257), birch–oak allergy (258), latex–hymenoptera allergy (239–241). IgE cross reactivity to latex and parasites like *Schistosoma* has also been described (259, 260). In mice sensitized to birch pollen that also developed anaphylactic reactions to apple, desensitization to birch pollen also provided protection from anaphylaxis to apple (261). Similar experiences have been reported in allergic patients, where tolerance induction against one allergen also reduced reactivity toward other allergens (262). While IgE cross-reactivity between classical allergens is much more common than previously thought (263), cross-reactivity between autoallergens needs to be investigated in future studies.

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## Unanswered Questions?

Many questions on IgE autoantibodies remain unanswered.

- Is IgE to self different from IgE to exogenous antigens in terms of its biochemical properties, its glycosylation, or its folding?
- Where is auto-IgE produced and what B cells are involved?
- Does the auto-IgE come from CD5+ B1 B cells of the marginal zone of the spleen (poorly negatively selected B cells that often produce autoantibodies) or from B cells that were previously allergen or pathogen reactive?
- Does the production of auto-IgE precede the onset of autoallergic signs and symptoms and when and why does it stop?

These and other questions are currently addressed by ongoing research. The answers that will come from these and future studies will help to better understand the biology and relevance of IgE autoantibodies in disease and to develop better approaches for the prevention and treatment of autoallergies.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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