



Autoimmunity, IgE and FcεRI-bearing cells

Nicolas Charles^{1,2}

Antibody-mediated autoimmune diseases (AAID) involve several isotypes of autoreactive antibodies. In a growing number of AAID, autoreactive IgE are present with a significant prevalence and are often associated with the presence of IgG anti-IgE and/or anti-FcεRIα (high affinity IgE receptor α chain). FcεRI-bearing cells, such as basophils or mast cells, are key players in some of these AAID. Recent advances in the pathophysiology of these diseases led to the passed or current development of anti-IgE strategies that showed very potent effects in some of them. The present review centralizes the information on the relevance of autoreactive IgE and FcεRI-bearing cells in the pathophysiology of different AAID and the ones where the anti-IgE therapeutic strategy shows or may show some benefits for the patients.

Addresses

¹ Université de Paris, Centre de Recherche sur l'Inflammation, INSERM UMR1149, CNRS ERL8252, Faculté de Médecine site Bichat, Paris, France

² Université de Paris, Laboratoire d'Excellence Inflamex, Paris, France

Corresponding author: Charles, Nicolas (nicolas.charles@inserm.fr)

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Introduction

IgE-mediated hypersensitivity is central to the symptoms presented by atopic patients. This phenomenon implies several actors including IgE synthesis itself and cells expressing IgE receptors. The latter will be the key effectors inducing immune modulation, disease establishment and local and/or systemic reaction(s). In an IgE-mediated allergic context, IgE are often the unique, or at least the main, inducer of a deleterious immediate reaction leading the patient to develop debilitating symptoms that can be lethal in the case of systemic anaphylaxis [1]. Often, the absence or too low titers of antibodies from other isotypes raised against the allergens are responsible of the allergic condition [2]. This point led the scientific and clinical community to develop some desensitization

approaches by inducing IgG production against these same allergens with some real benefits for the patients [2].

Antibody-mediated autoimmunity may be defined as a humoral reaction of an organism against itself or at least against some self-antigens which vary from one given antibody-mediated autoimmune disease (AAID) to the other. These specificities will affect different organs due to different mechanisms involving various actors and dysregulated systems. Pathogenic autoantibodies originate from a break in self-tolerance for multifactorial but disease-specific reasons [3] and define the so-called disease-associated antigens (DAA) [4]. They can be defined as antibodies directly recognizing antigens from the targeted organ(s) (for instance anti-BP180 or anti-BP230 autoantibodies in Bullous Pemphigoid, BP) [5], or as antibodies indirectly inducing some dysregulation of the immune system resulting in organ damage (for instance autoantibodies targeting a cytokine like IL-24 in Chronic Spontaneous Urticaria (CSU) [6] or anti-TLR stimulating antigens like double stranded DNA (dsDNA) in Systemic Lupus Erythematosus (SLE) [7,8]). These autoantibodies drive the development and/or the amplification of AAID.

Specificities of autoantibodies determine their target, but their isotype determine their ability to modulate the activation state of various cell types and the interaction between targeted organs and immunologically and/or inflammatory active cells [7]. Receptors for Fc portions of immunoglobulins (Fc receptors, FcR) have cell-specific expression patterns that will determine the effects of autoantibodies on the immune cell compartments [9]. Monomeric autoantibodies recognize their specific target and the affinity of their cognate isotype-dependent Fc receptor determines their presence on the surface of an effector cell before antigen-induced crosslinking and subsequent activation [10]. In this context, only high affinity Fc receptors, such as FcεRI for IgE on mast cells and basophils, allow autoantibody binding to effector cells and immediate activation upon autoantigen-mediated crosslinking [10]. Immune complexes (IC) in AAID contain oligomerized autoantibodies from multiple isotypes aggregated to their target and to complement factors. Increased avidity of such multimeric complexes allows the binding of IC to all corresponding Fc receptors that can induce activating and/or inhibitory signals [9,10]. The integration of these signals determines the functional outcome of such IC binding to a given cell. Depending on the expressed Fc receptors, the integrated signal leads to either activation or inhibition of the targeted cell [11].

As for the regular organization of the humoral immunity, pathogenic autoantibodies can be of several isotypes. Autoantibodies of IgM isotype are often associated with a protective role in various autoimmune diseases whereas autoreactive IgG have a pathogenic function in most of them [7]. Even though autoantibodies of IgA and IgD isotypes are the less extensively studied, they are as well described in various autoimmune diseases but, often, their pathogenic or protective properties still have to be defined [7,12,13]. If IgE-mediated autoimmunity may not be a really accurate term, immune regulatory role of IgE and activation of cells bearing their high affinity receptor (FcεRI) through IgE-containing immune complexes were recently validated as pathogenic factors in various autoimmune conditions where significant prevalence of autoreactive IgE, along with autoantibodies of other isotypes, has been described. At least for some AAID, IgE-mediated activation of mast cells, basophils, eosinophils, plasmacytoid dendritic cells (pDC) and/or Langerhans cells (LC) have been described and validated in the pathophysiological mechanisms of these diseases.

Recent advances in the understanding of the role and prevalence of autoreactive IgE in various autoimmune conditions will be discussed as well as their related effector FcεRI-bearing cells when self-reactive IgE are validated as pathogenic and/or as efficient therapeutic targets.

IgE receptors

The relevance of autoreactive IgE in AAID depends on their surface receptors expressed on effector cells that are responsible for IgE function at the cellular and systemic levels. Two transmembrane receptors with highly significant affinity for IgE are described. The high affinity receptor for IgE or FcεRI ($K_d = 10^{-9}$ mol/L), in humans, can be found in a tetrameric form composed of a high affinity IgE binding alpha chain, a signal amplifier associated beta chain and a dimer of gamma signaling subunits common to other FcR [14]. This $[\alpha\beta\gamma_2]$ form is known to be mainly expressed by mast cells and basophils and is able to induce full activation of these cells after cross-linking in optimized conditions. Mainly studied in the IgE-related atopic context, basophil and mast cell activation via the FcεRI induces both immediate release of granular content and delayed secretion of pro-inflammatory and anti-inflammatory mediators including arachidonic acid derivatives and cytokines [15]. A trimeric form $[\alpha\gamma_2]$ is described in humans as being expressed (constitutively or induced) by other cell types such as dendritic cells (pDC; type 2 conventional DC, cDC2; LC), eosinophils and monocytes/macrophages [14].

The lower, but still high (K_d up to 10^{-8} mol/L), affinity receptor for IgE is the CD23 or FcεRII, mainly expressed by B cells but as well by T cells, DCs, monocytes, LCs, eosinophils, platelets and some epithelial cells for one of

its two isoforms. This C-type lectin is well described in the regulation of IgE synthesis through its effects on the B cell compartment in its membranous and soluble forms and may have some pro-inflammatory and/or anti-inflammatory roles in both allergic and autoimmune conditions [13,16]. A review nicely summarizing the knowledge on this receptor has been recently published in the allergy context [17]. Galectin-3 is a secretory lectin able to bind some glycosylated cell surface and extracellular proteins including IgE and FcεRI. It is expressed and secreted by FcεRI-bearing cells, neutrophils, T and B cells, and can activate IgE-loaded cells [16]. Autoantibodies raised against galectin-3 are found in SLE, and this lectin is involved in the pathophysiology of a large number of autoimmune conditions, including SLE, RA, AD, MS, SSc, GS and BP [18]. However, whether these roles in AAID are dependent on galectin-3 abilities to bind IgE and FcεRI are still poorly understood [16,18].

The following sections focus on the FcεRI-mediated effects of autoreactive IgE and FcεRI-aggregating autoantibodies (anti-IgE or anti-FcεRIα) in the autoimmune context. Since CD23 is also known to facilitate antigen presenting cells loading through internalization of IgE-containing immune complexes by B cells [19], CD23-mediated immune dysregulation in autoimmune conditions has to be kept in mind as an important parameter that may influence the titers of autoreactive IgE and their ability to activate FcεRI-bearing and/or CD23-bearing cells in secondary lymphoid organs and/or in targeted organs.

Autoimmune diseases with autoreactive IgE and FcεRI-aggregating autoantibodies

IgE, IgG anti-IgE and IgG anti-FcεRIα autoantibodies in various AAID have been described over the last five decades. Autoreactive IgE are highly prevalent in systemic lupus erythematosus (SLE) [13], chronic spontaneous urticaria (CSU) [6*,16], bullous pemphigoid (BP) [16], mixed connective tissue disease (MCTD) [20**,21], multiple sclerosis (MS) [22], Graves disease (GD) [23], Hashimoto disease [23], Gougerot-Sjogren syndrome (GS) [24], systemic sclerosis (SSc) [25], rheumatoid arthritis (RA) [26,27] and autoimmune uveitis (AU) [28] (Table 1). Atopic dermatitis (AD) is not considered an AAID per se but exhibit a high prevalence of autoreactive IgE which are associated with several autoimmune diseases and arise from molecular mimicry between well characterized allergens and their human counterparts [29,30*,31]. Zeller *et al.* identified over 100 autoantigens with detectable autoreactive IgE in AD patients [31]. Prevalence and relevance to the disease of some of these autoreactive IgE in AD patients have been recently reviewed [29,30*]. No report on the presence and the prevalence of autoreactive IgE in eosinophilic granulomatosis with polyangiitis (EGPA or Churg-Strauss Syndrome) was found in the literature. However, since anti-IgE therapy is known to be efficient in some EGPA patients [32–34] and since FcεRI-bearing cells are involved in its

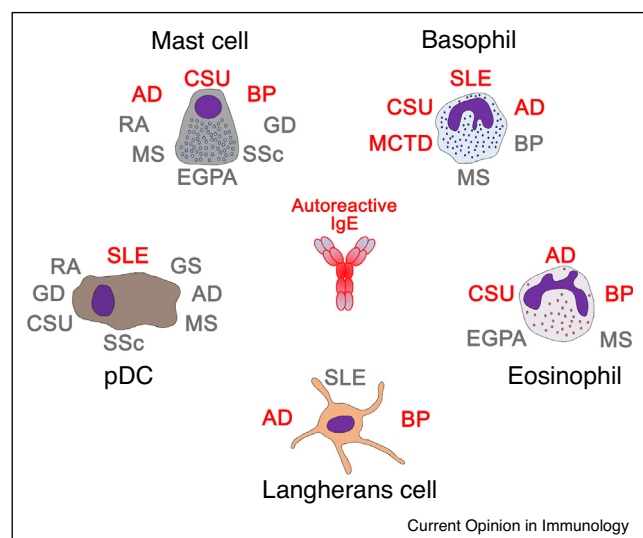
Table 1

Autoreactive IgE, IgE and anti-IgE therapy in Antibody-mediated Autoimmune Diseases

Autoimmune Disease	Specificities of autoreactive IgE	Prevalence	Related articles or reviews	Serum total IgE titers increased?	Anti-IgE therapy tested?	Efficacy	Ref.
Systemic Lupus Erythematosus (SLE)	dsDNA	35–55%	[13,21,51*,73,74]				
	ANA	42%	[27]				
	Sm RNP	7–48%	[73,74]				
	SSA	8–48%	[73,74]				
	SSB	4–7%	[73,74]				
	nRNP	62%	[73]				
	Nucleosome	79%	[73]	Yes [13]	Yes	Promising	[64*]
	CLIP4	11%	[74]				
	APEX	13%	[74]				
	MPG	11%	[74]				
	RPLP2	31%	[75]				
Bullous pemphigoid (BP)	IgG anti-IgE	34%	[38,39]				
	IgG anti-Fc ϵ RI α	20%	[38]				
	BP-180	22–100%	[16]			Yes OMZ	
	BP-230	67–100%	[16]	Yes [44]	Yes	No LGZ	[44]
Atopic dermatitis (AD)	IgG anti-Fc ϵ RI α	13%	[38]				
	IgG anti-IgE	86%	[41]			No OMZ	
	100+ autoantigens associated with AD	Overall 72% variable	[31,29,30*]				
	MnSOD	10–42%	[30*]	Yes [29]	Yes	Yes OMZ, pediatrics	[61,63]
	Trx	5–23%	[30*]				
Multiple sclerosis (MS)	RPLP2	8%	[76]				
	myelin-derived peptides	100%	[22]	No [77]	No	–	
Systemic Sclerosis (SSc)	Elastin	20%	[25]				
	Collagen I	20%	[25]				
	Collagen IV	20%	[25]	No [78]	No	–	
	IgG anti-IgE	21%	[42]				
Chronic Spontaneous Urticaria (CSU)	TPO	0–61%	[16]				
	IL-24	100%	[6*]				
	dsDNA	NA	[81]	Yes [79]	Yes	Yes OMZ and LGZ	[60**,80]
	IgG anti-IgE	45–76%	[37,40]				
	IgG anti-Fc ϵ RI α	28–59%	[37,38]				
Mixed Connective Tissue Disease (MCTD)	U1-snRNP 70K	78%	[20**]				
	nRNP	NA	[21]				
	ssDNA	NA	[21]	No [20**]	No	–	
	dsDNA	NA	[21]				
	Sm RNP	NA	[21]				
Eosinophilic Granulomatosis with Polyangiitis (EGPA)	NA	NA		Yes [32]	Yes	Steroid sparing effect	[32–34]
Graves disease (GD)	TPO	72%	[23]	Yes [82]	No	–	
Hashimoto disease	TPO	70%	[23]	No [83]	No	–	
Gougerot-Sjögren syndrome (GS)	SSA	33%	[24]				
	SSB	41%	[24]				
	dsDNA	15%	[24]	No [84,85]	No	–	
	Sm RNP	25%	[24]				
Rheumatoid Arthritis (RA)	ANA	32%	[27]				
	IgE-IC	36%	[26]	Yes [86,87]	No	–	
	IgG anti-IgE	NA	[87]				
Autoimmune uveitis (AU)	Retinal S antigen	68%	[28]	Yes [28]	No	–	

Abbreviations used: ANA: Anti-Nuclear Antibodies, APEX: APEX nuclease 1, BP-180: Bullous pemphigoid antigen of 180 kDa (COL17), BP-230: Bullous pemphigoid antigen of 230 kDa, CLIP4: CAP-GLY domain-containing linker protein family member 4, dsDNA: double stranded DNA, IgE-IC: IgE-containing immune complexes, LGZ: ligelizumab, MnSOD: Manganese superoxide dismutase, MPG: N-methylpurine-DNA glycosylase, NA: Not assessed, nRNP: nuclear ribonucleoprotein, OMZ: omalizumab, RPLP2: Ribosomal protein P2, ssDNA: single stranded DNA, Sm: Smith antigen, TPO: Thyroid peroxidase, Trx: Thioredoxins, U1-snRNP 70k: U1 small nuclear ribonucleoprotein subunit of 70 kDa.

Figure 1



Autoreactive IgE and FcεRI-bearing cells in antibody-mediated autoimmune diseases (AAID).

FcεRI-bearing mast cells [16,29,36,43,45–48,88[•]], basophils [13,20[•],29,37,43,46,68,89], plasmacytoid dendritic cells [51[•],52,53,90–93], eosinophils [29,35,44,46,54] and Langerhans cells [29,56,57[•]] are known to be involved in the pathophysiology of various AAID (abbreviations indicated in circle around each cell type). In red are indicated the AAID where the contribution of these cells in the pathogenesis has clearly been linked to their responsiveness to autoreactive IgE or FcεRI-targeting autoantibodies. In grey are indicated the AAID where the FcεRI-bearing cell has been shown to contribute but where their IgE-mediated activation has not been clearly established in this AAID context. Abbreviations used: SLE: Systemic lupus erythematosus; BP: Bullous pemphigoid; AD: Atopic dermatitis; MS: Multiple sclerosis; SSc: Systemic sclerosis; CSU: Chronic spontaneous urticaria; MCTD: Mixed connective tissue disease; EGPA: Eosinophilic granulomatosis with polyangiitis; Graves disease (GD); GS: Gougerot-Sjögren syndrome; RA: Rheumatoid arthritis; pDC: plasmacytoid dendritic cell.

pathogenesis [35,36], autoreactive IgE occurrence may be relevant to EGPA pathophysiology (Table 1, Figure 1). IgG anti-IgE and/or anti-FcεRIα, with FcεRI-aggregating abilities, have been described as well in SLE, CSU, BP, SSc, RA and AD [37–42]. The Table 1 summarizes the autoimmune conditions where such FcεRI-aggregating autoantibodies have been described. Except for MS, SSc, MCTD and GS, total serum IgE levels in all other aforementioned AAID are elevated when compared to healthy populations (Table 1) suggesting to the least a T Helper type 2 (TH2) component in their pathophysiology. As these autoreactive antibodies are relevant to FcεRI-bearing cell activation, some of the latter have been clearly identified as key actors in various AAID.

FcεRI-bearing cells described in the pathophysiology of autoimmune diseases

Mast cells and basophils are the main [αβγ₂] FcεRI-bearing cells and have been demonstrated as key cells

contributing to AAID where autoreactive IgE or FcεRI aggregating autoantibodies have been described. pDC, eosinophils, and LC are other FcεRI-expressing cells (most probably[αγ₂]) that are key actors in a number of AAID through either IgE-dependent or non-IgE-dependent mechanisms.

Mast cells are known to be key contributors to CSU [43], BP [44] and AD [29] for which their activation through the FcεRI has clearly been shown to contribute to the pathophysiology of these AAID (Figure 1). The involvement of mast cells in RA [45], MS [46], GD [47], SSc [48] and EGPA [36] are clearly established, but not necessarily yet in the FcεRI-mediated activation context (Figure 1).

Basophils are described as being activated in an IgE-dependent manner during the course of SLE [13], MCTD [20[•]], CSU [43] and AD [29]. Their contribution to BP [44] and MS [46] are as well established, but not yet directly in the IgE context (Figure 1).

pDC are major producers of type I IFN involved in antiviral immunity, allergy and as well in a number of autoimmune diseases [49,50] (Figure 1). Their IgE-mediated contribution to the pathophysiology of SLE has been clearly established [51[•]] and their contribution to RA [52] and GS [53] may be linked or modulated by FcεRI-targeting self-antibodies (Figure 1).

FcεRI expressed by eosinophils link them to the pathophysiology of CSU [54], AD [29], and BP [44]. Their contribution to EGPA is obvious [35] and the sensitivity of this autoimmune disease to anti-IgE approach (see below and Ref. [32]) suggest that self-IgE may be involved in their pathogenicity. Eosinophils are as well described in MS pathophysiology [46] (Figure 1).

LC are major antigen presenting cells in the human skin [55] and express the FcεRI [56]. This latter parameter links them to the pathological mechanisms of BP [56] and AD [29]. Their contribution to SLE [57[•]] still has to be studied in the FcεRI context (Figure 1).

The relationship among elevated total serum IgE levels, autoreactive IgE and the activation of FcεRI-bearing cells in some AAID strongly suggest that preventing IgE binding to their receptors may block their deleterious role in such diseases (Table 1). This approach led the scientific and medical community to assess the safety and/or the efficacy of anti-IgE biotherapies in these AAID.

Anti-IgE therapy

Since IgE, autoreactive IgE and FcεRI-bearing cells are well described for their contribution of some AAID (see above), IgE has been considered as a very promising therapeutic target. IgE targeting strategy has been primarily developed for allergic diseases. Omalizumab was

the first anti-IgE humanized monoclonal antibody approved for the treatment of severe uncontrolled asthma in adults [58]. Omalizumab binds free IgE in biological fluids as well as the BCR (B cell receptor) of IgE isotype. It prevents binding of IgE to FcεRI and limits the production of IgE resulting in a marked decrease of free IgE levels and a reduction of FcεRI expression on FcεRI-bearing cells [58]. It has recently been approved for the treatment of CSU [58] (Table 1). Two other anti-IgE biotherapies are currently under development in atopic diseases and CSU: ligelizumab and UB-221 [59,60**].

Anti-IgE approach is known to be effective in CSU and since the approval of omalizumab in this indication, a recent clinical trial using ligelizumab in CSU patients validated the efficacy of this approach [58,60**]. AD was an evident atopic condition in which anti-IgE approach should have been successful. However, ten years ago, omalizumab was shown not to be more efficient in this disease than the standard of care [61]. This point was confirmed in a later clinical trial in pediatric AD [62]. Finally, a recent clinical trial demonstrated efficacy of the anti-IgE in pediatric AD [63]. Omalizumab showed as well to be efficient in BP as described in numerous case reports [44]. Unexpectedly, ligelizumab was tested in a recent randomized, double blind and placebo-controlled study and did not achieve the defined criteria of efficacy [44]. Further studies are needed to validate the anti-IgE approach in BP. As mentioned previously, omalizumab use in EGPA showed some beneficial corticoid-sparing effects in patients [32–34]. Recently, a phase Ib clinical trial for the use of omalizumab in SLE showed a good safety of the approach in SLE patients with some preliminary data suggesting a promising efficacy for the anti-IgE therapy in SLE [64*] (Table 1).

Patients suffering of other AAID may benefit of an anti-IgE approach (Table 1). For instance, patients with GD or RA have all the pathophysiological parameters suggesting a putative benefit of this approach: elevated total serum IgE levels, high prevalence of autoreactive IgE and involvement of FcεRI-bearing cells in their pathogenesis. To our knowledge, no clinical trial targeting IgE are currently ongoing in GD, RA, AU, GS, SSc or MCTD but may represent a promising approach to evaluate.

Conclusions

In the last decade, it became evident that, beyond allergy, IgE and FcεRI-bearing cells were involved in a number of autoimmune conditions. Basic science, translational research and clinical research could validate the targeting of IgE, mast cells, basophils, eosinophils and pDC as efficient or at least promising therapeutic modalities. This short review aimed at centralizing the information on the relevance of autoreactive IgE and FcεRI-targeting auto-antibodies in AAID in which FcεRI-bearing cells are known to contribute to the pathophysiology and to

underline that patients with other AAID may benefit of the anti-IgE therapeutic strategy.

In line with this approach, other drugs modulating IgE production and/or the activation status of immune cells, including FcεRI-bearing cells, are currently in pre-clinical or clinical development in multiple AAID [65*]. For instance, B cell receptor and activating Fc receptors share multiple signaling effectors and are involved in all the AAID discussed above [9]. Consequently, several kinase inhibitors targeting spleen tyrosine kinase (SYK) and Burton tyrosine kinase (BTK) are clinically explored in several AAID [65*]. Kinase inhibitors and biotherapies targeting cytokines, cytokine receptors, toll-like receptors (TLR), cell–cell interaction molecules and/or their signaling pathways are currently under investigation and along with B-cell depleting approaches may show in the near future some therapeutic efficacy for AAID patients [65*,66]. However, most of these approaches may as well have some off-target and/or on-target side effects by inhibiting non-inflammatory pathways in which some targeted kinases are involved or by inducing long term immunosuppression in B cell-depleted patients [65*,66,67].

Direct targeting of pathogenic factors such as IgE in the discussed diseases or other disease-specific pathways involving FcεRI-bearing cells may then represent safer therapeutic modalities. For instance, we recently showed, in a pre-clinical setting, that targeting both prostaglandin D2 receptors, PTGDR-1 (or DP) and PTGDR-2 (or CRTH2 for Chemoattractant Receptor homologous molecule expressed on Th2 cells), in SLE may be of clinical interest by preventing the deleterious role of basophils during the course of the disease [68]. Either targeting of pDC or their related pathways are as well under development in SLE, RA, SSc and SG [69] and eosinophil depletion, along with mast cell inhibition, may as well be beneficial in some AAID [70] (Figure 1). A soluble form of the FcεRI (sFcεRI) is detected in the serum of atopic individuals and can prevent IgE binding to FcεRI-bearing cells, limiting their IgE-mediated activation [71,72]. sFcεRI relevance to AAID still needs to be investigated but may represent an efficient tool to prevent IgE-mediated effects during the course of these diseases.

Future clinical and scientific studies will hopefully validate these promising therapeutic modalities for AAID in which IgE and FcεRI-bearing cells are involved and where specific treatments allowing to satisfyingly treat the affected patients without deleterious side effects are still lacking.

Conflict of interest statement

NC holds two patents related to compositions and methods for treating or preventing lupus (W020120710042 and W02016128565A1). No other disclosures relevant to this article are reported.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Galli SJ, Gaudenzio N, Tsai M: **Mast cells in inflammation and disease: recent progress and ongoing concerns.** *Annu Rev Immunol* 2020, **38**:49-77.
2. Paranjape A, Tsai M, Mukai K, Hoh RA, Joshi SA, Chinthrajah RS, Nadeau KC, Boyd SD, Galli SJ: **Oral immunotherapy and basophil and mast cell reactivity in food allergy.** *Front Immunol* 2020, **11**:602660.
3. Theofilopoulos AN, Kono DH, Baccala R: **The multiple pathways to autoimmunity.** *Nat Immunol* 2017, **18**:716-724.
4. Jacqueline C, Finn OJ: **Antibodies specific for disease-associated antigens (DAA) expressed in non-malignant diseases reveal potential new tumor-associated antigens (TAA) for immunotherapy or immunoprevention.** *Semin Immunol* 2020, **47**:101394.
5. Shih YC, Wang B, Yuan H, Zheng J, Pan M: **Role of BP230 autoantibodies in bullous pemphigoid.** *J Dermatol* 2020, **47**:317-326.
6. Schmetzer O, Lakin E, Topal FA, Preusse P, Freier D, Church MK, Maurer M: **IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria.** *J Allergy Clin Immunol* 2018, **142**:876-882.
- This study identifies IL-24 as a common, specific, and functional autoantigen of IgE antibodies in patients with CSU. These autoreactive IgE are able to crosslink FcεRI to activate mast cells and should contribute to disease activity.
7. Dema B, Charles N: **Autoantibodies in SLE: specificities, isotypes and receptors.** *Antibodies (Basel)* 2016, **5**.
8. Fillatreau S, Manfroi B, Dorner T: **Toll-like receptor signalling in B cells during systemic lupus erythematosus.** *Nat Rev Rheumatol* 2021, **17**:98-108.
9. Ben Mkaddem S, Benhamou M, Monteiro RC: **Understanding Fc receptor involvement in inflammatory diseases: from mechanisms to new therapeutic tools.** *Front Immunol* 2019, **10**:811.
10. Daeron M: **Fc receptors as adaptive immunoreceptors.** *Curr Top Microbiol Immunol* 2014, **382**:131-164.
11. Daeron M: **Innate myeloid cells under the control of adaptive immunity: the example of mast cells and basophils.** *Curr Opin Immunol* 2016, **38**:101-108.
12. Altrichter S, Zampeli V, Ellrich A, Zhang K, Church MK, Maurer M: **IgM and IgA in addition to IgG autoantibodies against FcγεpsilonRIα are frequent and associated with disease markers of chronic spontaneous urticaria.** *Allergy* 2020, **75**:3208-3215.
13. Lamri Y, Charles N: **IgE in the pathogenesis of SLE: from pathogenic role to therapeutic target.** *Antibodies (Basel)* 2020, **9**.
14. Kinet JP: **The high-affinity IgE receptor (Fc εRI): from physiology to pathology.** *Annu Rev Immunol* 1999, **17**:931-972.
15. Mukai K, Tsai M, Saito H, Galli SJ: **Mast cells as sources of cytokines, chemokines, and growth factors.** *Immunol Rev* 2018, **282**:121-150.
16. Maurer M, Altrichter S, Schmetzer O, Scheffel J, Church MK, Metz M: **Immunoglobulin E-mediated autoimmunity.** *Front Immunol* 2018, **9**:689.
17. Engeroff P, Vogel M: **The role of CD23 in the regulation of allergic responses.** *Allergy* 2020. online ahead of print.
18. de Oliveira FL, Gatto M, Bassi N, Luisetto R, Ghirardello A, Punzi L, Doria A: **Galectin-3 in autoimmunity and autoimmune diseases.** *Exp Biol Med (Maywood)* 2015, **240**:1019-1028.
19. Ding Z, Dahlin JS, Xu H, Heyman B: **IgE-mediated enhancement of CD4(+) T cell responses requires antigen presentation by CD8α(-) conventional dendritic cells.** *Sci Rep* 2016, **6**:28290.
20. Lamri Y, Vibhushan S, Pacreau E, Boedec E, Saidoune F, Mailloux A, Crestani B, Blank U, Benhamou M, Papo T *et al.*: **Basophils and IgE contribute to mixed connective tissue disease development.** *J Allergy Clin Immunol* 2020. online ahead of print.
- This study shows an activated phenotype of basophils and the high prevalence of autoreactive IgE in mixed connective tissue disease (or Sharp syndrome) patients. Removal of basophils or IgE in a mouse model dramatically dampen the associated lung pathology identifying them as very promising therapeutic target.
21. Camussi G, Tetta C, Benveniste J: **Detection of basophil sensitization by IgE antibodies to nuclear antigens in connective tissue diseases.** *Int Arch Allergy Appl Immunol* 1982, **69**:358-362.
22. Mikol DD, Dittlow C, Usatin D, Biswas P, Kalbfleisch J, Milner A, Calenoff E: **Serum IgE reactive against small myelin protein-derived peptides is increased in multiple sclerosis patients.** *J Neuroimmunol* 2006, **180**:40-49.
23. Guo J, Rapoport B, McLachlan SM: **Thyroid peroxidase autoantibodies of IgE class in thyroid autoimmunity.** *Clin Immunol Immunopathol* 1997, **82**:157-162.
24. Danielides S, Dema B, Rivera J, Illei GG: **IgE autoantibodies against SSA and SSB in patients with Sjogren's syndrome and healthy controls.** *Arthritis Rheum* 2012, **64**:S930.
25. Daskalova M, Taskov H, Dimitrova E, Baydanoff S: **Humoral and cellular immune response to elastin in patients with systemic sclerosis.** *Autoimmunity* 1997, **25**:233-241.
26. De Clerck LS, Struyf NJ, Bridts CH, Breedveld FC, Westedt ML, Cats A, Stevens WJ: **IgE-containing immune complexes in synovial fluid of patients with rheumatoid arthritis.** *Clin Rheumatol* 1990, **9**:176-181.
27. Permin H, Wiik A: **The prevalence of IgE antinuclear antibodies in rheumatoid arthritis and systemic lupus erythematosus.** *Acta Pathol Microbiol Scand C* 1978, **86C**:245-249.
28. Muino JC, Juarez CP, Luna JD, Castro CC, Wolff EG, Ferrero M, Romero-Piffiguer MD: **The importance of specific IgG and IgE autoantibodies to retinal S antigen, total serum IgE, and sCD23 levels in autoimmune and infectious uveitis.** *J Clin Immunol* 1999, **19**:215-222.
29. Pellefigues C: **IgE autoreactivity in atopic dermatitis: paving the road for autoimmune diseases?** *Antibodies (Basel)* 2020, **9**.
30. Badloe FMS, De Vriese S, Coolens K, Schmidt-Weber CB, Ring J, Gutermuth J, Kortekaas Krohn I: **IgE autoantibodies and autoreactive T cells and their role in children and adults with atopic dermatitis.** *Clin Transl Allergy* 2020, **10**:34.
- This recent systematic review exhaustively summarizes the prevalence, the specificities and the pathophysiological roles of autoreactive IgE and T cells in atopic dermatitis.
31. Zeller S, Rhyner C, Meyer N, Schmid-Grendelmeier P, Akdis CA, Cramer R: **Exploring the repertoire of IgE-binding self-antigens associated with atopic eczema.** *J Allergy Clin Immunol* 2009, **124**:278-285.
32. Celebi Sozener Z, Gorgulu B, Mungan D, Sin BA, Misirligil Z, Aydin O, Bavbek S: **Omalizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA): single-center experience in 18 cases.** *World Allergy Organ J* 2018, **11**:39.

33. Detoraki A, Di Capua L, Varricchi G, Genovese A, Marone G, Spadaro G: **Omalizumab in patients with eosinophilic granulomatosis with polyangiitis: a 36-month follow-up study.** *J Asthma* 2016, **53**:201-206.
 34. Jachiet M, Samson M, Cottin V, Kahn JE, Le Guenno G, Bonniaud P, Devilliers H, Bouillet L, Gondouin A, Makhlouf F *et al.*: **Anti-IgE monoclonal antibody (Omalizumab) in refractory and relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss): data on seventeen patients.** *Arthritis Rheumatol* 2016, **68**:2274-2282.
 35. Furuta S, Iwamoto T, Nakajima H: **Update on eosinophilic granulomatosis with polyangiitis.** *Allergol Int* 2019, **68**:430-436.
 36. Schroeder JW, Folci M, Losappio LM, Chevallard M, Sinico RA, Mirone C, De Luca F, Nichelatti M, Pastorello EA: **Anti-neutrophil cytoplasmic antibodies positivity and anti-leukotrienes in eosinophilic granulomatosis with polyangiitis: a retrospective monocentric study on 134 Italian patients.** *Int Arch Allergy Immunol* 2019, **180**:64-71.
 37. Eckman JA, Hamilton RG, Gober LM, Sterba PM, Saini SS: **Basophil phenotypes in chronic idiopathic urticaria in relation to disease activity and autoantibodies.** *J Invest Dermatol* 2008, **128**:1956-1963.
 38. Fiebigler E, Hammerschmid F, Stingl G, Maurer D: **Anti-FcεpsilonR1alpha autoantibodies in autoimmune-mediated disorders. Identification of a structure-function relationship.** *J Clin Invest* 1998, **101**:243-251.
 39. Gruber BL, Kaufman LD, Marchese MJ, Roth W, Kaplan AP: **Anti-IgE autoantibodies in systemic lupus erythematosus. Prevalence and biologic activity.** *Arthritis Rheum* 1988, **31**:1000-1006.
 40. Izaki S, Toyoshima S, Endo T, Kanegae K, Nunomura S, Kashiwakura JI, Sasaki-Sakamoto T, Nakamura R, Akiyama H, Ra C *et al.*: **Differentiation between control subjects and patients with chronic spontaneous urticaria based on the ability of anti-IgE autoantibodies (AABs) to induce FcεpsilonR1 crosslinking, as compared to anti-FcεpsilonR1alpha AABs.** *Allergol Int* 2019, **68**:342-351.
 41. Nawata Y, Koike T, Hosokawa H, Tomioka H, Yoshida S: **Anti-IgE autoantibody in patients with atopic dermatitis.** *J Immunol* 1985, **135**:478-482.
 42. Kaufman LD, Gruber BL, Marchese MJ, Seibold JR: **Anti-IgE autoantibodies in systemic sclerosis (scleroderma).** *Ann Rheum Dis* 1989, **48**:201-205.
 43. Bracken SJ, Abraham S, MacLeod AS: **Autoimmune theories of chronic spontaneous urticaria.** *Front Immunol* 2019, **10**:627.
 44. Messingham KN, Crowe TP, Fairley JA: **The intersection of IgE autoantibodies and eosinophilia in the pathogenesis of bullous pemphigoid.** *Front Immunol* 2019, **10**:2331.
 45. Rivellesse F, Rossi FW, Galdiero MR, Pitzalis C, de Paulis A: **Mast cells in early rheumatoid arthritis.** *Int J Mol Sci* 2019, **20**.
 46. Brown MA, Weinberg RB: **Mast cells and innate lymphoid cells: underappreciated players in CNS autoimmune demyelinating disease.** *Front Immunol* 2018, **9**:514.
 47. Zdor VV, Geltser BI, Eliseikina MG, Markelova EV, Tikhonov YN, Plekhova NG, Karaulov AV: **Roles of thyroid hormones, mast cells, and inflammatory mediators in the initiation and progression of autoimmune thyroid diseases.** *Int Arch Allergy Immunol* 2020, **181**:715-726.
 48. Pattanaik D, Brown M, Postlethwaite BC, Postlethwaite AE: **Pathogenesis of systemic sclerosis.** *Front Immunol* 2015, **6**:272.
 49. Ettinger R, Karnell JL, Henault J, Panda SK, Riggs JM, Kolbeck R, Sanjuan MA: **Pathogenic mechanisms of IgE-mediated inflammation in self-destructive autoimmune responses.** *Autoimmunity* 2017, **50**:25-36.
 50. Alculumbre S, Raieli S, Hoffmann C, Chelbi R, Danlos FX, Soumelis V: **Plasmacytoid pre-dendritic cells (pDC): from molecular pathways to function and disease association.** *Semin Cell Dev Biol* 2019, **86**:24-35.
 51. Henault J, Riggs JM, Karnell JL, Liarski VM, Li J, Shirinian L, Xu L, Casey KA, Smith MA, Khatry DB *et al.*: **Self-reactive IgE exacerbates interferon responses associated with autoimmunity.** *Nat Immunol* 2016, **17**:196-203.
- This study demonstrates the key contribution of anti-dsDNA autoreactive IgE on plasmacytoid dendritic cells, in the SLE context, and their ability to induce a large production of type I interferons in an FcεRI-dependent and TLR9-dependent mechanism.
52. Nehmar R, Mariotte A, de Cauwer A, Sibilia J, Bahram S, Georgel P: **Therapeutic perspectives for interferons and plasmacytoid dendritic cells in rheumatoid arthritis.** *Trends Mol Med* 2018, **24**:338-347.
 53. Bodewes ILA, Bjork A, Versnel MA, Wahren-Herlenius M: **Innate immunity and interferons in the pathogenesis of Sjogren's syndrome.** *Rheumatology (Oxford)* 2019.
 54. Altrichter S, Frischbutter S, Fok JS, Kolkhir P, Jiao Q, Skov PS, Metz M, Church MK, Maurer M: **The role of eosinophils in chronic spontaneous urticaria.** *J Allergy Clin Immunol* 2020, **145**:1510-1516.
 55. Kashem SW, Haniffa M, Kaplan DH: **Antigen-presenting cells in the skin.** *Annu Rev Immunol* 2017, **35**:469-499.
 56. Kwiek B, Lesniewska A, Kowalewski C, Wozniak K: **Langerhans cells are predominant high affinity immunoglobulin E receptor bearing cells in the epidermis of bullous pemphigoid skin.** *J Dermatol Sci* 2017, **85**:60-63.
 57. Shipman WD, Chyou S, Ramanathan A, Izmirly PM, Sharma S, Pannellini T, Dasoveanu DC, Qing X, Magro CM, Granstein RD *et al.*: **A protective Langerhans cell-keratinocyte axis that is dysfunctional in photosensitivity.** *Sci Transl Med* 2018, **10**.
- This study identifies the Langerhans cells (FcεRI-bearing cells) as a key contributor of the photosensitivity in SLE patient skin. It would be of primary interest to study the contribution of autoreactive IgE in the mechanism involving this cell type.
58. Okayama Y, Matsumoto H, Odajima H, Takahagi S, Hide M, Okubo K: **Roles of omalizumab in various allergic diseases.** *Allergol Int* 2020, **69**:167-177.
 59. Kolkhir P, Altrichter S, Munoz M, Hawro T, Maurer M: **New treatments for chronic urticaria.** *Ann Allergy Asthma Immunol* 2020, **124**:2-12.
 60. Maurer M, Gimenez-Arnau AM, Sussman G, Metz M, Baker DR, Bauer A, Bernstein JA, Brehler R, Chu CY, Chung WH *et al.*: **Ligelizumab for chronic spontaneous urticaria.** *N Engl J Med* 2019, **381**:1321-1332.
- This clinical trial study demonstrates the stronger efficacy of the new generation of anti-IgE monoclonal antibody ligelizumab in Chronic spontaneous urticaria.
61. Heil PM, Maurer D, Klein B, Hultsch T, Stingl G: **Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course — a randomized, placebo-controlled and double blind pilot study.** *J Dtsch Dermatol Ges* 2010, **8**:990-998.
 62. Iyengar SR, Hoyte EG, Loza A, Bonaccorso S, Chiang D, Umetsu DT, Nadeau KC: **Immunologic effects of omalizumab in children with severe refractory atopic dermatitis: a randomized, placebo-controlled clinical trial.** *Int Arch Allergy Immunol* 2013, **162**:89-93.
 63. Chan S, Cornelius V, Cro S, Harper JJ, Lack G: **Treatment effect of omalizumab on severe pediatric atopic dermatitis: the ADAPT randomized clinical trial.** *JAMA Pediatr* 2019, **164**:29-37.
 64. Hasni S, Gupta S, Davis M, Poncio E, Temesgen-Oyelakin Y, Joyal E, Fike A, Manna Z, Auh S, Shi Y *et al.*: **Safety and tolerability of omalizumab: a randomized clinical trial of humanized anti-IgE monoclonal antibody in systemic lupus erythematosus.** *Arthritis Rheumatol* 2019, **71**:1135-1140.
- This study is the first report of a clinical trial using omalizumab in SLE showing a good safety and tolerability of this anti-IgE in lupus patients and suggesting a promising efficacy.
65. Zarrin AA, Bao K, Lupardus P, Vucic D: **Kinase inhibition in autoimmunity and inflammation.** *Nat Rev Drug Discov* 2021, **20**:39-63.
- This recent review nicely centralizes and summarizes the ongoing development of kinase inhibitors and biotherapies in autoimmune diseases.

66. Lee DSW, Rojas OL, Gommerman JL: **B cell depletion therapies in autoimmune disease: advances and mechanistic insights.** *Nat Rev Drug Discov* 2021, **20**:179-199.
 67. Roberts DM, Jones RB, Smith RM, Alberici F, Kumaratne DS, Burns S, Jayne DR: **Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease.** *J Autoimmun* 2015, **57**:60-65.
 68. Pellefigues C, Dema B, Lamri Y, Saidoune F, Chavarot N, Loheac C, Pacreau E, Dussiot M, Bidault C, Marquet F *et al.*: **Prostaglandin D2 amplifies lupus disease through basophil accumulation in lymphoid organs.** *Nat Commun* 2018, **9**:725.
 69. Ye Y, Gaugler B, Mohty M, Malard F: **Plasmacytoid dendritic cell biology and its role in immune-mediated diseases.** *Clin Transl Immunol* 2020, **9**:e1139.
 70. Youngblood BA, Leung J, Falahati R, Williams J, Schanin J, Brock EC, Singh B, Chang AT, O'Sullivan JA, Schleimer RP *et al.*: **Discovery, function, and therapeutic targeting of siglec-8.** *Cells* 2020, **10**.
 71. Monino-Romero S, Erkert L, Schmidthaler K, Diesner SC, Sallis BF, Pennington L, Jardtetzky T, Oettgen HC, Bohle B, Fiebiger E *et al.*: **The soluble isoform of human FcγεRI is an endogenous inhibitor of IgE-mediated mast cell responses.** *Allergy* 2019, **74**:236-245.
 72. Monino-Romero S, Lexmond WS, Singer J, Bannert C, Amoah AS, Yazdanbakhsh M, Boakye DA, Jensen-Jarolim E, Fiebiger E, Szepefalusi Z: **Soluble FcγRI: a biomarker for IgE-mediated diseases.** *Allergy* 2019, **74**:1381-1384.
 73. Atta AM, Santiago MB, Guerra FG, Pereira MM, Sousa Atta ML: **Autoimmune response of IgE antibodies to cellular self-antigens in systemic lupus erythematosus.** *Int Arch Allergy Immunol* 2010, **152**:401-406.
 74. Dema B, Pellefigues C, Hasni S, Gault N, Jiang C, Ricks TK, Bonelli MM, Scheffel J, Sacre K, Jablonski M *et al.*: **Auto-reactive IgE is prevalent in systemic lupus erythematosus and is associated with increased disease activity and nephritis.** *PLoS One* 2014, **9**:e90424.
 75. Rhyner C, Daigle I, Cramer R: **Auto-reactive IgE responses to acidic ribosomal P2 protein in systemic lupus erythematosus.** *Allergy* 2011, **66**:1127-1129.
 76. Mayer C, Appenzeller U, Seelbach H, Achatz G, Oberkofler H, Breitenbach M, Blaser K, Cramer R: **Humoral and cell-mediated autoimmune reactions to human acidic ribosomal P2 protein in individuals sensitized to *Aspergillus fumigatus* P2 protein.** *J Exp Med* 1999, **189**:1507-1512.
 77. Karimi P, Modarresi SZ, Sahraian MA, Shokouhi Shoormasti R, Mahlooji M, Kazemnejad A, Pourpak Z: **The relation of multiple sclerosis with allergy and atopy: a case control study.** *Iran J Allergy Asthma Immunol* 2013, **12**:182-189.
 78. Amblard P, Raymond JL: **IgE levels in various dermatoses.** *Arch Dermatol* 1978, **114**:289-290.
 79. Staubach P, Vonend A, Burow G, Metz M, Magerl M, Maurer M: **Patients with chronic urticaria exhibit increased rates of sensitisation to *Candida albicans*, but not to common moulds.** *Mycoses* 2009, **52**:334-338.
 80. Agache I, Rocha C, Pereira A, Song Y, Alonso-Coello P, Sola I, Beltran J, Posso M, Akdis CA, Akdis M *et al.*: **Efficacy and safety of treatment with omalizumab for chronic spontaneous urticaria: a systematic review for the EAACI biologicals guidelines.** *Allergy* 2021, **76**:59-70.
 81. Hatada Y, Kashiwakura J, Hayama K, Fujisawa D, Sasaki-Sakamoto T, Terui T, Ra C, Okayama Y: **Significantly high levels of anti-dsDNA immunoglobulin E in sera and the ability of dsDNA to induce the degranulation of basophils from chronic urticaria patients.** *Int Arch Allergy Immunol* 2013, **161**(Suppl. 2):154-158.
 82. Yamada T, Sato A, Komiya I, Nishimori T, Ito Y, Terao A, Eto S, Tanaka Y: **An elevation of serum immunoglobulin E provides a new aspect of hyperthyroid Graves' disease.** *J Clin Endocrinol Metab* 2000, **85**:2775-2778.
 83. Latifi-Pupovci H, Gacaferri-Lumezi B, Lokaj-Berisha V: **There is no elevation of immunoglobulin e levels in Albanian patients with autoimmune thyroid diseases.** *J Thyroid Res* 2014, **2014**:283709.
 84. Bansal A, Roberts T, Hay EM, Kay R, Pumphrey RS, Wilson PB: **Soluble CD23 levels are elevated in the serum of patients with primary Sjogren's syndrome and systemic lupus erythematosus.** *Clin Exp Immunol* 1992, **89**:452-455.
 85. Akiyama M, Sasaki T, Kaneko Y, Yasuoka H, Suzuki K, Yamaoka K, Takeuchi T: **Serum soluble interleukin-2 receptor is a useful biomarker for disease activity but not for differential diagnosis in IgG4-related disease and primary Sjogren's syndrome adults from a defined population.** *Clin Exp Rheumatol* 2018, **36**(Suppl. 112):157-164.
 86. Hunder GG, Gleich GJ: **Immunoglobulin E (IgE) levels in serum and synovial fluid in rheumatoid arthritis.** *Arthritis Rheum* 1974, **17**:955-963.
 87. Millauer N, Zuercher AW, Miescher SM, Gerber HA, Seitz M, Stadler BM: **High IgE in rheumatoid arthritis (RA) patients is complexed with anti-IgE autoantibodies.** *Clin Exp Immunol* 1999, **115**:183-188.
 88. Rivelles F, Mauro D, Nerviani A, Pagani S, Fossati-Jimack L, Messemaker T, Kurreeman FAS, Toes REM, Ramming A, Rauber S *et al.*: **Mast cells in early rheumatoid arthritis associate with disease severity and support B cell autoantibody production.** *Ann Rheum Dis* 2018, **77**:1773-1781.
- This recent study demonstrates the involvement of mast cells in the early development of rheumatoid arthritis both in humans and mice via their B cell supporting abilities. Investigating whether this phenomenon is IgE-dependent would be of primary interest.
89. Charles N, Hardwick D, Daugas E, Illei GG, Rivera J: **Basophils and the T helper 2 environment can promote the development of lupus nephritis.** *Nat Med* 2010, **16**:701-707.
 90. Futata E, Azor M, Dos Santos J, Maruta C, Sotto M, Guedes F, Rivitti E, Duarte A, Sato M: **Impaired IFN-α secretion by plasmacytoid dendritic cells induced by TLR9 activation in chronic idiopathic urticaria.** *Br J Dermatol* 2011, **164**:1271-1279.
 91. Ah Kioon MD, Tripodo C, Fernandez D, Kirou KA, Spiera RF, Crow MK, Gordon JK, Barrat FJ: **Plasmacytoid dendritic cells promote systemic sclerosis with a key role for TLR8.** *Sci Transl Med* 2018, **10**.
 92. Garnier A, Laffont S, Garnier L, Kaba E, Deutsch U, Engelhardt B, Guery JC: **CD49d/CD29-integrin controls the accumulation of plasmacytoid dendritic cells into the CNS during neuroinflammation.** *Eur J Immunol* 2019, **49**:2030-2043.
 93. Ruiz-Riol M, Barnils Mdel P, Colobran Oriol R, Pla AS, Borrás Serres FE, Lucas-Martin A, Martínez Cáceres EM, Pujol-Borrell R: **Analysis of the cumulative changes in Graves' disease thyroid glands points to IFN signature, plasmacytoid DCs and alternatively activated macrophages as chronicity determining factors.** *J Autoimmun* 2011, **36**:189-200.