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REVIEW ARTICLE

Pathogenic mechanisms of IgE-mediated inflammation in self-destructive autoimmune responses

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Abstract

Autoantibodies of the IgG subclass are pathogenic in a number of autoimmune disorders such as systemic lupus erythematosus. The presence of circulating IgE autoantibodies in autoimmune patients has also been known for almost 40 years. Despite their role in allergies, IgE autoantibodies are not associated with a higher rate of atopy in these patients. However, recently they have been recognized as active drivers of autoimmunity through mechanisms involving the secretion of Type I interferons by plasmacytoid dendritic cells (pDC), the recruitment of basophils to lymph nodes, and the activation of adaptive immune responses through B and T cells. Here, we will review the formation, prevalence, affinity, and roles of the IgE autoantibodies that have been described in autoimmunity. We also present novel evidence supporting that triggering of IgE receptors in pDC induces LC3-associated phagocytosis, a cellular process also known as LAP that is associated with interferon responses. The activation of pDC with immune complexes formed by DNA-specific IgE antibodies also induce potent B-cell differentiation and plasma cell formation, which further define IgE's role in autoimmune humoral responses.

Keywords

Atopic dermatitis, autoimmunity, B cells, basophil, class switch recombination, chronic spontaneous urticaria, IgE, interferon, pemphigus bullous, plasmacytoid dendritic cells, systemic lupus erythematosus

History

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Introduction

There are five immunoglobulin classes (isotypes) of antibody molecules found in serum: Immunoglobulin (Ig)D, IgM, IgG, IgA, and IgE. IgE, the last class of antibody discovered, was described approximately 50 years ago [1]. Among all Ig isotypes, IgE is the least abundant and understood. Unique to mammals, the role of IgE in allergy has been thoroughly documented. Allergic reactions are mediated by IgE-driven release of cytoplasmic granules in mast cells and basophils. These granules contain not only bioactive amines such as histamine, but also serine proteases (tryptase and chymase), carboxypeptidase A, and proteoglycans, that are key for triggering local inflammation [2]. Despite its well-established role in allergy, a physiological role for IgE has been more difficult to unveil. However, recently it has become clear that IgE is a key player in expulsion of obnoxious parasites or substances (such as toxins, irritants, venoms, or xenobiotic) that come in contact with epithelia covering external barriers such as the skin, digestive tract, or respiratory tract [3].

Shortly after the recognition of IgE as a new subclass of antibodies, reports identified the presence of self-reactive IgE in disorders such as systemic lupus erythematosus (SLE) and

rheumatoid arthritis (RA) [4]. Much later, self-reactive IgE was also described in a range of dermatological diseases such as bullous pemphigoid (BP) [5,6], chronic spontaneous urticaria (CSU) [7,8], and even in diseases where autoimmunity is not thought to be a main driver such as atopic dermatitis (AD) [9]. A field that was mainly focused on allergy largely ignored these reports. Recently, however it is becoming increasingly clear that autoreactive IgEs are present in autoimmune disorders where they contribute to pathogenesis by mechanisms that appear unrelated to allergic reactions. For instance, elevated concentration of total IgE found in serum of SLE patients is not associated with increased rate of allergic reactions. Autoimmunity in SLE is markedly characterized by the presence of a wide spectrum of autoantibodies consisting of all four of the secreted Ig classes. These autoantibodies bind primarily to nucleic acids (or protein that are bound to nucleic acids such as nucleosomes) that trigger the secretion of Type I interferons (type I IFNs) when sensed by the nucleic acid sensors Toll-like receptor (TLR)-7 and TLR9 in intracellular compartments of plasmacytoid dendritic cells (pDC). pDC are a subset of dendritic cells (DCs) that represent less than 1% of total peripheral blood mononuclear cells (PBMCs). pDCs are antigen presenting cells (APC) that are capable of engulfing IgG immune complexes (ICs) by a process known as LC3-associated phagocytosis (or LAP), which is central to the activation of

the interferon pathway that underlies SLE pathogenesis. Recently, it has been shown that pDC also secrete type I IFNs in response to ICs formed with IgE autoantibodies found in SLE upon internalization through Fc-epsilon RI (FcεRI) [10], however it is not known whether this receptor also triggers LAP. Type I IFNs have pleiotropic effects on the immune system, and the majority of lupus patient have elevated levels of type I IFN-induced genes in circulation, also known as type I IFN gene signature. This signature has been shown to correlate with active disease, flares, and disease severity [11]. Type I IFNs are thought to perpetuate autoimmunity by promoting the formation of antibody-secreting plasma cells that secrete autoantibodies [12]. Plasma cells arise from B-cell activation and differentiation and are capable of secreting autoantibodies of all Ig subclasses, including IgE. Studies focusing on the antigen specificities of IgE autoantibodies are uncovering that they bind to similar autoantigens as those previously described for IgG autoantibodies, whose roles in autoimmunity have been better studied. It is now becoming increasingly clear that IgE autoantibodies are not innocent bystanders that appear subsequent to the formation of IgG autoantibodies. Instead an emerging number of studies are revealing that they are key active drivers of disease pathogenesis. In this review, we will focus on the current understanding of the formation, prevalence, affinity, and roles of the IgE autoantibodies that have been described in autoimmunity.

IgE specificities and prevalence in autoimmunity

Since the first report of the presence of IgE autoantibodies in SLE and RA [4], the list of autoimmune disorders that present with this class of autoantibodies is growing, and includes dermatological autoimmune disorders such as BP and CSU. It was hypothesized that the appearance of IgE autoantibodies may be linked with a higher rate of allergies in autoimmune patients but this hypothesis has been thoroughly tested in SLE with most reports showing no association. The recognition that IgE autoantibodies may be contributing to pathogenesis led to the testing of omalizumab, an anti-IgE monoclonal antibody preventing the interaction of IgE with FcεR1 in clinical trials of autoimmune diseases. Omalizumab is now approved for the treatment of PB and CSU validating the role of IgE autoantibodies in autoimmunity [13–16]. Furthermore, a phase I clinical trial investigating omalizumab in SLE is currently ongoing (NCT01716312). In this section, we will review the current knowledge linking IgE autoantibodies to autoimmunity, including prevalence and affinities.

IgE autoantibodies in SLE

SLE is a chronic inflammatory disease affecting multiple organs with circulating self-reactive antibodies that follows a relapsing and remitting course. More than 90% of cases of SLE occur in women, frequently starting at childbearing age.

Total IgE is elevated in SLE patients [17] and correlates with more severe disease manifestations [18–21] but not with atopy. In fact, the frequency of environmental allergies, food allergy, insect allergy, and skin allergy are remarkably similar between SLE patients and controls [17,20,22–24]. A majority

of SLE patients, 65% of total and 83% with active disease, are seropositive for IgE autoantibodies [25]. At least a fraction of the elevated circulating IgE are self-reactive, with nearly all of the autoantigens reported being either nucleic acids or proteins that bind to nucleic acids (for example nucleosome or ribonucleoproteins) which is also the case for most lupus IgG autoantibodies [26]. The level of IgE autoantibodies correlates with that of IgG in the same patient, with IgG autoantibodies present at higher concentrations compared to IgE [10,25,27], suggesting their formation is co-regulated. Recently however, three new antigens (APEX nuclease 1, N-methylpurine DNA-glycosylase, and CAP-Gly domain-containing linker protein family member 4) were identified in patients with lupus nephritis that trigger the formation of IgE, but not IgG autoantibodies [25].

Anti-double-stranded DNA (dsDNA) IgG antibodies are a well-characterized marker of SLE and are part of the SLE classification criteria. They are found in all patient subgroups, with levels predominantly elevated in lupus nephritis [28]. IgE specific for dsDNA has also been found in patients and their levels correlate with disease activity [25]. Multivariate statistical analysis has shown that its presence is a risk factor for SLE disease activity independent of the concentration of their dsDNA-specific IgG counterpart [10]. Anti-dsDNA IgE are found in all subsets of lupus patients investigated, including those SLE with discoid lupus, thrombocytopenia, acute cutaneous lupus, or secondary Sjogren's [10]. However patients with lupus nephritis are more likely to present with them. About 70% of patients with lupus nephritis present with anti-dsDNA IgE, and the prevalence increases to 82% in class IV patients, the most severe form of lupus nephritis [10]. This is in contrast to IgE autoantibodies that bind other common lupus autoantigens from the same individual, including Sm, SS-A, and SS-B, which despite being positively associated with active disease do not associate with nephritis [25]. The presence of IgE autoantibodies in circulation and IgE deposits found in kidney biopsies [10,29], suggest that this class of autoantibody may directly contribute to immunopathology leading to nephritis in SLE.

IgE autoantibodies in bullous pemphigoid

BP is an autoimmune disorder whereby autoantibodies and T cells attack the basement membrane of the skin that connects the epidermis to the dermis. Binding of the antibodies to the basement membrane triggers chronic sub-epidermal inflammation and the formation of skin blisters. The main autoantigens described in BP are the hemidesmosomal proteins BP230 and BP180, which are expressed by keratinocytes and situated in the dermal–epidermal junction [30]. BP180 is the most studied autoantigen and by far IgG autoantibodies are the most abundant class of immunoglobulin. A great majority of patients (70–90%) are also seropositive for autoantibodies of the IgE subclass [5,31], and their concentration correlates with disease severity [32,33].

The mechanisms by which IgE autoantibodies contribute to BP are through both Fc-receptor (FcR)-dependent and independent mechanisms. Deposition of IgE in the basement membrane zone of affected skin [31,34] leads to internalization of BP180, decrease of hemidesmosomes, and cytokine

release, which results in a loss of adhesion and compromised epidermal cell-extracellular matrix integrity [5]. IgE binding to autoantigens also triggers FcεR1-mediated degranulation of mast cells [35] and basophils [31], which are also central to pathogenesis [36,37]. Final proof for a pathogenic role of IgE autoantibodies in BP comes from clinical trials with omalizumab, which resulted in clinical improvements despite the presence of excess amounts of IgG autoantibodies with similar autoantigen specificity, suggesting that only relatively low titers of IgE autoantibodies are sufficient to contribute to BP pathology.

IgE autoantibodies in chronic spontaneous urticaria

CSU, also referred to as chronic idiopathic urticaria, is a disease characterized by spontaneous emergence of hives and angioedema of the skin [38]. The underlying causes are largely unknown, but CSU frequently presents with other autoimmune disorders [39,40] and autoimmunity is suspected to be a contributor in at least a subset of patients [41,42]. The first evidence connecting CSU with autoimmunity came in 1946 [43], but it remained unnoticed until 1983 when Leznoff reported the presence of autoimmune thyroid antibodies in patients suffering from CSU [44]. Autoantibodies of the IgE subclass that bind ds-DNA [8,45], thyroglobulin, and thyroperoxidase [8,46,47] have now been found in a subset of patients. FcεR1-dependent degranulation of mast cells and basophils seems to be the predominant mechanism by which IgE autoantibodies contribute to CSU [45,48]. Degranulation can also be triggered by the presence of anti-IgE and anti-FcεRI autoantibodies of the IgG1 and IgG3 subclasses, reviewed here [48]. These autoantibodies are often associated with high total IgE, thyroiditis, and SLE [8].

IgE autoantibodies in other disorders

A number of reports have demonstrated the presence IgE autoantibodies in several other autoimmune diseases such as RA [4], systemic sclerosis [49], thyroiditis [50,51], and multiple sclerosis [52]. The potential functional contributions of IgE autoantibodies to pathological expressions of any of the above autoimmune diseases remain poorly understood.

AD, also named atopic eczema, is a skin disease that can appear in adults but occurs more often within the first year of life and is outgrown by most patients within a few years [2,3]. Compromised skin barrier function and hypersensitivity to environmental allergens are believed to predispose individuals to the development of AD, which presents with high levels of IgE and Th2-skewed response. The predominant antigens for IgE present in AD patients are environmental allergens; however, new evidence is emerging demonstrating the presence of IgE autoantibodies in patients. More than 140 autoantigens that trigger IgE autoantibodies in AD have been described in a majority of patients [9,53–56]. Indeed, several studies have shown a correlation between the presence of IgE autoantibodies and disease, suggesting a causal connection [9,57]. Notably, the presence of IgE autoantibodies has not been reported in other allergic diseases like allergic asthma or allergic rhinitis [58–60]. At least some of them seem to be originated through molecular mimicry as they cross-react with known allergens [54,61]. Also known as autoallergens,

autoantibodies originated by molecular mimicry have also been reported in SLE [27]. Itching is a feature of AD and scratching of the skin may result in the release of autoantigens that bind to IgE autoantibodies and potentially exacerbate the disease. In that situation, IgE-mediated presentation of autoantigens to T cells [55,62] could also potentially contribute to chronicity and severity even in the absence of external allergens. Despite the presence of self-reactive IgE antibodies in AD, it is presently unclear to what degree, if any, these autoantibodies contribute to pathogenesis and future studies are required to fully address this question.

Control and regulation of IgE formation in health and disease

Of the Ig subtypes in mouse and human, IgE represents the smallest fraction. Whereas IgG can be found as high as 10 mg/ml in the circulation, IgE is found at ng/ml levels. Studying the control and regulation of IgE is hampered by the fact that although IgE can be measured in the sera, finding and isolating IgE + memory B cells or plasma cells from human samples are exceedingly difficult. Moreover, whereas *in vitro* differentiation of IgG plasma cells is easily obtained using IL-21co-stimulation, *in vitro* induction of IgE-expressing memory B cells and plasma cells remains elusive despite IL-4 being considered the pivotal IgE-inducing cytokine. Recently, a number of genetic mutations have been described resulting in hyper IgE syndromes that have started to shape our understanding of how IgE is regulated in human disease.

Changing the Ig isotype from IgM to another Ig isotype is mediated by a process called class-switch recombination (CSR). During this process, a segment of DNA, between switch regions located 3' of the VDJ heavy chain variable domain and 5' of an IgG, IgA, or IgE constant (C) region, is excised, and the double-stranded DNA break is usually repaired by nonhomologous end joining to link the variable domain exon with the desired downstream constant domain exon. The nicking, breaking at the two switch regions is mediated by a series of enzymes including activation-induced (cytidine) deaminase (AID), uracil DNA glycosylase, and AP-endonucleases. The process of CSR therefore retains the original antibody specificity and exchanges the IgM constant domain with the constant domain of either an IgG1, 2, 3, 4, IgA1, 2, or IgE isotype thereby altering the antibodies properties and facilitating alternate effector functions.

For CSR to IgE, it has been well established that the Th2-cytokines, IL-4, and IL-13 along with CD40 signaling drive Cε class switch [63–65]. IL-4 binds to a complex of IL-4R with the common gamma chain receptor (γc), whereas IL-13 binds to either a heteromeric complex formed by the IL-4Rα chain with IL-13Rα1 (expressed not only on B cells but also on other cell types), or it can also bind to another monomeric receptor termed IL-13Rα2. The role of CD40 in CSR in humans is exemplified in X-linked hyper IgE syndromes, where loss of the CD40 pathway greatly reduced CSR to all downstream isotypes [66]. On the molecular level, IL-4 activates STAT6, and CD40 ligation activates NFκB, both of which translocate into the nucleus and synergize to induce AID [67] necessary for CSR to IgE (and other isotypes).

However, several mediators have been shown to effectively increase or inhibit CSR to IgE.

The cytokines that enhance IgE can do so by increasing IL-4/13-driven responses of Th2 cells. IL-18 is a proinflammatory IL-1 family cytokine member produced by macrophages, DCs, and other cell types. This cytokine is increased in several autoimmune diseases, including SLE where it correlates with disease severity and renal disease [68]. Depending on the cytokine milieu, IL-18 can activate Th1 or Th2 cytokine release as well as upregulation of CD40L expression on T cells. IL-18 binds two receptors, termed IL-18R1 and IL-18RAP (IL-18R α/β), expressed on the B-cell surface as well as other cell types. In regard to IgE production, IL-18 has been shown to increase IgE through its ability to induce Th2 polarization, IL-4, and IL-13 production, CD40L expression, and STAT6 activation [69]. Moreover, injection of IL-18 *in vivo*, especially in combination with IL-2, results in 20–70-fold increase of IgE levels [70,71]. The TNF family members B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) have the ability to induce CSR in a CD40L-independent manner [72,73] following activation of dendritic cells with IFN α , IFN γ , or CD40 ligation and can potentiate IL-4-driven IgE by activating germline and mature C ϵ transcripts [73]. BAFF binds three receptors expressed on the surface of B cells, BAFFR, and TACI, as well as BCMA expressed on plasmablasts and plasma cells, whereas APRIL binds to TACI and BCMA, but not BAFFR. Both BAFF and APRIL are overexpressed in SLE [74] and may potentially contribute to lupus pathogenesis through increasing autoreactive IgE B cells.

Several cytokines have been shown to inhibit IL-4-driven IgE CSR, either by inhibiting Th2-cell differentiation, IL-4/IL-13 production, or by directly blocking the molecular mediators induced by IL-4/13 and CD40L pathways. Of interest, IL-21, produced by T follicular helper cells (T_{FH}) cells in the germinal center (as well as by most CD4⁺ T cell subtypes), is a potent cytokine belonging to the γ_c family of cytokines. IL-21 is increased in SLE patients [75] (and personal observation) further linking IL-21 to the disease, T cells from patients overexpress this cytokine [76] and polymorphisms in both IL-21 [77] and IL-21R [78] have been described in SLE. IL-21 binds to a complex of IL-21R/ γ_c receptors expressed on the B-cell surface, as well as a number of other hematopoietic and nonhematopoietic cell types [79]. In regard to B cells, IL-21 is the most potent cytokine inducing B-cell activation, differentiation, or death and an important factor driving CSR to IgG1 and IgG3 of naïve B cells [80,81]. However IL-21 also has the ability to inhibit IgE production. In animal models, mice deficient in either IL-21 or IL-21R display increased serum IgE [82,83], whereas injection or intranasal treatment with IL-21 into immunized or sensitized mice reduces antigen-specific IgE [84,85]. Moreover, the ability of IL-21 to inhibit allergic IgE production and anaphylaxis is dependent on the inhibitor of differentiation 2 (Id2) transcriptional regulator [86], shown to play an important role in CSR of IgE through regulation of AID [87,88]. Consistent with murine studies, in humans, families with loss-of-function mutations in either IL-21 or the IL-21R also display increased serum IgE [89–91], and IL-21

added into peripheral blood mononuclear cells inhibits IL-4-driven IgE production *in vitro* [92,93]. Through its ability to induce IFN γ production [94], IL-21 can inhibit IgE production in cultures of PBMCs [92]. IL-21 can also inhibit IgE by directly inhibiting IL-4-driven C ϵ transcription [85], or by inducing apoptosis of IgE B cells [95]. However, IL-21 synergizes with IL-4 to drive CSR to IgE [96] (and personal observation) in cultures of purified B cells, which is further increased by addition of IL-12 [97]. Importantly, the ability of IL-21 to either increase or decrease IgE production has been reported to be dependent on the B-cell density used in the *in vitro* assay [97], which presumably determines the number of cell divisions the B cell can undergo.

The ability of IL-21 to regulate IgE CSR appears to be dependent on activation of STAT3, where IL-21 synergizes with IL-4 to induce IgE production of naïve human B cells from normal donors, but not STAT3-deficient donors [96]. However, like IL-21/IL-21R-deficient mice, patients with STAT3 genetic mutations also present with hyper IgE syndrome [98–101], supporting the concept that functional deletion of IL-21 or downstream molecular targets may result in a loss of a negative regulator (such as IFN γ), which may not be present in cultures of purified B cells.

Another potent cytokine that determines the fate of CSR is IFN γ . While IFN γ can drive CSR to IgG, IFN γ can also reduce CSR to IgE through its ability to inhibit Th2-cell differentiation via reduction of IL-4 [102]. However, IFN γ can directly inhibit IL-4-driven C ϵ CSR [94,103–105]. Other cytokines such as IL-12 have been shown to inhibit IgE, through induction of IFN α [106]. Although IFN α produced by pDC has been shown to be important for plasma cell differentiation [10,12], type I IFNs have been reported to inhibit IL-4-driven IgE production [103,107].

Other mediators influence CSR to IgE. Activation of TLR9 by CpG inhibits allergic inflammation by reducing IgE, which correlates with increased T-bet expression in B cells [108]. T-bet is driven by CpG in B cells [108–110] where loss of T-bet results in increased IgE production and a block in IgG2a CSR [111]. Moreover, deficiency of B cell-expressed T-bet also results in greatly reduced lupus disease manifestations [111], suggesting that the autoimmune humoral repertoire may largely originate from T-bet⁺ B cells. These data suggest that the control and regulation of IgE are not only influenced by the cytokines any given B cell encounters at the time of CD40 engagement, but subpopulations of B cells may also be more poised than others to respond to these signals.

Not only do soluble cytokines influence the ability of B cells to class switch to IgE, cell surface molecules also shape the fate of CSR. Below we discuss the ability of B cell-expressed CD23, the low-affinity IgE receptor, CD95/FAS, the TNFR family member, and CTLA4, the CD28 family member, to influence IgE CSR.

There are distinct FcR for the various Ig isotypes. In regard to IgE, there are two receptors, the high-affinity Fc ϵ R, expressed on mast cells, basophils, eosinophils, and pDC, and the low-affinity Fc ϵ R, CD23. CD23 is expressed on B cells and myeloid cells and has been shown to regulate IgE production. Ligation of CD23 with IgE, IgE-ICs, or anti-CD23 mAb greatly reduces IgE production [112]. Conversely, soluble CD23 which is increased in both SLE and pSS [68]

enhances IL-4-induced IgE by acting as a decoy, binding soluble IgE, and preventing cell surface engagement of CD23 [113,114]. In clinical trial, Lumilixilab, an anti-CD23 activating Ab, has been shown to reduce IgE levels in Asthma [115]. The increased soluble CD23 in autoimmune disease may serve as a means to expand autoreactive IgE memory cells, which would otherwise be inhibited by engagement of IgE to cell surface CD23 expressed on the autoreactive (and other) B cells.

Although CTLA4 is largely thought of as a T-cell inhibitory receptor, it is induced on B cells following IL-4 and CD40L activation. Engagement of CTLA4 following B-cell stimulation was shown to inhibit IL-4-driven NF κ B and STAT6, leading to the reduction of C ϵ (and C γ 1) germline mRNA and IgE+ (and IgG1) B cells [116]. As CTLA4 ligands CD80/B71 and CD86/B72 are co-expressed on activated B cells, this may serve as a means to downregulate excessive IgE CSR following B-cell activation.

CD95/Fas is a TNF family member involved in activation-induced cell death (AICD). CD95 is highly expressed on germinal center (GC) B cells and believed to control the output of the GC reaction through killing of self-reactive B cells. Recently, however it has been reported that CD95/Fas is not required for removal of conventional self-reactive GC B cells, but appears to control development of rogue GC B cells that initiate IgE and autoantibody production. Strikingly, in both humans and mice whose CD95/Fas pathway is not intact due to genetic silencing, greatly elevated IgE is observed [117]. In Fas-deficient, *lpr* mice, and FasL-deficient, *gld* mice, as well as in humans with autoimmune lymphoproliferative syndrome (ALPS) due to genetic mutation in either Fas or FasL, greatly increased IgE is observed with 50–100 times higher serum IgE noted in mice, and up to 8000 times higher IgE seen in ALPS patients.

In summary, CSR to IgE is largely driven by IL-4, IL-13, and CD40L provided by Th2 cells, where cytokines from other cell types impact IgE production through influencing Th2-cell development, IL-4/IL-13 production, or directly impact IL-4/IL-13/CD40-driven downstream signaling events on the molecular level. Moreover, B-cell surface receptors also regulate CSR to IgE either by interacting with soluble ligands, ligands that are expressed on other cell types, or by auto-regulation of ligand/receptor pairs upregulated on activated B cells (Figure 1). Although many of the studies that address control and regulation of IgE CSR have been done in animal models, humans with functional deletion of key genes giving rise to altered IgE levels provide insight to how animal studies can translate to human disease. In regard to autoimmunity, although IgE and IgE autoantibodies are increased in several autoimmune diseases including SLE [10,19,21,23,118,119], there is still much to be learnt regarding the drivers of IgE antibodies with autoreactive specificities.

Pathogenic mechanisms of IgE-mediated inflammation and autoimmunity

IgE binding to Fc ϵ R at the surface of mast cells and basophils triggers cellular degranulation. *In vitro* experiments have shown that IgE autoantibodies can trigger similar responses

when bound to autoantigens. In this section, we will cover nonclassical mechanistic responses triggered by this class of autoantibodies such as IgE-dependent release of interferon by pDCs, and the effect of IgE autoantibodies in adaptive responses, including nonclassical basophils functions.

Type I interferons

Type I IFNs have pleiotropic roles in the immune system by promoting the function of monocytes, DC, T cells, NK cells, and B cells. They are key drivers of autoimmunity as they trigger the activation and proliferation of B cells, and the differentiation of plasma cells into autoantibody-producing cells [120]. Unabated secretion of type I IFNs is central to SLE, and the involvement of the IFN pathway in SLE pathogenesis has now been clinically validated in two phase-2 proof of concept studies using inhibitors that block either IFN- α [121] or the type I IFN receptor [122]. The aberrant IFN response found in SLE is thought to be largely caused by pDCs. Initially described as plasmacytoid T cells by pathologists studying inflamed lymphoid tissue [123], pDCs are a distinct population of DCs in the peripheral blood and secondary lymphoid organs. Activation of pDCs by circulating nucleic acids plays a critical role in the secretion of inflammatory mediators and the production of autoantibodies that contribute to autoimmune disease pathology. In contrast to other DC subsets, human pDCs express two endosomal receptors, TLR7 and TLR9, that capacitate them to respond to circulating RNA and DNA, respectively [124]. pDCs internalize nucleic acids when bound to autoantibodies through cell surface Fc γ -receptor IIa (Fc γ RIIa) [125]. Nucleic acid containing ICs are then internalized by LC3-associated phagocytosis (also called LAP) [126], a process that involves the recruitment of the autophagy protein LC3 to the phagosome which mature into lysosomal compartments where the nucleic acid components of the ICs are sensed by TLR7 and/or TLR9 [127]. As a result, pDCs mature and release up to 1000 times more type I IFN than any other cell type [128], leading to local and systemic upregulation of type I IFN-inducible genes, which are measured in blood as the type I IFN signature [11].

We have recently shown anti-DNA autoantibodies of the IgE class, such as those found in SLE patients, can trigger the activation of pDCs upon binding Fc ϵ RI at the cell surface and triggering massive secretion of IFN α [10]. This response seems to be restricted to human cells, as mouse pDCs do not express Fc ϵ RI (Figure 2). Fc ϵ RI 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 [129]. Human pDCs however express a trimeric form of the Fc ϵ RI as they lack the beta-chain [130]. As previously described for particles internalized by IgG, Fc ϵ RI-mediated internalization of IgE-ICs recruits TLR9 to the phagosome and upon sensing DNA it triggers the translocation of the interferon regulatory factor 7 (IRF-7) to the nucleus, a transcription factor responsible for initiating interferon responses [10].

We have previously shown that the secretion of IFN α in response to IgG autoantibodies depends also on the

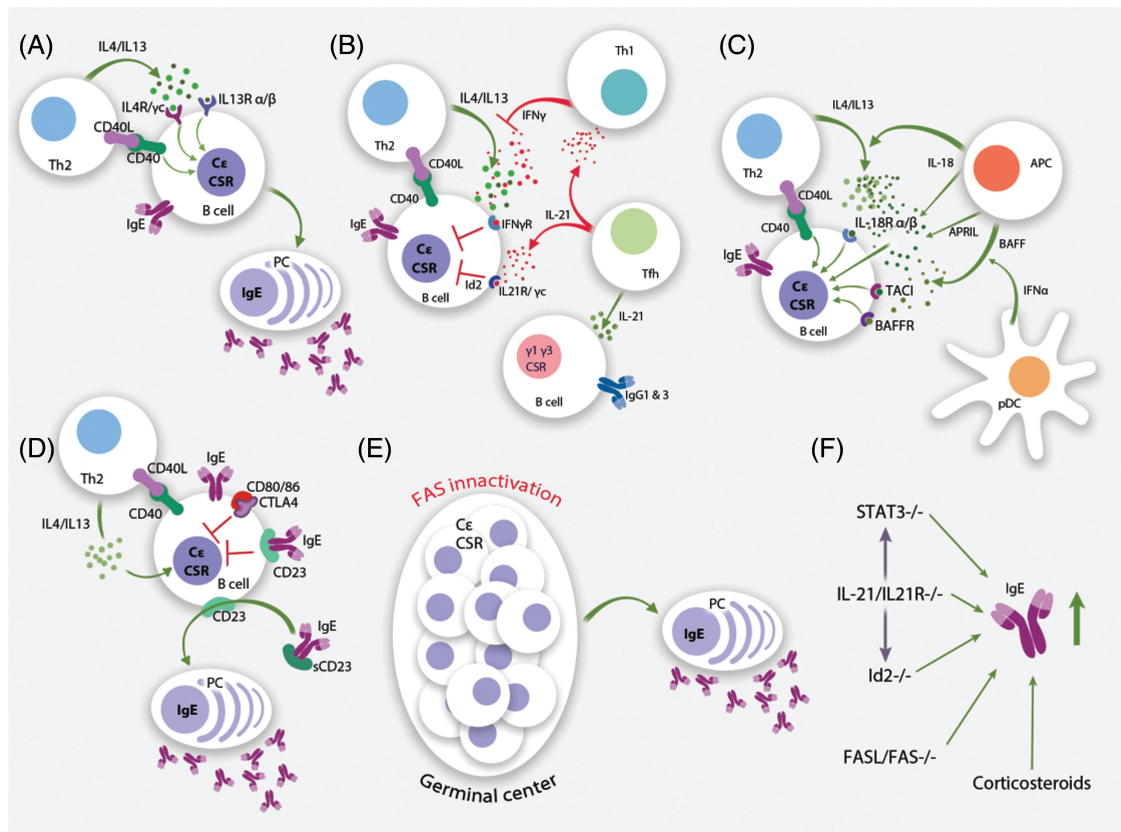


Figure 1. Control and regulation of Cε CSR are greatly influenced by local cytokine milieu. (A) While IL-4, IL-13, and CD40L expressed by Th2 cells are the major driver of Cε CSR. (B) IFN γ expressed by Th1 cells inhibits both Th2 cell differentiation and IL-4 production as well as directly blocks Cε CSR. IL-21, expressed largely by Tfh cells, induces IFN γ and Id2, thereby inhibiting Cε CSR, while driving CSR to other isotypes. (C) IL-18 increases Cε CSR through Th2 cell polarization, induction of IL-4, IL-13, and CD40L expression as well as STAT6 activation. BAFF and APRIL produced by APCs potentiate IL-4-driven IgE by activating germline and mature Cε transcripts where IFN α from pDC and other stimuli increase BAFF levels. (D) Cell surface molecules also shape the fate of CSR. Binding of IgE to cell surface CD23, the low-affinity IgE receptor, inhibits Cε CSR, while soluble CD23, through its ability to act as a decoy binds soluble IgE, resulting in increased IgE production. B cell expressed CTLA4, and its ligands, CD80/CD86 are increased after B-cell activation. Ligation of CTLA4 inhibits Cε CSR, possibility as a negative feedback loop to control IgE production. (E) The apoptotic antigen, CD95/FAS, significantly controls germinal center output, where FAS or FASL inactivation results in greatly increased differentiation of IgE plasma cells. (F) Genetic mutations have been shown to result in increased IgE, as well as Corticosteroids, relevant to SLE.

recruitment of LC3 to phagosomes [126]. We therefore investigated whether IgE triggers LAP as well. To this end, we employed a macrophage cell line that expresses fluorescent LC3-mCherry and TLR9-GFP [126] that was subsequently transduced with the human alpha chain of Fc ϵ RI for monitoring the subcellular location of LC3 and TLR9 upon the engulfment of beads coated with IgG or IgE. As expected, IgG beads triggered the recruitment of LC3 in both the parental cell line and Fc ϵ RI⁺ cells as both express Fc ϵ /γ receptors. However, a robust recruitment of LC3 was observed only on Fc ϵ RI⁺ cells upon internalization of IgE-beads, indicating that Fc ϵ RI triggers LAP (Figure 3A). Both LC3 and TLR9 co-localized to the same compartment (Figure 3B), and the degree of LAP and TLR9 recruitment initiated by IgE was similar to that triggered by IgG (Figure 3A). This is consistent with our findings that IgE autoantibodies form ICs that trigger the release of IFN α , TNF, and IL-6 from pDCs in a TLR9-dependent manner, to a similar degree as their IgG counterparts [10].

As the concentration of IgG anti-DNA autoantibodies is at least 10 times the magnitude of IgE anti-DNA autoantibodies [10], it is important to understand the contribution of each isotype to the pathogenic inflammatory response that

underlies lupus. We have recently provided evidence supporting IgE as a key driver of pathogenesis. The levels of IgE anti-DNA autoantibodies correlate with disease activity and *in vitro* experiments have shown that IgE synergizes with IgG to trigger the secretion of IFN α and other proinflammatory mediators. The synergy was mechanistically explained by an enhanced uptake of dsDNA-containing ICs as a result of the combined action of activating FcγRIIa and Fc ϵ RI at the cell surface [10]. This was even the case when the concentration of IgE was several orders of magnitude lower than that of IgG in the ICs, a scenario that resembles what was found in SLE patients. Accordingly, when IgE antibodies were neutralized in the serum from dsDNA-IgE-seropositive SLE patients using a blocking anti-IgE antibody, IFN α produced by PBMCs in response to patient's serum was significantly reduced, supporting the notion that IgE autoantibodies have an active role in the disease [10].

T-cells responses

The activation and expansion of autoimmune CD4 and CD8 T cells are central to autoimmunity. APCs initiate T-cell

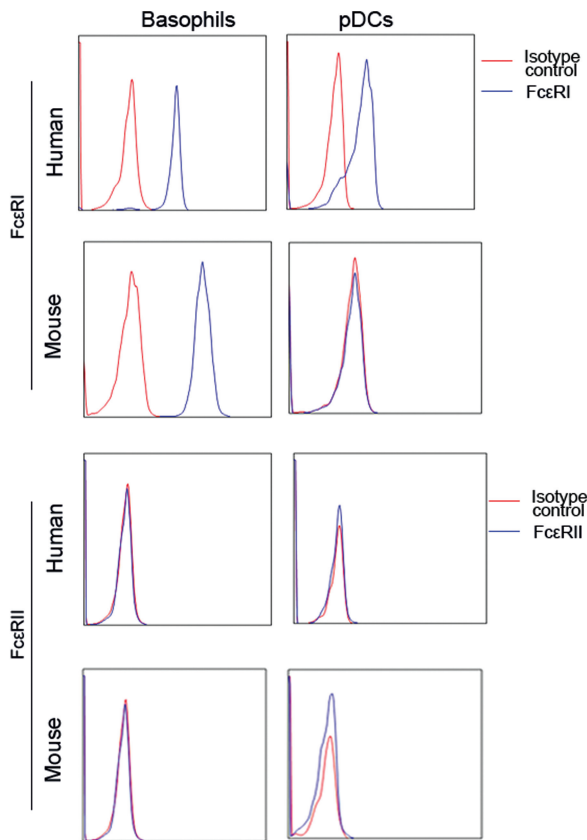


Figure 2. Human but not mouse pDCs express Fc ϵ RI. Human PBMCs and murine (C57BL/6) splenocytes were stained with antibodies to different pDC and basophil markers and analyzed by FACS that were prepared using standard protocols. Fc ϵ RI and Fc ϵ RII were detected using anti-human Fc ϵ RI ab (clone- AER 371; CRA1), anti-mouse Fc ϵ RI ab (clone- MAR-1), anti-human Fc ϵ RII ab (clone- EBVCS5), anti-mouse Fc ϵ RII ab (clone- B3B4). Appropriate isotype controls were used. Dead cells were excluded using LIVE/DEAD[®] Fixable Blue Dead Cell Stain Kit during FACS analysis. Overlaid histograms depicting expression of Fc ϵ RI and Fc ϵ RII on the surface of human basophils (HLA-DR⁺, CD123⁺, CRTH2⁺), human pDCs (HLA-DR⁺, CD123⁺, and BDCA2⁺), murine Basophils (CD19⁺, CD117⁺, CD49b⁺, CD123⁺, and CD200R3⁺), and murine pDCs (B220⁺ PDCA-1⁺, Siglech⁺) were shown. Human, but not mouse, pDCs express the high-affinity Fc ϵ RI. Fc ϵ RII is not expressed by pDCs in neither species.

responses by engaging their T-cell receptors (TCR) at the cell surface. Peptides generated by proteasomal degradation of endogenous cytosolic and nuclear antigens are loaded onto MHC class I molecules and presented to CD8 T cells through distinct intracellular pathways. Exogenous antigens are partially digested in lysosomal compartments and antigens are presented to CD4 T cells on MHC class II molecules. Among APCs, DCs can also present exogenous antigens to CD8 T cells through a process referred to as cross-presentation [131]. IgE receptors can trigger uptake of antigens in DCs [132–134], which raises the possibility that in the context of autoimmune diseases, autoantigens are also shuttled inside DCs through Fc ϵ -receptors. Most studies focusing on the antigen presentation properties of IgE have focused on the induction of CD4⁺T-cell responses and T_H2-type cytokine profiles due to the importance of this cytokine in allergy. However, it is becoming clear that IgE can also direct antigens to MHC class I molecules and promote antigen cross-presentation triggering CD8 T cells and cytotoxic

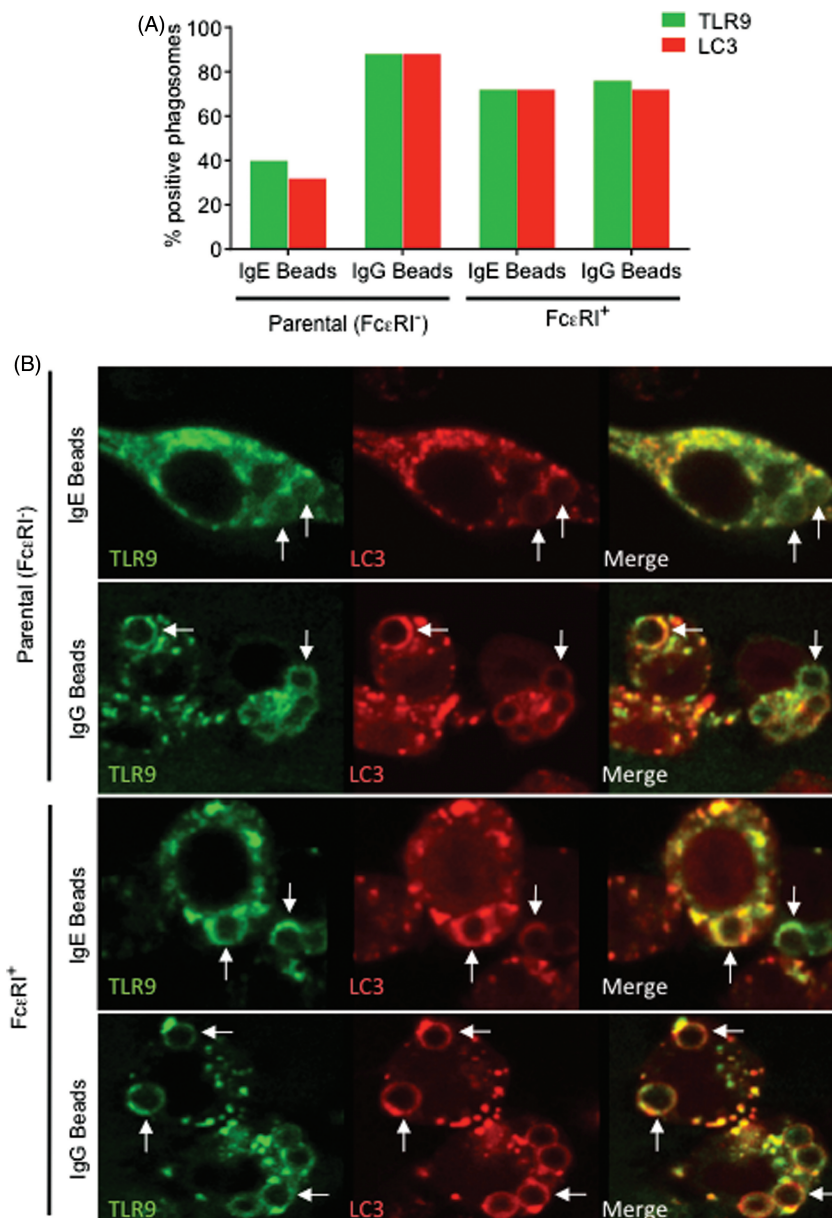
responses. This was recently demonstrated in a transgenic animal model that mimics the human expression pattern of Fc ϵ RI on DCs, where IgE-mediated cross presentation via Fc ϵ RI induced the proliferation of OT-I CD8 T cells as well as the production of granzyme B [135]. *In vitro* co-cultures of pDCs and T cells have shown that IgE autoantibodies are capable of triggering antigen-dependent proliferation of CD8 T cells and the induction of IFN γ secretion, to the same extent as ICs formed with IgG [10]. IgE autoantibodies could also promote T-cell responses indirectly through induction of IL-6 and type-I IFN secretion. IL-6 is important for T_H17 lineage commitment, is a driver of IL-17-secreting CD4 or CD8 T cells, and inhibits T_{reg}-cell function. Importantly, IL-6 promotes humoral immunity and the perpetuation of autoimmunity through its effects on T_{FH} cells, thereby linking T-cell and B-cell responses [136]. Like IL-6, type I IFNs strongly influence T-cell responses, enhance both T cell and NK cytotoxicity and survival, promote Th1 and Th17 commitment in CD4 T cells, and suppress T_{reg} activity [137–139].

B-cells responses

Biopsies from a subset of lupus patients reveal prominent IgE deposition in the kidney, infiltration of pDCs, and expression of the IFN-regulated protein MxA, suggesting a mechanistic link between IgE and the local IFN response [10]. pDCs and B cells have also been found in close proximity in some biopsies, indicating possible cell–cell interactions. Notably, *in vitro* studies demonstrate that pDCs activated with IgE-ICs have the capacity to drive B-cell expansion and plasma cell differentiation [10]. IL-21 is a pleiotropic cytokine known to induce B-cell activation and differentiation and is widely regarded as the most potent driver of humoral immune responses in humans [80,140]. Thus we directly compared the ability of IL-21 co-stimulation to induce plasma cell differentiation with that of IgE-IC. Strikingly, in the majority of individuals, pDCs activated with IgE-IC induced plasma cell differentiation to a similar degree as that observed in response to IL-21 co-stimulation (Figure 4A and B). Further, there was a significant increase in the frequency and number of CD27⁺ CD38⁺ IgD⁺ plasmablast-like cells in response to pDCs activated by DNA-IgE IC that was not observed to the same extent with IL-21 co-stimulation (Figure 4A and B).

The ability of IgE-ICs-activated pDCs to induce plasma cell differentiation is reliant on soluble factors such as type-I IFN and IL-6 [10]. Direct cell–cell contact has also been reported to be required for productive B-cell activation by pDCs [141]. To address this possibility, supernatants from DNA-IgE ICs-activated pDCs were used to stimulate B cells. Importantly, in combination with anti-CD40 co-stimulation, supernatants from IC-activated pDCs induced robust plasma cell differentiation *in vitro*, suggesting that soluble factors derived from pDCs are not only required but also sufficient to drive B-cell responses with CD40 engagement (Figure 4C). Of note, however, plasma cell differentiation was further increased in response to supernatants from co-cultures of B cells and DNA-Ig IC-activated pDCs (Figure 4C), suggesting that the interaction of B cells and pDCs together leads to a

Figure 3. Fc ϵ RI triggers LAP and TLR9 recruitment to phagosomes. Activation of Fc ϵ RI by IgE-adsorbed beads leads to LC3 recruitment to the phagosome. Mouse macrophages expressing the alpha chain of the human Fc ϵ RI (Fc ϵ RI⁺) and Fc ϵ RI⁻ parental cells (parental) were generated as previously described [10,126]. Cells were incubated with polystyrene beads adsorbed with either human IgE (IgE beads) or human IgG (IgG beads) [10]. Following bead phagocytosis, intracellular trafficking of TLR9-GFP and LC3-mCherry was visualized using time lapse confocal microscopy as previously described [126]. (A) The percentage of phagosomes positive for TLR9-GFP and LC3-mCherry was quantified 30 minutes after bead internalization ($n = 25$ phagosomes per group). (B) Representative frames taken 30 min after bead internalization are shown. Arrows point to internalized beads.



quantitative or qualitative change in the soluble factors secreted that drive plasma cell differentiation. Further, while supernatants from cultures of pDCs activated by either DNA-IgE or DNA-IgG ICs induced plasma cell differentiation, the response was significantly greater with supernatants from IgE-IC-activated pDCs. These data are consistent with previous observations that DNA-IgE ICs induce pDCs to secrete proinflammatory cytokines to a similar or greater degree than DNA-IgG ICs counterparts [10].

Cumulatively, these data suggest that IgE autoantibodies specific for DNA-containing antigens that are capable of activating pDCs have the capacity to induce potent

humoral responses and represent a mechanism that could support the generation of pathogenic autoantibodies in lupus patients.

Basophils-mediated responses

IgE contribute to autoimmune disorders through the activation of basophils. Circulating basophils in SLE patients show elevated L-selectin, which is associated with disease activity. L-selectin confers basophils with the ability to perform trans-endothelial migration into secondary lymphoid organs. As a result, they are found in the lymph nodes and spleen of SLE patients. Elevation of L-selectin and HLA-DR

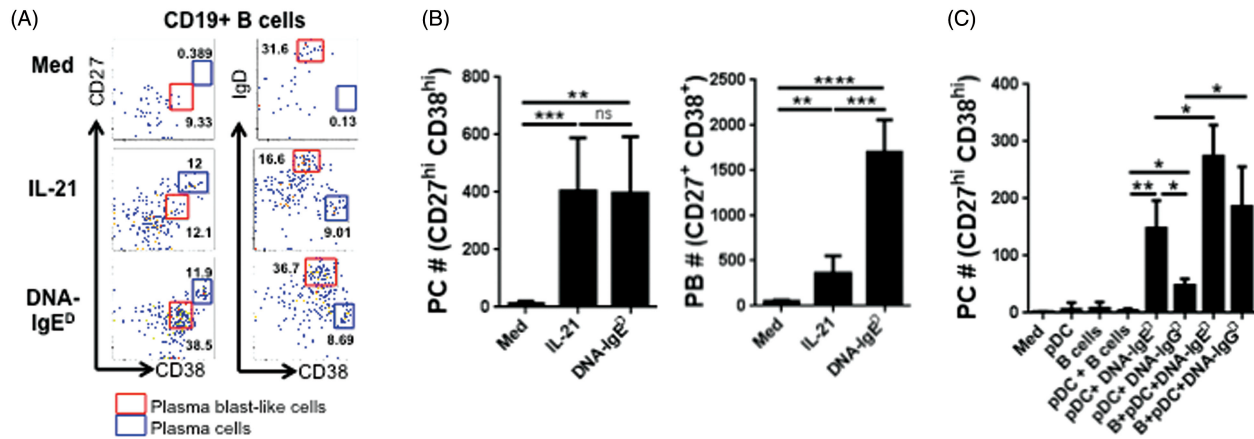


Figure 4. pDCs activated by DNA-specific IgE-ICs induce potent B-cell differentiation. (A–B) B cells (7.5×10^4) and pDCs (3.75×10^3) were cultured in 96-well round-bottom plates, along with 1.5 nM mega CD40L (Enzo Biosciences) as described previously [10]. ICs generated by combining 2.5 μ g/mL of IgE^D with 1 μ g/mL of CG50 plasmid DNA were added to the co-cultures. Recombinant human IL-21 (30 ng/ml) was used as a positive control. Cells were cultured for 7 days at 37°C and 5% CO₂, washed, and stained with CD123-FITC (clone 7G3), CD19-BV421 (clone HIB19), CD27-PerCPy5.5 (clone M-T271), IgD-PE (clone IA6-2), and CD38-APC (clone HIT2). (A) Flow cytometry analysis of human CD19+ B cells from pDC/B cell co-cultures. Frequency of plasmablast-like cells (red boxes) and plasma cells (blue boxes) is indicated. (B) Quantification of plasma cell (PC) and plasmablast-like cell (PB) number from cultures described in (A). Shown is the number of cells acquired for a fixed amount of time per well. (C) B cells (7.5×10^4) and pDCs (3.75×10^3) were stimulated for 24 hours with mega CD40L (1.5 nM) in the presence or absence of ICs as indicated. Supernatants collected after 24 hours were used to stimulate purified human B cells. Flow cytometry was performed after 7 days of B-cell stimulation, and PCs were quantified by flow cytometry as CD19⁺ CD27^{hi} CD38^{hi} cells. Data are presented as mean $\pm$ SD and are representative of at least three unique donors.

expressed on basophils is associated with active disease [142] and *in vitro* experiments have shown that basophils granulate in response to IgE bound to common SLE autoantigens [45,143]. Studies using a Lyn^{-/-} lupus-prone mouse model suggest that basophils infiltrated in lymphoid organs contribute to disease through secretion of IL-4, and expression of cell surface MHC class II and BAFF. This model is dependent on the presence of IgE autoantibodies and suggests that IgE-mediated basophil responses are partly responsible for the loss of self-tolerance by contributing to T-cell activation as well as B cell and plasma cell survival in lymphoid tissues, which ultimately leads to an amplification of autoantibody production [142,144].

Autoantibodies found in CSU and BP have been shown to activate basophils and mast cell degranulation [45]. FcεRI-mediated degranulation is largely responsible for pathogenesis, however additional mechanisms, such as epithelial detachment of the basement membrane, and cytokine release from the epithelial cells are also key contributors that are triggered by IgE-autoantibody deposition on involved tissues [5,31,34].

Conclusions

Recent research has expanded the roles of IgE from allergies to rheumatological diseases. The presence of self-reactive IgE has now been shown in a number of autoimmune disorders and they appear to be present in a significant subgroup of patients. Their appearance is often associated with worse disease outcome, and successful clinical trials in BP and CSU have proven their pathogenic nature. As other active clinical trials progress, the relative contribution of self-reactive IgE to other disorders will be revealed and likely the number of diseases they are linked to further expanded. The mechanisms by which IgE autoantibodies contribute to disease are starting to emerge. They bind to autoantigens and deposit in tissues causing alterations in

structural cells, and inflammation not only through basophils and mast cells but also through novel pathways such as induction of IFN secretion of pDCs that among other effects can induce plasma cell differentiation. Their presence is associated with the perpetuation of autoimmunity as self-reactive IgE promotes adaptive immune responses against self through both T-cell and B-cell activation. These linkages between IgE and autoimmunity are still poorly understood, and it is predictable that future studies aiming to determine the prevalence, affinity, and mechanisms of IgE in autoimmunity are likely to expand our understanding of how this subclass of antibodies contribute to rheumatologic disorders.

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Declaration of interest

RE, JLK, SKP, JMR, RK, MAS are full-time MedImmune employees and shareholders of MedImmune/AstraZeneca.

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