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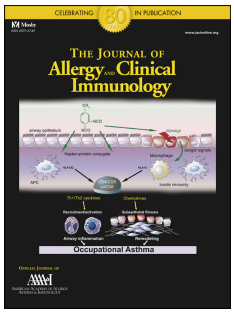

The Role of IgE in Autoimmunity

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PII: S0091-6749(16)30190-7

DOI: 10.1016/j.jaci.2016.04.007

Reference: YMAI 12081

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 5 April 2016

Revised Date: 21 April 2016

Accepted Date: 21 April 2016

Please cite this article as: Sanjuan MA, Sagar D, Kolbeck R, The Role of IgE in Autoimmunity, *Journal of Allergy and Clinical Immunology* (2016), doi: 10.1016/j.jaci.2016.04.007.

Title: The Role of IgE in Autoimmunity

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Keywords: IgE, autoimmunity, interferon, plasmacytoid dendritic cells, basophil, systemic lupus erythematosus, bullous pemphigoid, chronic spontaneous urticaria, atopic dermatitis

Abbreviations used

AAb	autoantibody
AD	atopic dermatitis
APEX	APEX nuclease 1
BAFF	B-cell activating factor
BP	bullous pemphigoid
CLIP4	CAP-Gly domain-containing linker protein family member 4
CSU	chronic spontaneous urticaria
DAMP	damage-associated molecular pattern molecule
dsDNA	double-stranded DNA
FcεR	Fc-epsilon receptor
FcγR	Fc-gamma receptor
GATA3	GATA binding protein 3
IFN	interferon
IgE	immunoglobulin E
IgG	immunoglobulin G
IRF-7	interferon regulatory factor 7
MHC	major histocompatibility complex
MPG	N-methylpurine DNA-glycosylase
MyD88	adaptor protein myeloid differentiation primary response gene 88
NF- κB	nuclear factor κB
PAMP	pathogen-associated molecular pattern
pDC	plasmacytoid dendritic cell
RA	rheumatoid arthritis
RNP	ribonucleoprotein
SLE	systemic lupus erythematosus
SS-A	Sjögren's-syndrome-related antigen A
SS-B	Sjögren's-syndrome-related antigen B
TLR7	toll-like receptor 7
TLR9	toll-like receptor 9

ABSTRACT

There is accumulating evidence to suggest that IgE plays a significant role in autoimmunity. The presence of circulating self-reactive IgE in patients with autoimmune disorders has been long known, but at the same time largely understudied. Studies have shown, however, that the increased IgE concentration is not associated with higher prevalence for atopy and allergy in autoimmune diseases like systemic lupus erythematosus. IgE-mediated mechanisms are conventionally known to facilitate degranulation of mast cells and basophils and promote Th2 immunity, mechanisms that are not only central to mounting an appropriate defense against parasitic worms, noxious substances, toxins, venoms and environmental irritants, but which also trigger exuberant allergic reactions in allergies. More recently, IgE autoantibodies have been recognized to participate in the self-inflicted damaging immune responses that characterize autoimmunity. Such autoimmune responses include direct damage on tissue-containing autoantigens, activation and migration of basophil to lymph nodes, and, as observed most recently, the induction of Type 1 interferon responses from plasmacytoid dendritic cells. The importance of IgE as a central pathogenic mechanism in autoimmunity has now been clinically validated by the approval of omalizumab, an anti-IgE monoclonal antibody for patients with chronic spontaneous urticaria, and for the clinical benefit of patients with bullous pemphigoid. In this review, we summarize recent reports describing the prevalence of self-reactive IgE and discuss novel findings that incriminate IgE as central in the pathogenesis of inflammatory autoimmune disorders.

INTRODUCTION

Five decades ago, the last of the antibody classes, immunoglobulin E (IgE), was uncovered. Found only in mammals, IgE is the least abundant immunoglobulin isotype. IgE signals through two types of Fc-epsilon receptors (FcεR), the high-affinity receptor FcεRI and the low-affinity receptor FcεRII. The role of IgE for host defense is mainly triggering reactions that result in protection against parasitic worms (helminths) and the expulsion of environmental substances that include toxins, venoms, irritants and xenobiotics. Allergies represent the pathogenic detrimental response of IgE to environmental innocuous substances, commonly referred to as allergens, which in the most severe cases can result in systemic anaphylaxis and death.[1-3] In both these cases, IgE recognizes exogenous antigens and triggers an immunological response that is associated with mast cell degranulation, which results in the release of biogenic amines, lipid mediators, proteases and cytokines. Elevated IgE levels have also been reported in systemic lupus erythematosus (SLE) and other autoimmune disease that are driven by the aberrant production of interferon and self-damaging autoantibodies (AAb). SLE has been characterized by a wide spectrum of AAb from all five immunoglobulin classes that combine with autoantigens triggering self-targeted immune responses. AAb to nucleic acid-containing antigens are common in SLE patients and they include antibodies that react with DNA directly, nuclear histones, nuclear acidic protein antigens, Smith (Sm) antigen, ribonucleoprotein (RNP) and Sjögren's-syndrome-related antigen A and B (SS-A, SS-B). The production of these AAb by antibody-secreting plasma B-cells fluctuates during the course of the disease and is central to disease pathogenesis. Plasma B-cells that arise from B-cell proliferation and differentiation in the presence of B-cell activating

factor (BAFF) or IL-6, secrete self-reactive AAb of all subclasses, including IgE. The presence of circulating IgE-AAb in SLE and other autoimmune diseases is not a recent discovery, having been described for the first time almost 40 years ago.[4] However, this area of research has made significant strides since its inception. Applying new technologies with improved sensitivities for IgE detection and the use of protein expression libraries, have strongly advanced our understanding of IgE-AAb prevalence and antigen specificity in recent years. In addition, most of the original work had focused on understanding whether IgE-AAb trigger allergic responses in patients, a hypothesis that has thus far not gained much traction. Instead, as will be discussed in this review, a number of more recent studies have uncovered that IgE-AAb are not just bystanders in autoimmune diseases, but rather are active contributors to disease pathogenesis. Research has shown a positive correlation between serum IgE and disease activity in SLE compared to controls.[5-8] Self-reactive IgE-AAbs have also been described in a number of dermatological conditions such as bullous pemphigoid (BP), chronic spontaneous urticaria (CSU) and atopic dermatitis (AD). They either have been shown to specifically bind to self-antigens, or to cross-react with environmental substances. Those self-antigens, which share IgE cross-reactivity with environmental allergens, are often referred to as “autoallergens” in the literature. In what capacity and circumstances IgE-AAb contribute to diseases remains largely obscure, though some of their functions are starting to emerge. Successful clinical trials with omalizumab, a monoclonal antibody that binds to the Fc-portion of IgE and blocks its interaction with FcεR, in patients with CSU clearly indicate a pathogenic function of IgE in CSU. Similarly, patients with BP have been shown to benefit from treatment with omalizumab. Ongoing clinical research

and additional clinical studies with anti-IgE therapies may shed additional light on the pathogenic activity of IgE-AAb in autoimmune diseases. Here we will discuss our current understanding of the role of IgE in autoimmunity and propose future areas of research.

IMMUNOGLOBULIN-E IN SLE

After the discovery of IgE, the scientific community focused on understanding its physiological importance for the host defense against parasitic infestations and its pathophysiological role in allergies. It was shortly after its discovery though that the presence of IgE-AAb in patients with rheumatoid arthritis (RA) and with active SLE was reported and a role in autoimmunity postulated.[4] Initial studies, however, performed measurements of IgE-AAb in small cohorts using methodologies with poor sensitivity, which underreported their prevalence. Further, incidence of elevated IgE in allergy and parasitic infestation confounded any studies linking IgE to the pathogenic mechanism of autoimmunity, making this phenomenon understudied and frequently ignored. Recently, a number of studies in diseases such as SLE or pemphigus have started to reveal that IgE-AAb are more prevalent in autoimmunity than previously suspected along with emerging evidence that associates IgE-AAb with key pathophysiological mechanisms of autoimmunity.

Prevalence and specificities of IgE-AAb in SLE

SLE is a syndrome affecting multiple organs with circulating self-reactive antibodies of complex specificities. Hypergammaglobulinemia and IgG antinuclear antibodies are common laboratory findings in patients with active SLE. Several studies have shown that total IgE is also elevated, which correlates with more severe disease manifestations.[5-8] In studies demonstrating elevated serum IgE, frequency of atopy (eczema, allergic rhinitis and asthma) did not concurrently increase in adult patients.[7, 9-11] Even in SLE individuals with childhood onset of allergies, no association with high total IgE levels was

observed.[10] In fact, all aforementioned studies and information gathered by Morton and colleagues,[12] cumulatively show that frequencies of food allergy, insect allergy, allergic skin disease and atopy were remarkably similar between SLE patients and controls.

The abnormal elevation of IgE in SLE prompted further investigation into their specificities. From these studies, it is now clear that at least a fraction of the circulating IgE are self-reactive, with nearly all IgE-AAbs reported binding directly or indirectly to nucleic acids, as it is also the case for the most important IgG-AAbs found in this disease.[13] A study of a SLE cohort that included patients from France and the USA, revealed the presence of self-reactive IgE against at least seven autoantigens, for which 65% of the subjects presented IgE-AAb to one or more of them (Table I).[14] The prevalence was even greater within the subgroup of patients with active disease (83%). The levels of IgE specific for double-stranded DNA (dsDNA) showed the most significant association with disease activity and hypocomplementemia.[14] This observation is further supported by our own studies showing that in a majority of patients, the level of anti-dsDNA IgE in circulation is a risk factor for SLE activity, independent of the concentration of their dsDNA-specific IgG counterpart.[15] All other IgE-AAb identified (including those against Sm, SS-A, and SS-B) correlated with disease activity.[14] For some of the autoantigens described in SLE however, it is unclear whether the IgE-AAb formed against them is the result of autoimmunity or cross-reaction (molecular mimicry) against an allergen. This is the case for anti-ribosomal P2 IgE, which is found in SLE but is also recognized as a minor allergen in fungal allergy.[16]

Interestingly, the study of the French-American cohort discovered circulating IgE-AAbs with specificities for three new autoantigens, APEX nuclease 1 (APEX), N-methylpurine DNA-glycosylase (MPG) and CAP-Gly domain-containing linker protein family member 4 (CLIP4). These autoantigens were unique in that they seemed specific for eliciting IgE-AAb, but not AAb of the IgG class.[14] This is different from what has been typically described for other autoantigens, for which high levels of specific IgEs are significantly correlated with the presence of high levels of IgGs[14-16], suggesting their formation is co-regulated. Considering that the discovery of IgE-AAb in lupus has been largely assisted by the previous knowledge of the specificities of known IgG-AAb, it is reasonable to hypothesize that further studies focusing on the discovery of IgE-specific autoantigens will most likely yield IgE-AAb with new specificities in SLE. In summary, IgE-AAb are highly prevalent in SLE and are linked to disease activity. This strongly suggests that their presence contributes to autoimmune pathobiology associated with SLE, which is the premise for treatment of patients in SLE in an ongoing clinical trial that uses anti-IgE antibody (omalizumab) (NCT01716312).

Anti-dsDNA IgE in lupus nephritis

Anti-dsDNA IgG AAb are a well-characterized marker of SLE and are part of the SLE classification criteria. Increased levels of IgG antibodies to dsDNA are found in a majority of patients, and their levels are significantly higher in the most severe forms of lupus nephritis (class IV).[17] IgE-AAbs against dsDNA are found in all subsets of patients investigated, including those with discoid lupus, thrombocytopenia, acute cutaneous lupus or secondary Sjogren's. Notably, their incidence was much greater in patients with

lupus nephritis (70%), suggesting a key link with kidney pathogenesis.[15] Further evidence supporting this notion was the presence of IgE precipitates in kidney biopsies from patients[18,15] and the fact that a great majority (82%) of the patients with the most severe form of lupus nephritis were positive for anti-dsDNA IgE.[15] The Franco-American cohort also found a significant association between anti-dsDNA-specific IgE and lupus nephritis, while the levels of IgE against other classical nucleic acid-containing autoantigens found in lupus (Sm, SS-A/Ro, SS-B/La) were not associated with the kidney manifestations of the disease.[14] Intriguingly, all of the newly discovered antigens that were associated predominantly with IgE-mediated autoimmunity and did not trigger IgG-AAb (APEX, MPG, and CLIP4) also showed a highly significant association with active nephritis. About half of the patients with SLE develop nephritic manifestation during the course of the disease.[19] These studies suggest that IgE-AAb has the potential to be a key player in the pathophysiological mechanisms leading to nephritis in SLE. It is, then, highly plausible that research focused on the discovery of novel kidney autoantigens will provide new evidence that will guide our understanding of how the disease develops in this subset of SLE patients.

IgE-AAb and interferons in SLE

Interferons (IFN) have pleiotropic roles in the immune system. They are key drivers of autoimmunity, as they support the functions of monocytes and T-cells, the activation and proliferation of B-cells, and the differentiation of plasma cells into autoantibody-producing cells.[20, 21] Their involvement in SLE pathogenesis has now been clinically validated in two phase 2 proof of concept studies using sifalimumab[22] and anifrolumab[23],

which block IFN-α and the Type I IFN receptor, respectively. Plasmacytoid dendritic cells (pDCs) are a subset of dendritic cells capable of releasing up to 1000 times more Type 1 interferon than any other cell type,[24] and there is a mounting body of evidence that highlights their role as the main producers of pathogenic interferons in SLE.[25, 26] They also have a vital role to play in antiviral responses[27] through intracellular sensing of viral nucleic acids by TLR7 (RNA) and TLR9 (DNA). Upon binding to these receptors, nucleic acids trigger the recruitment of the adaptor protein myeloid differentiation primary response gene 88 (MyD88) to the plasma membrane and initiate a signal transduction cascade that involves the sequential phosphorylation of kinases IRAK4/1 and TRAF6 and subsequent activation of the transcription factors nuclear factor κB (NF-κB) and interferon regulatory factor 7 (IRF-7).[28, 29] Activation of these transcription factors are ultimately responsible for initiating a complex antiviral response, characterized by the release of substantial amounts of Type 1 interferons (mainly IFN-α), by the secretion of pro-inflammatory cytokines and chemokines, and by the maturation of pDCs into antigen presenting cells (Fig 1). The reclusion of TLR7 and TLR9 in intracellular compartments is critical to restrict the access of these receptors to circulating self-nucleic acids, thus limiting inappropriate activation and maintaining self-tolerance. The criticality of this reclusion is particularly highlighted in a study in which animals develop lethal auto-inflammatory disease when TLR9 was engineered to be expressed at the cell surface.[30] AAb raised against self-nucleic acids or associated proteins (like nucleosomes, Sm, or RNP) that are found in SLE undermine these aforementioned safeguards by shuttling the nucleic acids via interaction with cell-surface Fc-gamma receptor IIa (FcγRIIa) directly into intracellular compartments where they activate TLR7

and TLR9,[31] thereby triggering interferon secretion. Recently, we have shown that IgE-AAb can deliver nucleic acids to the same intracellular compartment via the high-affinity FcεRI expressed on pDCs (Fig 1). IgE blockade reduced the secretion of IFN-α in peripheral blood mononuclear cells that were incubated with serum from dsDNA-IgE seropositive SLE patients, suggesting a role for pathogenic IgE-AAb in the interferon responses underlying the disease.[15] Along with inducing robust IFN-α release, in vitro immune complexes formed by DNA plus anti-dsDNA IgE triggered the secretion of proinflammatory cytokines from pDCs and induced pDC maturation, migration and antigen presentation to T-cells with similar or better intensity than dsDNA/IgG immune complexes. Furthermore, IgE synergized with IgG to trigger all the responses described above, which can be explained by the combined action of FcγRIIa and FcεRI for enhanced uptake of ds-DNA containing immune complexes and subsequent TLR9 activation. This was even the case when IgE was several orders of magnitude below the amount of IgG in the immune complexes formed in vitro, a scenario that resembles what is found in patients. The profound effect that IgE-AAb have on pDCs despite their significantly lower concentrations in comparison to IgG-AAb in SLE may be explained by the high affinity of FcεRI for IgE[32] in comparison to FcγRIIa for IgG.[33] FcεRI is a tetrameric receptor complex in mast cells and basophils consisting of one alpha chain that binds to IgE, two gamma chains that initiate signal transduction, and one beta-chain that amplifies the signal. pDCs however do not express the beta-chain,[34] and neither the low affinity FcεR.[15] Therefore all these novel responses described for pDCs seem to be driven by the trimeric form of FcεRI. However, it is not known whether unique signaling

generated by this receptor (as compared to the tetramer form, or low affinity FcεR) plays any role orchestrating them, which remains an interesting area for future research.

Additional evidence for a pathological role of IgE-AAb in SLE comes from the presence of IgE deposits, pDC infiltration, and expression of the interferon-regulated protein MxA in the kidney of lupus patients, suggesting a mechanistic link between IgE and the local interferon responses (Fig 2). There were also areas in SLE kidney where both pDCs and B-cells were in close proximity, indicating possible cell-cell interactions. Indeed, in vitro pDC/B-cell co-cultures stimulated with DNA-IgE immune complexes promoted B-cell proliferation and plasma cell differentiation, which was found to be dependent on pDC-mediated secretion of Type I IFN and IL-6.[15]

Finally, it is worth noting that IgE against allergens most likely will not result in the induction of interferon responses similar to IgE-AAb in SLE. This is likely due to the nature of the antigen and the response it elicits. The pathogenic autoantigens found in SLE are largely associated with nucleic acids, while that is not the case for most allergens. Therefore IgE against lupus autoantigens have the ability to trigger interferon-mediated responses via TLR7 and/or TLR9, while IgE against allergens lack this capability. In fact, cross-linking of FcεRI at the cell surface of pDCs in the absence of accompanied nucleic acids results in the blocking of interferon responses induced by experimental TLR7/9 agonists,[15, 35, 36] and omalizumab prevents fall asthma exacerbations, which is associated with high levels of IFN-α production in the responders.[37] The recognition that IgE-AAb trigger IFN-α responses also provides

mechanistic insights into why allergies may not be more common in SLE. IFN-α has been found to reduce allergic responses by preventing GATA3 from enhancing its own expression in T-cells, thus destabilizing Th2 lineage commitment.[38, 39] IFN-α also inhibits degranulation of eosinophils,[40] the release of histamine in mast cells,[41] and prevents IL-3-mediated priming of basophils.[42] Finally, due to the expression of the inhibitory Fc-gamma receptor IIb (FcγRIIb) on mast cells and basophils, but not pDCs, simultaneous activation of FcγRIIb in SLE may suppress FcεRI and FcγRIIa activation by immune complexes on mast cells and basophils,[43] but not on pDCs.

IgE-AAb and basophils in SLE

Basophils are the least abundant granulocyte in blood. In vitro experiments suggest they are capable to degranulate in response to IgE bound to common SLE autoantigens.[44, 45] Circulating basophils in SLE subjects presented with an activated phenotype. Patients' basophils had elevated L-selectin, a cell adhesion molecule that confers transendothelial migration into secondary lymphoid organs, which, accordingly, facilitated infiltration of the basophils into the lymph nodes and spleen of SLE patients but not control subjects. A small number of basophils expressed HLA-DR in mild and active disease states, suggesting the potential for this subgroup of cells to act as antigen presenting cells in the secondary lymphoid tissues. Notably, both of these cell surface proteins were associated with increased disease activity and active lupus nephritis.[46] The activated phenotype of basophils in SLE suggests that they are linked to disease pathogenesis; however, the mechanistic links between them and the disease remains to be fully elucidated. Mouse models of spontaneous lupus-like disease have provided some answers to this question.

Autoimmunity in these models is driven by the formation of AAb for which IL-4 and IgE are partly responsible. Basophils secreted IL-4 and expressed MHC-II and BAFF, suggesting they could potentially be involved in the activation of T-cells and survival of B-cells and plasma cells in lymphoid tissues, which ultimately leads to an amplification of autoantibody production (Fig 2).[46, 47] Despite the presence of nephritis, this preclinical model of lupus seemed to mostly recapitulate the roles of basophils only in lymphoid tissues, because the detection of IgE deposits in the kidney of mice,[15, 18] in contrast to that in human SLE subjects, has been notoriously difficult. In summary, basophils may participate in the loss of tolerance to self by homing to lymphoid organs and acting on plasma cells, resulting in the amplification of autoantibody production.

IGE-AAB IN BULLOUS PEMPHIGOID

Pemphigoid diseases are a heterogeneous group of diseases that are clinically characterized by skin blistering that results from an autoimmune attack against hemidesmosomal proteins situated in the dermal-epidermal junction (Fig 2).[48] Accounting for approximately 80% of all cases, BP is the most common pemphigoid condition, ranging from 13–62 cases per 1 million in central Europe and in the UK.[49] The main autoantigens identified in patients with BP are the hemidesmosomal proteins BP230 and BP180. BP180, the best studied autoantigen in BP, is a cell-substrate adhesion molecule expressed by keratinocytes. Although BP180-specific IgG-AAb have been identified to be by far the most abundant immunoglobulin class, AAb of the IgE class with the same epitope specificity have also been described in about 70–90% of BP patients.[50, 51] In all cases, both classes of AAb co-existed in patients, with increasing

levels associated with disease severity.[52, 53] The initial phase of lesion development in BP is characterized by urticarial plaques, dermal edema, eosinophilic inflammation and mast cell activation, suggesting a pathogenic mechanism involving IgE-AAb-mediated activation of mast cells in the skin triggered by local sources of soluble BP180.[54, 55] Indeed, injection of IgE purified from BP patients into human skin grafted onto athymic nude mice recapitulated the initial phase of disease, characterized by elevated plaques and mast cell degranulation in comparison to injection of IgE from control subjects.[56] Further, basophils from BP patients, but not from control subjects, underwent degranulation in vitro upon BP180-induced cross-linking.[50] Together, these data suggested a pathogenic role of IgE-AAb in BP through FcεRI-induced degranulation of mast cells and basophils. In addition, deposition of IgE in the basement membrane zone of affected skin,[50, 57] along with evidence that binding of IgE to cell surface BP180 results in internalization, cytokine release and a decrease in the number of hemidesmosomes, provides an alternative explanation of FcεR-independent pathological activity of IgE.[51] The final proof for a pathogenic role of IgE-AAb in BP came from clinical trials with omalizumab, an anti-IgE monoclonal antibody preventing the interaction of IgE with FcεRI. Treatment with omalizumab resulted in decreased itching, decreased blister count, reduced urticarial plaques and a reduction in eosinophilic inflammation.[58, 59] These clinical improvements could be achieved despite the presence of excess amounts of IgG-AAb with similar autoantigen specificity, suggesting that only relatively low titers of IgE-AAb are sufficient to contribute to BP pathology, most likely due to their high affinity interaction with FcεRI.

IgE-AAB IN CHRONIC SPONTANEOUS URTICARIA

Chronic spontaneous urticaria (CSU), also referred to as chronic idiopathic urticaria, is a disease characterized by the spontaneous emergence of hives and angioedema of the skin, and whose underlying causes are largely unknown.[60] IgE-dependent activation of mast cells in the skin seems an important mechanism of CSU pathology, since patients with elevated tryptase levels are able to respond to anti-histamines.[61] In addition, patients benefit from treatment with omalizumab (anti-IgE), which has recently been approved for CSU,[62, 63] and for which a recent meta-analysis of randomized clinical trials concluded that it is consistently effective while showing a placebo-like safety profile.[64] Although CSU may not be considered a classic autoimmune disease, there is sufficient evidence for autoimmunity, at least in a subgroup of patients,[65] where circulating immune complexes lead to mast cell degranulation. CSU patients have also been found to respond to cutaneous injections of their own serum.[66] Major histocompatibility complex (MHC) class I and II alleles are highly associated with CSU, [67, 68] and its prevalence can coincide with other autoimmune conditions, including SLE.[65, 69] About 40% of patients with CSU develop IgG-AAb against FcεRI and/or IgE, which is associated with longer duration of disease and poor treatment response to anti-histamines.[70] Also described in CSU are AAb of the IgE class directed against ds-DNA[45, 71] and thyroglobulin and thyroperoxidase.[71-73] These AAb are often associated with high total IgE, thyroiditis and SLE.[71] In some patients anti-dsDNA IgE has been shown to activate basophils.[45] Overall, these data suggest that, in patients with CSU, IgE-AAb may contribute to symptoms of disease mainly through the activation of FcεRI on mast cells and basophils (Fig 2).[65]

IGE-AAB IN OTHER AUTOIMMUNE DISORDERS

In addition, there have been reports demonstrating the presence of elevated total IgE and IgE-AAb in other autoimmune diseases:

- IgE-AAb specific for retinal S antigen in patients with uveitis.[74]
- Granulocyte- and organ-specific antinuclear IgE-AAb in patients with rheumatoid arthritis.[4]
- Elevated IgE in patients with CD3γ deficiency [75] and anti-IgE-AAb in patients with systemic sclerosis.[76]
- IgE-AAb targeting thyroid peroxidase in Hashimoto's thyroiditis and Graves' disease.[77, 78]
- IgE reactive with myelin derived peptides in multiple sclerosis.[79]
- Anti-SS-A IgE in mothers with fetal loss.[80]

The potential functional contributions of IgE-AAb to pathological expressions of any of the above autoimmune diseases remain poorly understood.

IGE-AAB IN NON-AUTOIMMUNE DISORDERS

More than 140 autoantigens that trigger IgE-AAb in atopic dermatitis (AD) have been described;[81] however, the role of autoimmunity in AD is not clear. AD is a highly pruritic chronic inflammatory disease of the skin which develops early in life. Genetic traits that result in atopy, hypersensitivity to environmental allergens and a compromised skin barrier function are believed to predispose individuals for the development of AD. Highly elevated levels of total IgE in AD patients are pathogenic as disease severity is reduced in patients subjected to extracorporeal immunoadsorption of IgE.[82] They are most likely the

result of a pre-dominant Th2 inflammation that drives IgE class switching and therefore, it is not surprising that IgE, which binds to environmental allergens, represents the dominant elevated immunoglobulin in AD. In addition, 23–91% of patients present with IgE-AAb that can either be specific for autoantigens[83-85] (Homs 1-5, antinuclear antibodies, DFS70, p80-coilin)[81, 86], or cross-react with allergens through the recognition of shared conserved epitopes through molecular mimicry (manganese superoxide dismutase, thioredoxin, profilin, acidic ribosomal P2 protein).[83, 87] For the latter, it remains open what came first: autoantigen or allergen. Two main mechanisms for how IgE-AAb may contribute functionally to AD pathology have been discussed: (1) IgE cross-linking on the cell surface by autoantigens leading to immediate-type hypersensitivity reactions and (2) IgE-mediated presentation of autoantigens resulting in T-cell activation and cytokine secretion.[84] Scratching of the skin may result in the release of autoantigens that bind to IgE-AAb, thus contributing to disease chronicity and severity even in the absence of external allergens (Fig 2). Interestingly, allergen-mediated activation of reactive T-cells from AD patients has been shown to result preferentially in the secretion of the Th2 cytokines IL-4 and IL-13, whereas autoantigens preferentially induce the secretion of the Th1 cytokines IL-12 and IFN-γ, which coincide with the pathology of the late chronic phase of AD.[88] Indeed, several studies have shown a correlation of IgE-AAb with AD severity and chronicity, suggesting a causal connection.[86, 89] Notably, the presence of IgE-AAb has not been reported in other allergic diseases like allergic asthma or allergic rhinitis, which are characterized by elevated levels of total IgE.[90-92]

FUTURE DIRECTIONS

While most of the IgE-mediated responses to allergens occur through the activation of immune cells such as mast cells, basophils and eosinophils, as covered here, additional mechanisms occur in IgE-mediated autoimmunity. Mechanisms like direct interaction with cellular or extracellular autoantigens causing functional damage in tissues, the uptake of autoantigens by antigen-presenting cells via FcεR and IgE-AAb-mediated activation of receptors that bind to damage-associated molecular pattern molecules (DAMPs)[93] or to pathogen-associated molecular pattern molecules (PAMPs)[94] (like TLR7 and TLR9) have been demonstrated to participate in the disease pathogenesis. Therefore, investigation of the specificities of IgE-AAb and the nature of the autoantigens they bind to are warranted in order to fully understand the potential of IgE-dependent pathophysiological mechanisms in autoimmunity. It is important though, to not regard IgE as the unique immunoglobulin class binding to autoantigens. Other immunoglobulin classes have the capacity to do the same and are likely to be present as part of immune complexes that deposit in organs or trigger responses in immune cells. This is particularly important because different immune cells express different sets of Fc-receptors, whose activation by immune complexes is expected to strongly influence their integrated downstream response. Whether newly formed specificities for autoantigens are primarily raised in response to self or are the result of cross-reactivity with previously encountered pathogen-associated antigens, remains largely an open question that requires further investigation.

Finally, the novel pathogenic role of IgE-dependent activation of pDCs and secretion of IFN-α in response to nucleic acids could reveal new functions of IgE in the immune system. If small amounts of IgE are capable of triggering massive amounts of IFN-α in SLE,[15] it is plausible that IgE against viruses (which inherently contain nucleic acids and trigger interferon responses) could do the same. In fact, a number of studies have found circulating IgE antibodies that react against viral structures.[95-97] Similar to anti-dsDNA in SLE, concentrations of IgE and IgG class antibodies against respiratory syncytial virus correlate with each other,[96] suggesting similar mechanisms at play in SLE and viral defense regulating antibody formation. Whether the mechanisms of IgE response that were found in SLE could help unravel a role for IgE in viral defense represents a fascinating possibility that remains to be investigated.

SUMMARY

There is now sufficient evidence for a pathogenic function of IgE outside of allergies. Self-reactive IgE has now been reported in several autoimmune disorders, in some cases in a majority of patients. In SLE, total circulating IgE was associated with disease severity as was the case for specific IgE-AAb, like anti-dsDNA-IgE-AAb. These AAb contribute to SLE pathogenesis by triggering recruitment of basophils to lymphoid tissues and by triggering the secretion of IFN-α in plasmacytoid dendritic cells. The latter represents a novel role for IgE that opens up the exciting possibility that IgE could also trigger interferon in response to viral infections. There is also evidence indicating that IgE-AAb can act directly in involved organs. This is the case in SLE where IgE deposits are found in the kidney of patients with lupus nephritis, and notoriously is also the case in

the skin from patients with BP. In the latter case, IgE-AAb bind directly to hemidesmosomal proteins in the dermal-epidermal juncture where they disrupt dermal integrity. Insults to the skin in patients with CSU and AD, such as scratching, can result in the release of autoantigens, triggering IgE-mediated activation of mast cells and subsequent inflammation. This response depends largely on the local activation of IgE-AAb-driven mast cell degranulation. In the case of AD, it is not clear whether the autoimmune component of the disease is due to molecular mimicry. In CSU however, the predominant presence of IgE-AAb and the strong association with other disorders such as SLE or thyroiditis suggest that autoimmunity may be central to this dermatological disease.

The association of IgE with autoimmunity is still poorly recognized, suggesting that the number of autoimmune disorders with IgE-AAb presence will expand as studies continue. The approval of omalizumab for the treatment of CSU exemplifies an important example for the pathogenic role of IgE in a disease with substantial presence of IgE-AAb. Ongoing clinical trials with omalizumab will uncover the pathogenic role of IgE in other autoimmune diseases. Considering the recent advances in our understanding of how IgE-AAb contributes to mechanisms of self-inflicted damage, it is apparent that IgE will receive more attention in the study of autoimmunity in the coming years.

Table I. IgE-AAb reported in SLE, RA, CSU, and BP

Antigen category	Antigen	Disease association	Prevalence	Disease manifestation	Pathogenic mechanism	Presence of IgG against same antigen?	Reference
Nucleic acids	dsDNA	SLE CSU	SLE: 40.3–56.4% Lupus nephritis III: 67% Lupus nephritis IV: 82%	SLE: Disease activity, Active nephritis, Hypocomplementemia	Secretion of IFN-α	Yes for SLE No for CSU	14, 15, 45, 98, 99
Nucleic acids	Sm	SLE	> 7.6%	Disease activity, Active nephritis, Hypocomplementemia	Not studied	Yes	14, 98
Nucleic acids	SS-A/Ro	SLE	> 5.6%	Disease activity, Hypocomplementemia	Not studied	Yes	14, 98
Nucleic acids	SS-B/La	SLE	> 3.6	Disease activity, Hypocomplementemia	Not studied	Yes	14, 98
Nucleic acids	APEX	SLE	-	Active nephritis	Not studied	No	14
Nucleic acids	MPG	SLE		Active nephritis	Not studied	No	14
Nucleic acids?	CLIP4	SLE		Active nephritis	Not studied	No	14
Nucleic acids	Ribosomal P2	SLE	31%		Not studied	Yes	16
Nucleic acids	ANA	SLE, RA	SLE: 31.5–81% RA: 16–60%		Not studied	Yes	4, 5, 98, 100
Nucleic acids	RNP	SLE	-		Secretion of IFN-α	Not studied	4, 5, 15, 98
Nucleic acids	Nucleosome	SLE	-		Not studied	Not studied	98

Protein	BP230 and BP180	BP	70–90%	Disease severity	Mast cell degranulation, cellular inflammation, destruction of hemidesmosomal integrity	Yes	[52, 53, 101, 102]
Protein	Thyroid peroxidase	CSU	54%	Autoimmune thyroiditis	Not studied	Yes	[73, 103]
Protein	Thyroglobulin	CSU	-	-	Not studied	Yes	[73]

ANA, anti-nuclear antibody; *APEX*, APEX nuclease 1; BP, bullous pemphigoid; *CLIP4*, CAP-Gly domain-containing linker protein family member 4; *CSU*, chronic spontaneous urticaria; *dsDNA*, double-stranded DNA; *IFN-α*, interferon-alpha; *MPG*, N-methylpurine DNA-glycosylase; *RA*, rheumatoid arthritis; *RNP*, ribonucleoprotein; *SLE*, systemic lupus erythematosus

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FIGURE LEGENDS

FIG 1. Role of IgE and pDC in SLE. Physiologically, pDCs sense nucleic acids from viruses through TLR7 and TLR9 that are located intracellularly in endolysosomal compartments. Upon activation of these receptors, MyD88 is recruited and triggers the activation of the kinases IRAK4, IRAK1 and TRAF6. This results in the activation and translocation of transcription factors IRF-7 and NF-kB to the nucleus and subsequent IFN-α-secretion. Along with IFN-α, pDCs also secrete pro-inflammatory cytokines and chemokines. This is also accompanied by the upregulation of the chemokine receptor CCR7 that allows mature pDCs to traffic into lymphoid tissues and by the upregulation of T-cell costimulatory molecules, such as CD80 and CD86, that facilitate pDC-dependent antigen presentation. IFN-α secreted from pDCs has pleiotropic effects on the immune system, enhancing the functions of B-cells, T-cells, monocytes and dendritic cells. Together, pDC activation by viral pathogens results in a successful host defense. In SLE, pathogenic activation of pDCs can also be initiated in response to immune complexes containing IgE-AAb that are bound to either host DNA or RNA. These immune complexes bind to FcεRI at the cell surface, which triggers engulfment of the entire complex, delivery of the nucleic acids to intracellular TLR7 and TLR9, and ultimately result in the initiation of a downstream response, very similar to a viral infection.

FIG 2. Mechanisms linking IgE to autoimmunity. In SLE, (A) IgE-dependent recognition of AAb is associated with the activation and recruitment of basophils and possibly CCR7-positive pDCs to lymphoid tissues. Both of these cell types act upon B-cells, triggering their maturation, differentiation into plasma cells, and ultimately magnifying the formation of self-reactive AAb. Both, basophils and pDCs, also have the potential of triggering T-cell responses via expression of MHC-II. (B) Deposits of IgG in the kidney are a feature of lupus nephritis. Along with IgG, IgE deposits and infiltrating pDCs have also been reported. Additionally, there is evidence of local secretion of interferons, suggesting local activation of pDCs by a mechanism that involves deposition of both IgE and IgG autoantibodies. (C) IgE deposits are also found at the dermal-epidermal junction in BP, which is attributed to deposits of IgE-AAb reacting with hemidesmosomal cell surface proteins BP230 and BP180. These IgE-AAb trigger internalization of these proteins, reduce the number of hemidesmosomes important for the anchoring of basal keratinocytes to the lamina lucida of the basement membrane. (D) FcεRI-dependent degranulation of mast cells and eosinophils are also contributors to BP pathology. In CSU, mast cell activation through binding of autoantigens released from damaged skin to IgE on FcεRI is a central disease mechanism that has also been reported in AD. However, AD is largely driven by environmental allergens rather than autoimmunity.