

## REVIEW ARTICLE

# Regulatory T cells and immunoglobulin E: A new therapeutic link for autoimmunity?

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## Abstract

Autoimmune diseases have a prevalence of approximately 7 to 9% and are classified as either organ-specific diseases, including type I diabetes, multiple sclerosis, inflammatory bowel disease and myasthenia gravis, or systemic diseases, including systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome. While many advancements have been made in understanding of the mechanisms of autoimmune disease, including the nature of self-tolerance and its breakdown, there remain unmet needs in terms of effective and highly targeted treatments. T regulatory cells (Tregs) are key mediators of peripheral tolerance and are implicated in many autoimmune diseases, either as a result of reduced numbers or altered function. Tregs may be broadly divided into those generated in the thymus (tTregs) and those generated in the periphery (pTregs). Tregs target many different immune cell subsets and tissues to suppress excessive inflammation and to support tissue repair and homeostasis: there is a fine balance between Treg cell stability and the plasticity that is required to adjust Tregs' regulatory purposes to particular immune responses. The central role of immunoglobulin E (IgE) in allergic disease is well recognized, and it is becoming increasingly apparent that this immunoglobulin also has a wider role encompassing other diseases including autoimmune disease. Anti-IgE treatment restores the capacity of plasmacytoid dendritic cells (pDCs) impaired by IgE- high-affinity IgE receptor (FcεR1) cross-linking to induce Tregs in vitro in atopic patients. The finding that anti-IgE therapy restores Treg cell homeostasis, and that this mechanism is associated with clinical improvement in asthma and chronic spontaneous urticaria suggests that anti-IgE therapy may also have a potential role in the treatment of autoimmune diseases in which Tregs are involved.

## KEYWORDS

anti-IgE, autoimmune disease, immunoglobulin E, omalizumab, regulatory T cells

## 1 | INTRODUCTION

Autoimmune diseases have a prevalence of approximately 7 to 9%, with a significant, higher predominance in women;<sup>1,2</sup> recent work has shown that the relationship between genetic predisposition and factors related to biological sex are important in determining this difference between the sexes.<sup>1</sup> Autoimmune diseases may be classified as either organ-specific, such as type I diabetes (T1D), multiple sclerosis (MS), inflammatory bowel disease (IBD) and myasthenia gravis (MG), bullous pemphigoid (BP), Grave's disease, Hashimoto disease, autoimmune uveitis or systemic, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), mixed connective tissue disease, Gougerot-Sjogren syndrome and systemic sclerosis.<sup>2</sup> While there is undoubtedly a genetic basis for many autoimmune diseases,<sup>2</sup> the environmental exposome, including diet and changes to the gut microbiome, are believed to account for the increasing incidence of autoimmune disease in the Western world, as has also been shown for many other diseases such as cancer, metabolic syndrome, depression, neurodegenerative, cardiovascular and allergic diseases.<sup>3-7</sup>

Self-tolerance, which is impaired in autoimmune disease, refers to the lack of response of the organism to self-antigens. Better understanding of the molecular mechanisms involved in immunological self-tolerance provides knowledge of how weak immune responses, for example those against tumour antigens in malignancy or microbial antigens in chronic infections, can be boosted. It is also relevant in understanding how to dampen strong immune responses in autoimmune disease, allergic diseases and graft rejection, as well as how feto-maternal tolerance in pregnancy can be increased.<sup>8-12</sup> Numerous triggers and pathways are involved in the immunopathogenesis of autoimmune disease.<sup>2</sup> There are, however, two key stages: the first stage is central tolerance, which takes place within the thymus, while the second stage is mediated outside the thymus, in the periphery.<sup>13</sup> In the thymus, two mechanisms are involved in the development of self-tolerance and immune homeostasis, known as recessive and dominant.<sup>14</sup> In the recessive mechanism, the outcome for self-reactive lymphocytes exposed to antigens is intrinsic to the cell. The dominant or cell-extrinsic mechanism involves T regulatory cells (Tregs) specialized for immune suppression that regulate the activation and expansion of overreactive lymphocytes, specifically effector T cells.<sup>8</sup>

Tregs and regulatory B (Breg) cells are generated to suppress undesired and excessive immune responses, but under certain circumstances, their alterations can be also involved in the initiation of harmful immune responses, such as allergy or autoimmunity.<sup>9,11</sup> B-cell involvement in immunity involves the production of IgE, antigen presentation and cytokine production.<sup>11</sup> Breg cells are B cells with an anti-inflammatory function; several human Breg subtypes have been identified to date (B10 cell, transitional B cells, Br1 cells, plasmablasts, GrB<sup>+</sup>B cells and CD9<sup>+</sup> and CD5<sup>+</sup>CD1d<sup>+</sup> cells).<sup>11</sup> B-cell tolerance is determined in the bone marrow and in the periphery.<sup>2</sup>

Tregs play a critical role in preventing autoimmune disease through the regulation of immune responses, thereby maintaining

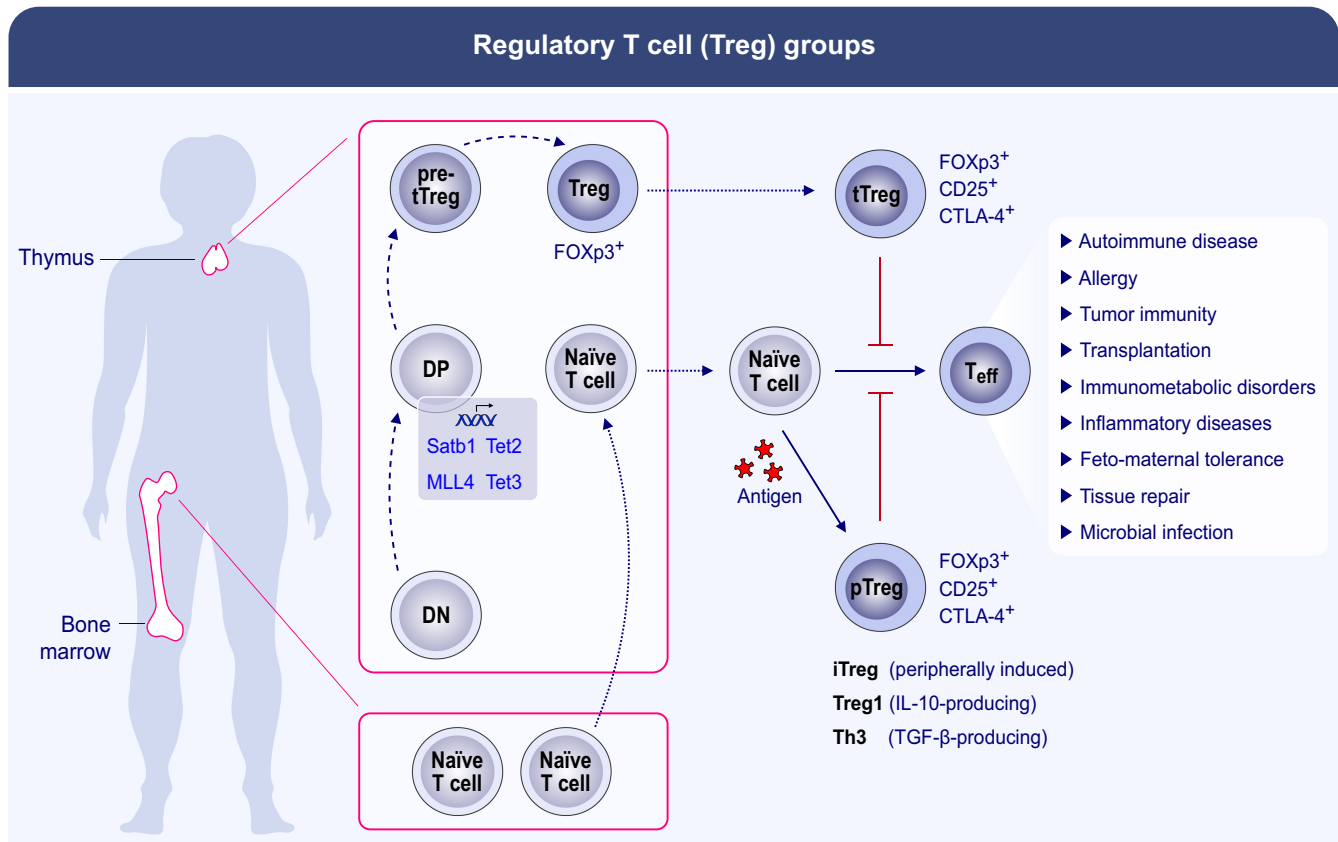
immune homeostasis and providing immune tolerance to both self- and non-self-innocuous antigens. There are numerous surface receptors that are specific for defined Treg cell subsets, indicating the heterogeneity of this cell population.<sup>15</sup>

Immunoglobulin E (IgE) is involved in many systemic and tissue-specific autoimmune diseases.<sup>16-19</sup> IgE is synthesized and secreted by B cells that have undergone heavy-chain class switching from IgM to IgE.<sup>20</sup> IgE acts by binding to either the high-affinity IgE receptor (FcεRI) or CD23 (also known as FcεRII). Anti-IgE therapy with omalizumab, a recombinant human monoclonal antibody against IgE, has been shown to restore Treg cell homeostasis in children with severe asthma, which is associated with clinical improvement and asthma control,<sup>21</sup> thus suggesting a possible role for anti-IgE therapy in the management of those autoimmune diseases that might be mediated by Tregs. Supporting this notion, previous studies have suggested potential clinically relevant Treg and IgE involvement within the context of the murine mutant, scurfy, as well as its human equivalent, immune dysregulation, polyendocrinopathy, enteropathy and X-linked syndrome (IPEX).<sup>9,22</sup> In addition, IgE might contribute to the mechanisms involved in breaking tolerance in autoimmunity by enhancing antigen uptake in antigen-presenting cells (APCs) via mechanisms depending on facilitated antigen presentation (FAP). This might in turn favour the generation of pathological autoantigen-specific T cells rather than suppressive Tregs.<sup>16</sup> Recent findings also demonstrated that IgE cross-linking on plasmacytoid dendritic cells (pDCs) impairs their capacity to generate Tregs in vitro, which can be restored by the anti-IgE monoclonal antibody, omalizumab.<sup>23</sup>

Understanding the mechanisms of autoimmune disease, the nature of self-tolerance and the breakdown of self-tolerance have advanced; however, effective, targeted treatments for many autoimmune diseases are still lacking.<sup>13</sup> Here, we review the evidence for the role of Tregs and IgE in the pathophysiology of autoimmune disease and discuss preliminary evidence for the therapeutic potential of targeting IgE to restore T-reg homeostasis.

## 2 | IMMUNOBIOLOGY OF REGULATORY T CELLS

Treg cells are a heterogeneous group of suppressive T-cell subsets that are essential for a number of functions including: prevention of disproportionate immune response to pathogens; induction of immune tolerance to environmental proteins; and prevention and management of the development of both autoimmune and allergic diseases.<sup>9,24-28</sup> Tregs are present at birth and the proportion at birth is a large determinant of the amount present throughout the first year of life.<sup>29</sup> Treg cells are broadly divided into two groups based on their origin (Figure 1),<sup>30</sup> either in the thymus (tTreg, also previously known as natural Tregs)<sup>31</sup> or in the periphery (pTregs).<sup>9,15</sup> Tregs may be further subdivided into naive-like central Tregs (also known as resting Tregs) and activated effector Tregs (also known as activated Tregs or effector memory Tregs).<sup>32</sup>



**FIGURE 1** Regulatory T cells largely divide into two groups based on their origin. Regulatory T cells can originate from either the thymus, known as tTregs, which are a functionally distinct population, or generated in the periphery, pTregs, which can be further differentiated into peripherally induced Tregs (iTregs), IL-10-producing Tregs and TGF- $\beta$ -producing Th3 cells. FOXP3<sup>+</sup> Tregs constitutively express CD25 and CTLA-4 on the cell surface. Thymic Treg development is regulated by transcriptional and epigenetic factors. Transcription factors bind promoter and conserved non-coding sequences at the FOXP3 locus, such as Satb1- and MLL4-dependent enhancer activation and Tet2- and Tet3-dependent DNA demethylation promoter activation Tregs function to control inflammation and pathological immune responses by regulating effector T cells

Three types of mature pTregs are generated outside the thymus after antigenic stimulation of naïve T cells: peripherally induced Forkhead Box 3 (FOXP3)+T cells (iTregs)<sup>33</sup>; interleukin (IL)-10-producing Treg cells (Tregs1)<sup>34</sup>; and transforming growth factor (TGF)- $\beta$ -producing T helper (Th) 3 cells.<sup>35,36</sup>

In peripheral tissues, for example the intestine, naïve CD4<sup>+</sup> T cells develop into pTreg cells on recognition of an antigen that is regarded as non-self. Thus, intestinal pTreg cells are thought to be mainly responsible for tolerance to non-self-antigens, such as environmental antigens, whereas tTreg cells would be preferentially involved in controlling autoreactive responses.<sup>37</sup> In the airways, a new population of CD103+FOXP3+ Tregs that maintain immune respiratory tract homeostasis via the selective suppression of Th2 responses and allergic airway inflammation has been identified.<sup>38</sup>

Other Treg populations include CD8<sup>+</sup> Tregs<sup>39</sup> and double negative CD4<sup>-</sup>CD8<sup>+</sup>TCR $\alpha\beta$ <sup>+</sup>,<sup>40</sup> both of which mediate tolerance in several experimental autoimmune diseases; and T-cell receptor (TCR) $\gamma\delta$  Tregs, which are involved in the inhibition of the immune response to tumours.<sup>41</sup> While several cell types are involved in suppressing innate and adaptive immune responses, Tregs expressing CD4, IL-2

receptor alpha chain (CD25), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the transcription factor FOXP3 are believed to be the key mediators of tolerance and autoimmunity (Figure 1). High expression of CD25 and FOXP3 are required for the development, function and stability of Tregs.<sup>15</sup>

The finding that FOXP3 is the master regulator of Treg cell development and function gave insight into the biology of Treg cells.<sup>9,15</sup> Specifically, scurfy mice, an X-linked recessive murine mutant (lethal in hemizygous mice), lack Treg cells and show dysregulated Th1 and Th2 responses, accompanied by severe multiorgan inflammation and generalized autoimmune disorders, as well as allergic airway inflammation with eosinophilia and hyper IgE. Also, mutations of the gene FOXP3 in humans lead to IPEX syndrome, the human equivalent of scurfy mice.<sup>42</sup> Patients with IPEX syndrome present with enteropathy, autoimmunity, dermatitis, eosinophilia and elevated serum IgE.<sup>43</sup> Women who are carriers of FOXP3 mutations have either reduced numbers of normal Tregs or are mosaic for normal Tregs and functionally deficient Tregs as a result of random X inactivation.<sup>8</sup>

Recently, knowledge of the molecular mechanisms involved in the control and development of Tregs, in particular at the level of

transcriptional and epigenetic regulation, has significantly improved. In the thymus, tTregs differentiate into competent cells, creating a T-cell lineage from the thymus to the periphery that is functionally stable (Figure 1).<sup>44</sup> During their development, tTregs go through several stages with specific transcriptional and epigenetic changes, as well as specific cytokine requirements. Treg signature genes are induced by the step-by-step creation of a suitable epigenetic landscape. Specific super-enhancers and DNA hypomethylation regions are associated with Treg signature genes, such as *FOXP3*, *CD25* and *CTLA-4*.<sup>45,46</sup> Two independently activated gene enhancers, *Foxp3*-CNS0 and *Foxp3*-

CNS3 cooperatively induce and maintain *FOXP3* expression.<sup>47</sup> The enhancer is primed by the binding of the genome organizer, special AT-rich sequence-binding protein-1 (Satb1) (dependent on mixed-lineage leukaemia 4 [MLL4]), and then activated by the presence of Satb1 and the binding of transcription factors. This leads to the activation of the gene promoter via histone acetylation<sup>48</sup> and DNA demethylation, which is dependent on Tet methylcytosine dioxygenase (Tet2) and Tet3 enzymes,<sup>45,49</sup> and induction of *FOXP3* and other genes. These DNA sequences and epigenetic processes are also likely involved in the maintenance of Treg stability.<sup>44</sup>

Demethylation of the conserved non-coding sequence 2 (CNS2), also known as the Treg cell-specific demethylated region (TSDR), is required for transcription of the *Foxp3* gene. CNS2 maintains T-cell identity, that is *Foxp3* expression that is essential for suppression of inflammation and prevents Treg differentiation into effector cells.<sup>50</sup> Methylation results in reduced transcription and loss of function of Tregs. Recent research has shown the role of the expression of the transcriptional regulator, Blimp 1 in regulation of the *Foxp3* gene.<sup>51,52</sup> In a model of inflammation (experimental autoimmune encephalitis: EAE), Blimp1 prevents methylation and reduced expression of *Foxp3*.<sup>51</sup> Furthermore, depletion of Blimp1 in *Foxp3*+ Tregs resulted in an exacerbated EAE with impaired recovery. Blimp1-deficient Tregs were converted to Th17-like effector cells, and contributed to abnormal T helper cell expansion and elevated production of antibodies, in particularly IgE.<sup>53</sup>

Tregs target many different immune cell subsets and tissues to suppress excessive inflammation and to support tissue repair and homeostasis (Figure 2).<sup>2,9,27</sup> Treg cells exert their suppressive function by mechanisms that depend, not only on soluble factors, but also on cell-to-cell contact, as exemplified by in vivo imaging showing clusters of Tregs together with activated autoreactive T cells in secondary lymphoid tissues.<sup>54</sup> Tregs also suppress immune responses through various mechanisms, including the secretion of inhibitory cytokines such as IL-10, TGF- $\beta$  and IL-35,<sup>15</sup> cytotoxicity (Granzyme B/A), and metabolic disruption (CD25, CD39, CD73), as well as by modulating the activation state and function of antigen-presenting cells (CTLA-4, PD1) (Figure 2).<sup>9,55</sup> Dendritic cells (DCs) play a key role in the generation of Treg cells. DCs may be broadly divided into two main groups: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). The original belief was that immature, or partially mature, DCs generate Tregs cells with suppressive capacity and that mature DCs polarize various subsets of effector T cells depending on the specific context<sup>56</sup>; it is now known, however, that functional Tregs may also be

induced by mature DCs in particular circumstances.<sup>57,58</sup> The ability of DCs to generate Tregs might be conditioned by *FOXP3*+ Tregs, pathogen-derived molecules and exogenous signals such as histamine, adenosine, flavonoids, vitamin D3 metabolites, retinoic acid, mannan or cannabinoids (Figure 2).<sup>59–66</sup> In addition, specific DCs subsets such as pDCs might well display intrinsic tolerogenic capacity and promote the generation of Treg cells under both Th1 and Th2 polarizing conditions.<sup>58</sup> This intrinsic tolerogenic capacity can be altered by proinflammatory signals, exogenous cues and environmental exposome.<sup>23,60,67,68</sup> Oral tolerance to common allergens (pollens and nut) and antigens is established through the generation of allergen-specific *FOXP3*+ Treg cells in human tonsils, which could be exploited to develop direct immune interventions in the treatment of allergic diseases and other immune tolerance-related disorders.<sup>58</sup> Alterations in functional pDCs and Treg cell numbers are correlated with asthma exacerbations and with the severity of type 2 inflammation.<sup>69–71</sup>

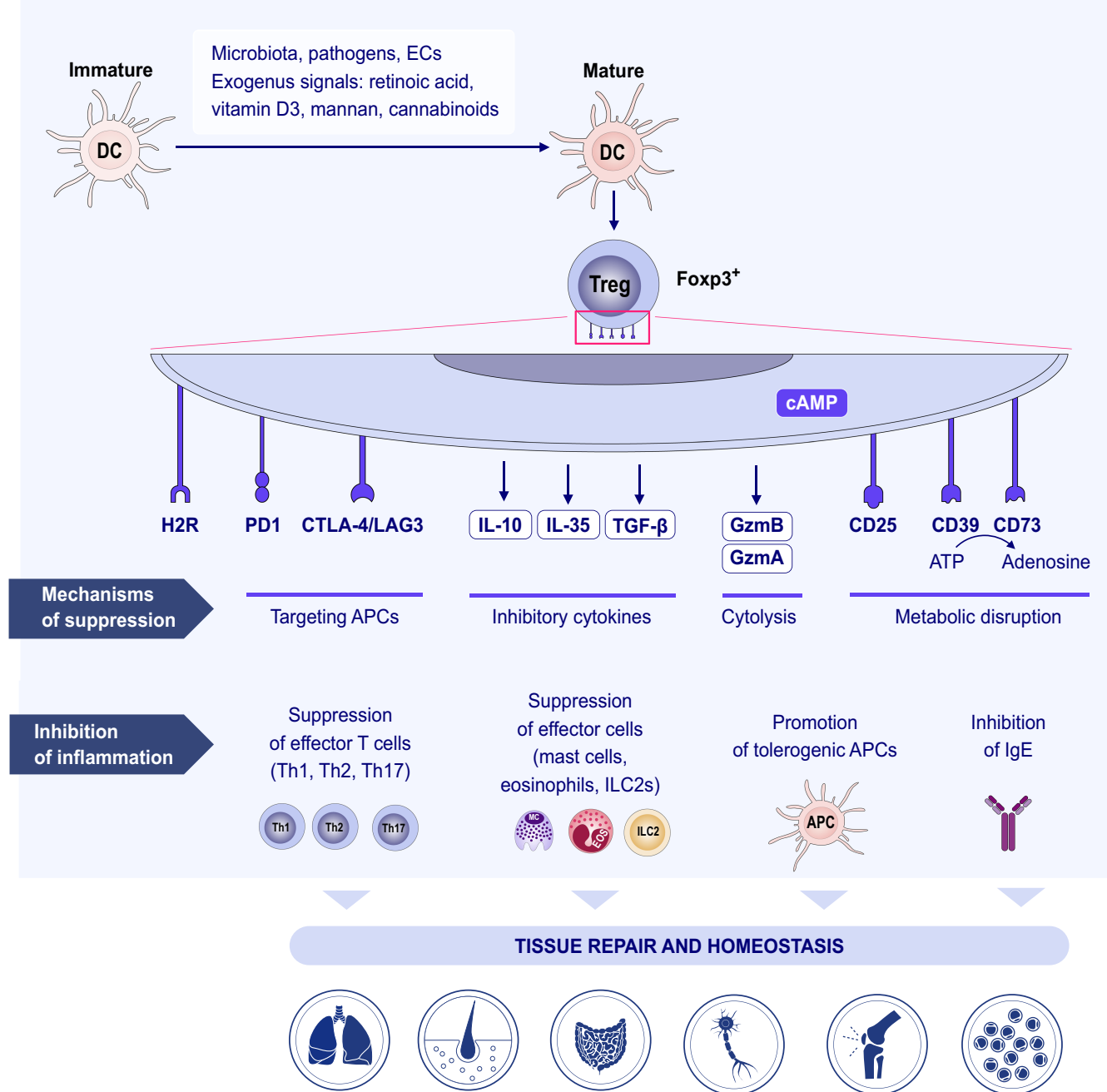
The development of most autoimmune diseases depends on the cytokines IL-2 and interferon-gamma (IFN- $\gamma$ ) produced by Th1 cells, whereas the development of allergic diseases requires IL-4 and IL-5, both of which are produced by Th2 cells. The reciprocal down-regulation of Th1 cells by Th2 cytokines and of Th2 cells by Th1 cytokines raises the possibility that these cytokines are involved in infection-mediated protection against allergy or autoimmunity.<sup>72</sup> Furthermore, Treg and T helper (Th)17 cells are linked from a developmental perspective, that is the same naive T-cell precursor pool that generates Treg cells also generates IL-17a-producing CD4+Th17 cells. Inflammation in IBD may be caused by the loss of homeostasis between Tregs and proinflammatory Th17 cells. IBD is associated with a reduced ratio of Treg to Th17 cells in peripheral blood and is characterized by a proinflammatory cytokine microenvironment, which supports the continued generation of Th17 cells.<sup>73</sup>

The so-called 'hygiene hypothesis' suggests that increased hygiene and consequent reduction in infectious diseases is responsible for the increased incidence of both allergic and autoimmune diseases.<sup>72</sup> The hypothesis is supported by a study comparing children from the isolated Amish and Hutterite communities, who, while being genetically similar, show significant differences in asthma prevalence and immune profiles, which are believed to result from differences in innate immunity resulting from differing microbial environment, suggesting that increased susceptibility to asthma may result from weak innate immune stimulation.<sup>74</sup> The lack of microbial exposure leads to reduced numbers of suppressive Tregs, resulting in excessive Th1 and Th2 responses with a consequent increase in the prevalence of both allergic diseases and autoimmune disorders.<sup>72,75</sup>

### 3 | THE ROLE OF REGULATORY T CELLS IN AUTOIMMUNE DISEASE

The key role of Tregs in autoimmunity was first illustrated by the work of Sakaguchi and colleagues<sup>76</sup> who showed that removal of the mouse thymus at a specific time (2–4 days after birth) resulted in autoimmune damage of organs including the thyroid, stomach, ovaries

## Treg generation by dendritic cells and mechanism of suppression in autoimmunity



**FIGURE 2** Treg generation by dendritic cells and mechanisms of suppression in autoimmunity. Treg cells are generated by two groups of DCs—myeloid DCs and plasmacytoid DCs (pDCs) which promote the generation of functional Treg cells, conditioned by different stimuli such as Treg cell-derived molecules, exogenous signals or specific molecules. The main mechanisms of suppression by Tregs are inhibitory cytokines, cytolysis, metabolic disruption and targeting DCs using a plethora of soluble and surface-bound molecules. Tregs limit inflammation by acting on many different cell types. Dysfunction of Tregs can result in immunological diseases such as autoimmune disease, immunopathology and allergy. APC, antigen-presenting cell; ATP, adenosine triphosphate; Bas, basophil; cAMP, cyclic adenosine monophosphate; CD25, alpha chain of IL-2 receptor; CTLA-4, cytotoxic T lymphocyte antigen-4; DC, dendritic cell; Eos, eosinophil; HR2, histamine receptor 2; IgE, immunoglobulin E; IL, interleukin.; MC, mast cell; PD-1, programmed cell death protein-1; T eff, effector T cell; Th 1, T helper type 1; Th 17, T helper type 17; Th 2, T helper type 2; Treg, regulatory T cell

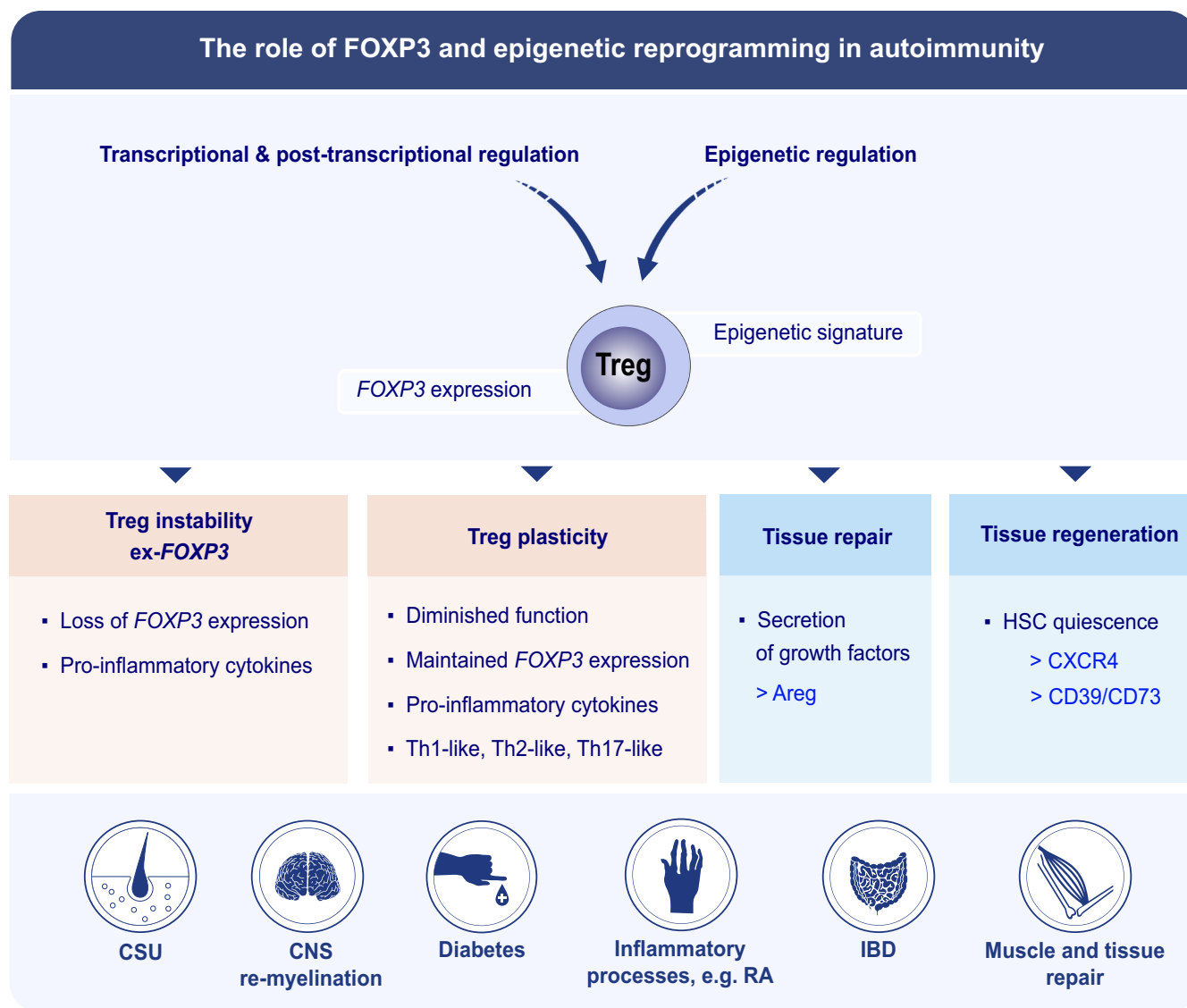
and testes; circulating tissue-specific autoantibodies were also noted. Furthermore, removal of the thymus and a number of rounds of sublethal X-ray of adult rats resulted in autoimmune thyroiditis

and TD1.<sup>76</sup> Conversely, injection of normal T cells, specifically CD4<sup>+</sup> or CD4<sup>+</sup>CD8<sup>-</sup> thymus cells from untreated syngeneic animals, prevented autoimmunity development.<sup>76,77</sup>

Together with transcriptional and post-translational regulation that contribute to stabilize *FOXP3* expression, the generation of a specific epigenetic signature that is acquired during development and finalized in the periphery is required for the correct functioning of Treg cells (Figure 3). Alteration of *FOXP3* expression levels or epigenetic changes are likely involved in Treg instability and aberrant plasticity observed in autoimmune conditions.<sup>15</sup> Echoing the immune system as a whole, there is a balance between Treg cell stability and the need for physiological

plasticity that is required to adjust Tregs' regulatory purposes to particular immune responses.<sup>13,78</sup>

In the healthy state, *FOXP3* expression is regulated and maintained by transcriptional regulation, epigenetic regulation, post-translational modifications, microRNAs and potentially other factors. The global epigenetic signature is regulated and maintained by histone acetyltransferases (HATs) and histone deacetylases (HDACs), DNA methylation, and other factors. In those who are genetically predisposed, environmental factors induce inflammation and a



**FIGURE 3** Role of FOXP3 and epigenetic reprogramming in autoimmunity: Treg stability and plasticity, and in tissue repair and regeneration. Treg stability and plasticity are modulated by FoxP3<sup>+</sup> expression and global epigenetic factors, such as histone modifications, DNA methylation, HATs and HDACs. Loss of FoxP3<sup>+</sup> expression can occur in susceptible individuals in response to environmental factors inducing inflammation (Treg instability, ex-FOXP3) which can promote autoimmunity. Treg plasticity is observed when FoxP3 expression is maintained yet function is diminished, secrete proinflammatory cytokines and Th1-, Th2- and Th17-like properties are acquired. Tregs can promote tissue repair and regeneration, secretion of growth factors, such as amphiregulin (Areg), can directly contribute to tissue repair. In the bone marrow, Tregs maintain hematopoietic stem cell (HSC) quiescence which is regulated by CXCR4 and CD39/CD73. Tregs play a role in the pathogenesis of numerous autoimmune diseases such as tissue-specific diseases affecting pancreas, skin, large intestine (type 1 diabetes, CSU, MS, IBD) and systemic diseases which have wide ranging effects (SLE, RA). Areg, amphiregulin; CSU, Chronic spontaneous urticaria; CXCR4, C-X-C Motif Chemokine Receptor 4; HATs, histone acetylases; HDACs, histone deacetylases; HSC, hematopoietic stem cells; IBD, inflammatory bowel disease

proportion of Tregs can lose *FOXP3* expression (known as ex-*FOXP3*) and become unstable, known as Treg cell instability (Figure 3). The resulting development of proinflammatory properties can promote autoimmunity and/or facilitate more effective tumour immunity. Mouse models of diabetes (non-obese diabetic: NOD) and multiple sclerosis (experimental autoimmune encephalomyelitis: EAE) are characterized by ex-*FOXP3* cells.<sup>79,80</sup> In a second scenario, *FOXP3* expression may be maintained while the global epigenetic signature is changed. This, along with the ability of Tregs to differentiate into other subsets, is known as Treg cell plasticity (Figure 3); these cells secrete proinflammatory cytokines and show reduced function. Tregs also show tissue-specific heterogeneity, for example visceral adipose tissue Treg, colon Tregs and small intestine Tregs may be found within the intestinal environment.<sup>81</sup> Plasticity in proinflammatory Tregs results in the development of Th1-like, Th2-like or Th17-like properties by the Tregs. While the mechanistic connection between Treg cell instability and Treg cell plasticity is not known, plastic Treg cells can revert to 'normal' Treg cells after resolution of inflammation. It remains to be determined whether this is also the case for Treg cell instability.<sup>15</sup> Tregs can also promote tissue repair and have a regenerative effect on the central nervous system and gut, suggesting potential additional functions of these cells beyond immune suppression (Figure 3).<sup>27</sup>

A plethora of experimental evidence shows that Tregs are implicated in many tissue-specific and systemic autoimmune diseases, either as a result of reduced numbers or altered function (Figure 3). In T1D, while there is an increase in the overall proportion of *FOXP3*-expressing CD4<sup>+</sup> T cells in new-onset disease compared with controls, this relates specifically to an increase in the CD45RA<sup>+</sup>CD25<sup>int</sup>*FOXP3*<sup>low</sup> subset that secretes significantly more IL-17 and is not suppressive compared with other *FOXP3*<sup>+</sup> subsets.<sup>82</sup> This finding, together with genomic association, transcriptional and functional studies, has provided the evidence that changes in *FOXP3*-expressing Tregs are immunopathological in T1D.<sup>83</sup> Treg deficiency is responsible for the development of autoimmune skin diseases such as vitiligo, alopecia areata (AA),<sup>84</sup> pemphigoid, pemphigus, psoriasis and systemic sclerosis.<sup>85</sup> Patients with AA have lower numbers of Tregs than controls and patients with atopic dermatitis (AD).<sup>84</sup> In psoriasis, Treg function in skin is poor.<sup>86</sup> Polyclonal Treg infusion therapy is being investigated in this condition. In neurological disorders such as MS and MG, Tregs display decreased *FOXP3* expression and compromised suppressive function.<sup>87,88</sup> Dysregulation of suppressive and migratory markers on Tregs have been linked to the pathogenesis of both MS and MG. Genetic mutations have been found in the Treg suppressive markers CTLA-4 and CD25, as well as decreased expression of *FOXP3* and IL-10. Moreover, raised levels of proinflammatory cytokines such as IL-6, IL-17 and IFN- $\gamma$  secreted by T effectors have been noted in MS and MG patients.<sup>89</sup> Tregs are also implicated in rheumatological disorders, for example the proportion of activated Tregs is reduced early in SLE<sup>90</sup> and defects in Treg function have been observed in RA.<sup>91</sup> IL-10 secreting Tregs are an essential part of tolerance in the gastrointestinal tract. In IBD, decreased Treg numbers are found with increased IL-17-producing

cells.<sup>73,92</sup> iTreg cell development may be driven by the need to maintain a non-inflammatory environment in the gut, to suppress immune responses to environmental and food allergens, and to decrease chronic inflammation, while tTreg cells prevent autoimmunity and raise the activation threshold for all immune responses.<sup>93</sup>

Treg cell-based therapies are being investigated in many immune and inflammatory diseases at present.<sup>94</sup> In vitro expanded Treg therapy is being investigated in several autoimmune diseases including: T1D and transplantation, including graft-versus-host disease and live donor kidney transplant.<sup>95</sup> The TRIBUTE trial is planned to investigate the use of autologous Tregs expanded ex vivo in the treatment of Crohn's disease [NCT03185000]. Two Treg-based treatment strategies are being investigated currently in T1D: ex vivo generation of optimized Tregs for re-introduction in patients with T1D and direct in situ stimulation and restoration of endogenous Treg function.<sup>96</sup> Low-dose IL-2 therapy has also shown potential in autoimmune disease including SLE, T1D and graft-versus-host disease.<sup>97–99</sup>

## 4 | THE ROLE OF IGE IN AUTOIMMUNITY

Since its discovery in 1969, our knowledge on the structure, function and pathophysiological role of IgE in the context of different diseases has significantly improved (Box 1).

In allergic conditions such as asthma, allergic rhinitis and food allergy, antigen exposure initially produces allergen-specific IgE during sensitization.<sup>108</sup> DCs present allergens to naive T cells, which differentiate to allergen-specific Th2 cells that are involved in the activation and B-cell isotype switching to produce high levels of allergen-specific IgE antibodies. Allergen-specific IgE released into the circulation binds to Fc $\epsilon$ RI on the surface of effector cells, such as mast cells and basophils, but also DC, eosinophils, Langerhans cells, macrophages, monocytes thus leading to sensitization (Figure 4).

IgE also binds to a second receptor, CD23 (but with lower affinity than Fc $\epsilon$ RI), expressed on many different immune cells, including B cells (regulating IgE synthesis), and on activated macrophages, eosinophils, dendritic cells, Langerhans cells and platelets (Figure 4).<sup>109</sup> After sensitization on the next encounter with the allergen, IgE mediates allergen-induced cross-linking of Fc $\epsilon$ RI on inflammatory cells and tissues, with a resultant degranulation and release of mediators that trigger allergic symptoms.

Self-reactive proteins with antigen-specific IgE that trigger autoimmunity against self can be categorized into three groups: autoallergens recognized by cross-reactive IgE to exogenous allergens, where molecular mimicry is likely to occur in proteins with similar sequence homology on the primary and tertiary protein structure; autoantigens without cross-reactivity to exogenous allergens; and autoantigens from autoimmune diseases whereby autoreactive IgE antibodies are generated that illicit an autoimmune self-destructive response.<sup>110–113</sup>

While the importance of IgE in allergic disease is well recognized, it is becoming increasingly apparent that this immunoglobulin has a wider role encompassing non-allergic diseases, such

**BOX 1 Building the evidence to understand the link between IgE and T regulatory cells**

Evidence	Year	References
Discovery of IgE	1969	Ishizaka et al <sup>100</sup>
Discovery of the role of IgE in autoimmune disease	1978	Permin and Wiik <sup>101</sup>
Human basophil degranulation test for autoimmune connective tissue diseases	1982	Camussi et al <sup>102</sup>
Anti-IgE therapy discovery	1991	Presta et al <sup>103</sup>
Role of Tregs in autoimmune disease	1995	Sakaguchi et al <sup>31</sup>
Identification of FOXP3 as the key transcription factor for Tregs	2001	Brunkow et al <sup>104</sup> Bennett et al <sup>105</sup> Wildin et al <sup>106</sup>
Interaction/relationship Tregs and IgE (FOXP3 mutations result in hyper IgE)	2005	Lin et al <sup>107</sup>
Anti-IgE therapy restores Treg homeostasis in vitro	2021	López-Abente et al <sup>23</sup>

as chronic spontaneous urticaria (CSU),<sup>114</sup> aspirin/nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (AERD/NERD)<sup>115</sup> and nasal polyposis.<sup>116</sup>

Although the disease mechanism of IgE in autoimmunity is still not well understood for certain diseases, some evidence suggests molecular mimicry that results in cross-reactivity of proteins is involved. For example, primary sensitization was demonstrated because of cross-reactivity of IgE to fungal (*Malassezia sympodialis*) and human manganese-containing superoxide dismutase (MnSOD). Furthermore, sensitization to *M. sympodialis* in up to 50% of AD patients was observed. Ten thioredoxin allergens of *M. sympodialis* have been described so far, including Mala s 11 and Mala s 13, for which cross-reactivity to human thioredoxin has been demonstrated at the IgE level.<sup>117</sup>

CSU is a mast cell-driven skin disease characterized by type I or type II hypersensitivity reactions. Type I autoimmunity involves cross-linking of antigen with IgE autoantibodies leading to activation of mast cells and basophils. With a type II autoimmune reaction, IgG autoantibodies bind to IgE or the high-affinity IgE receptor, FcεR1, activating mast cell and basophil degranulation.<sup>114</sup> Patients with CSU have positive serum levels for IgG-anti-IgE, IgG-anti-FcεR1 or both.<sup>114,118</sup>

Autoreactive IgE plays a role in many autoimmune diseases (Figure 5), including SLE,<sup>119</sup> BP,<sup>120</sup> mixed connective tissue disease,<sup>121</sup> Grave's disease,<sup>122</sup> Hashimoto disease,<sup>122</sup> Gougerot-Sjogren syndrome,<sup>123</sup> systemic sclerosis and<sup>124</sup> autoimmune uveitis,<sup>125</sup> and has also been implicated in mothers with foetal loss.<sup>126</sup> Increased IgE levels have been reported in IBD, particularly Crohn's disease, Crohn's disease with orofacial granulomatosis and ulcerative colitis.<sup>17-19</sup> Furthermore, food-specific IgGs against egg, milk, wheat, corn, rice, tomato, codfish and soybean are increased in patients with Crohn's disease.<sup>127</sup>

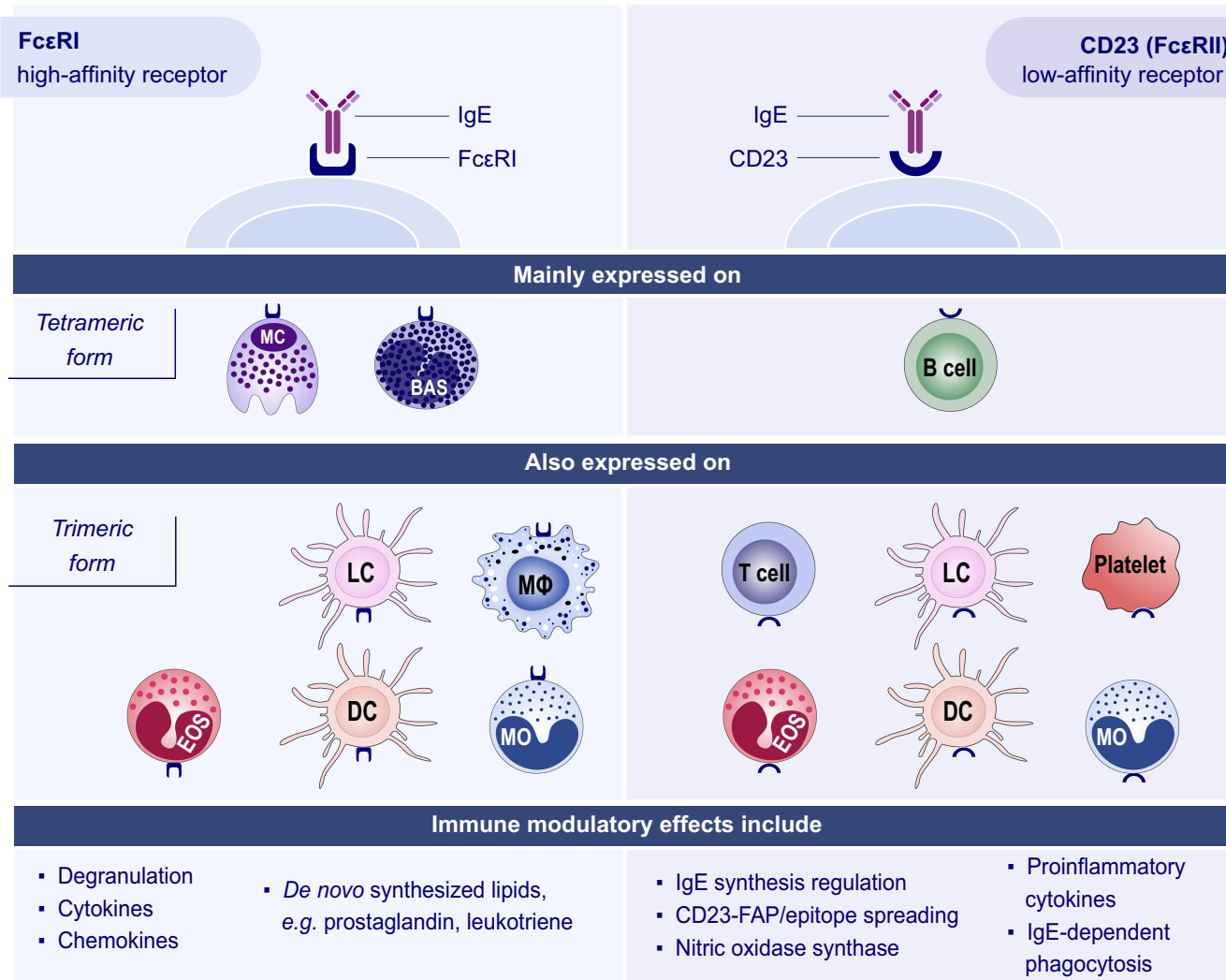
Reports indicate that the concentration of IgE against double-stranded DNA correlates with disease severity of SLE indicating a role in disease pathology.<sup>119,128,129</sup> Furthermore, SLE patients have high IgE levels directed against autoantigens, and IgE strongly decreased

circulating basophils, suggesting auto-IgE-dependent basophil activation in the blood.<sup>112</sup> Additionally, the pathogenic mechanisms of IgE-mediated inflammation in SLE were reported to trigger interferon responses that led to self-destructive autoimmune responses.<sup>129</sup> IgE antibodies specific for dsDNA in SLE patients were found to activate pDCs linked to viral defence, which led to the secretion of IFN-α and the concentration of dsDNA-specific IgE in patients' serum correlated with disease severity.<sup>129</sup> Research demonstrates counter regulation between FcεRI and TLR9 molecules expressed on pDC, such that binding of either weakens the expression and function of the other.<sup>130</sup> Furthermore, activation of the receptors TLR-7 and TLR-9 leads to activation of immune cells including pDCs and to pathogenic production of cytokines involved in SLE.<sup>131</sup> IgE inhibits TLR-7- and TLR-9-mediated expression of IFN-α by pDCs in patients with SLE, leading Khoryati and colleagues to speculate that non-autoreactive IgE may, in contrast to autoreactive IgE, be protective (the IgE paradox).<sup>132</sup>

The role of IgE in the indirect promotion of diseases has also been studied. In SLE, lupus nephritis onset induced by the activation of basophils by autoreactive IgE was explored. Basophil activity on lymph nodes promoted Th2 cell differentiation, which enhanced the production of self-reactive antibodies leading to lupus nephritis.<sup>128</sup>

The anti-IgE therapy, omalizumab, has shown effectiveness as a treatment for allergic diseases and for CSU in a number of clinical trials.<sup>133,134</sup> Both the mechanism of action of omalizumab and patient response times to omalizumab treatment have provided further insights into the disease mechanism of CSU, and have highlighted the importance of IgG interactions with FcεRI in treatment response times. A slow response time to omalizumab (patient response time took >8 days to achieve 7 consecutive days of a weekly urticaria activity score of ≤6 after treatment) was associated with the action of IgG antibodies on unoccupied FcεRI (unoccupied due to the sequestering of free IgE by omalizumab) to activate mast cell mediator release causing wheal and angioedema formation, thus leading to a delayed treatment response time.<sup>135</sup>

## Classical mechanisms of IgE modulating immune responses via FcεRI and/or CD23

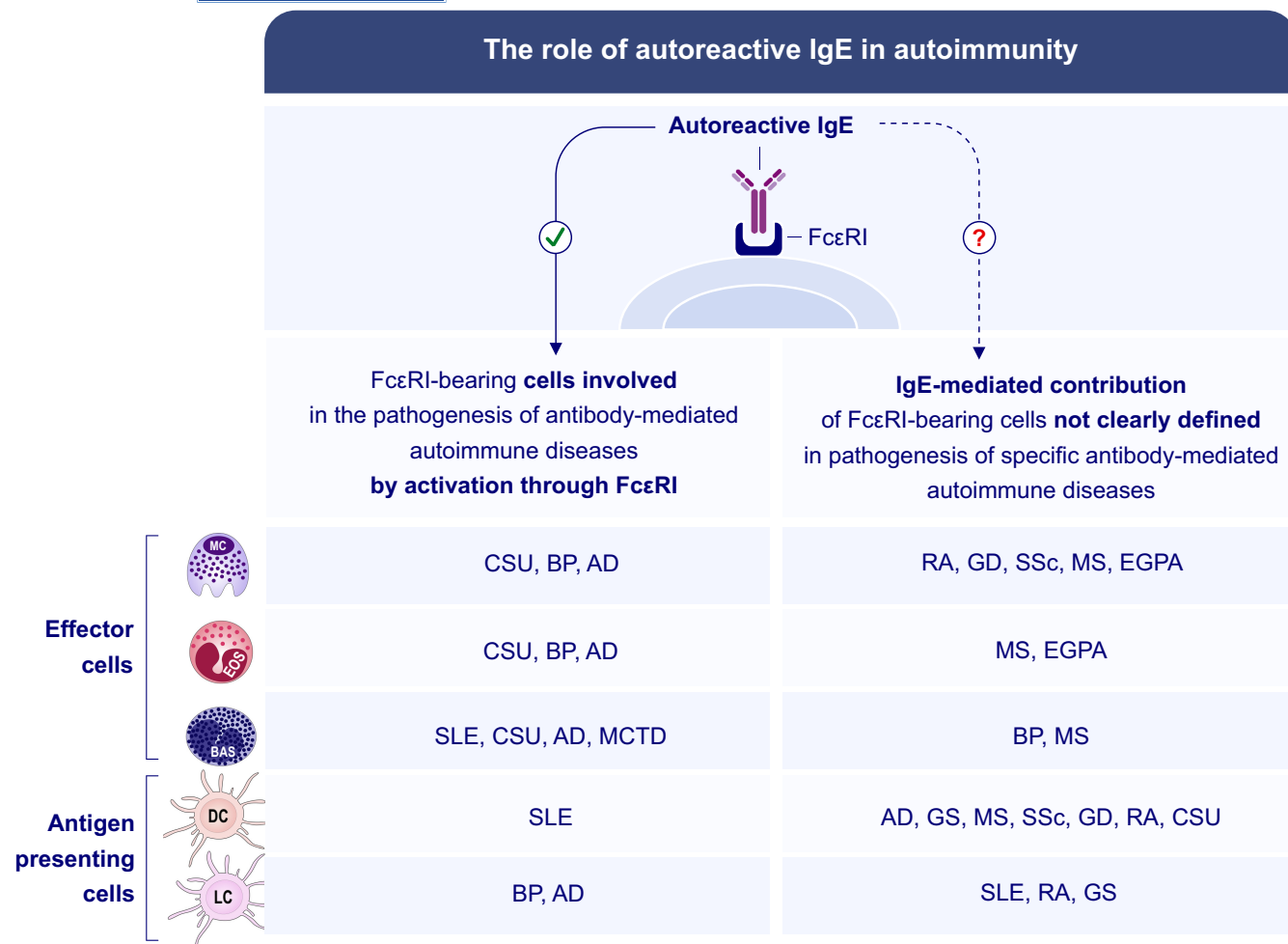


**FIGURE 4** Classical mechanisms of IgE modulating immune responses via FcεRI and/or CD23. IgE exerts important immunomodulatory effects by binding to its two receptors—a high-affinity receptor, FcεRI, and a low affinity receptor, FcεRII or CD23. FcεRI is found primarily on mast cells and basophils, signal transduction leads to activation or degranulation of these cells to release inflammatory mediators such as cytokines, chemokines and *de novo* synthesized lipids. CD23 is found mainly on mature B cells, regulating IgE synthesis, and found on activated macrophages, eosinophils, dendritic cells, Langerhans cells and platelets. CD23 bound IgE-antigen complexes are presented to T cells by facilitated antigen presentation (FAP), leading to presentation on B-cell surface by MHC-II. CD23-FAP can results in epitope spreading which may be important in the development of autoallergies. Engagement of CD23 on macrophages and monocytes induces proinflammatory cytokines and nitric oxide synthase and mediates IgE-dependent phagocytosis. Bas, basophil; DC, dendritic cell; Eos, eosinophil; FAP, IgE-facilitated antigen presentation; LC, Langerhans cell; MC, mast cell; MΦ, macrophage; MO, monocyte

## 5 | REGULATORY T CELLS AND IGE: POTENTIAL IMPLICATIONS IN AUTOIMMUNITY

Treg cell deficiency results in raised levels of serum immunoglobulins, including autoantibodies and IgE.<sup>107,136</sup> *FOXP3* knockout mice show increased levels of serum immunoglobulins including IgE and IgG; furthermore, these mice may be a useful tool for screening therapeutic agents for immune disorders caused by Treg abnormalities.<sup>137</sup>

IgE antibodies and autoreactive IgE activate pDCs, leading to the secretion of IFN-α.<sup>129</sup> IgE-FcεRI cross-linking on human pDCs from atopic donors is associated with an impaired capacity of pDCs to induce Tregs in vitro.<sup>23</sup> Other cells bearing FcεRI (and CD23) believed to have a role in Treg homeostasis include basophils, mast cells, DCs expressing FcεRI, eosinophils and Langerhans cells. Moreover, a recent study shows that CXCR5+ Tregs control both autoreactive and allergen-specific IgE T follicular regulatory cells and control IgG and IgE responses to vaccines, allergens and autoantigens and exert critical immunoregulatory functions.<sup>138</sup>

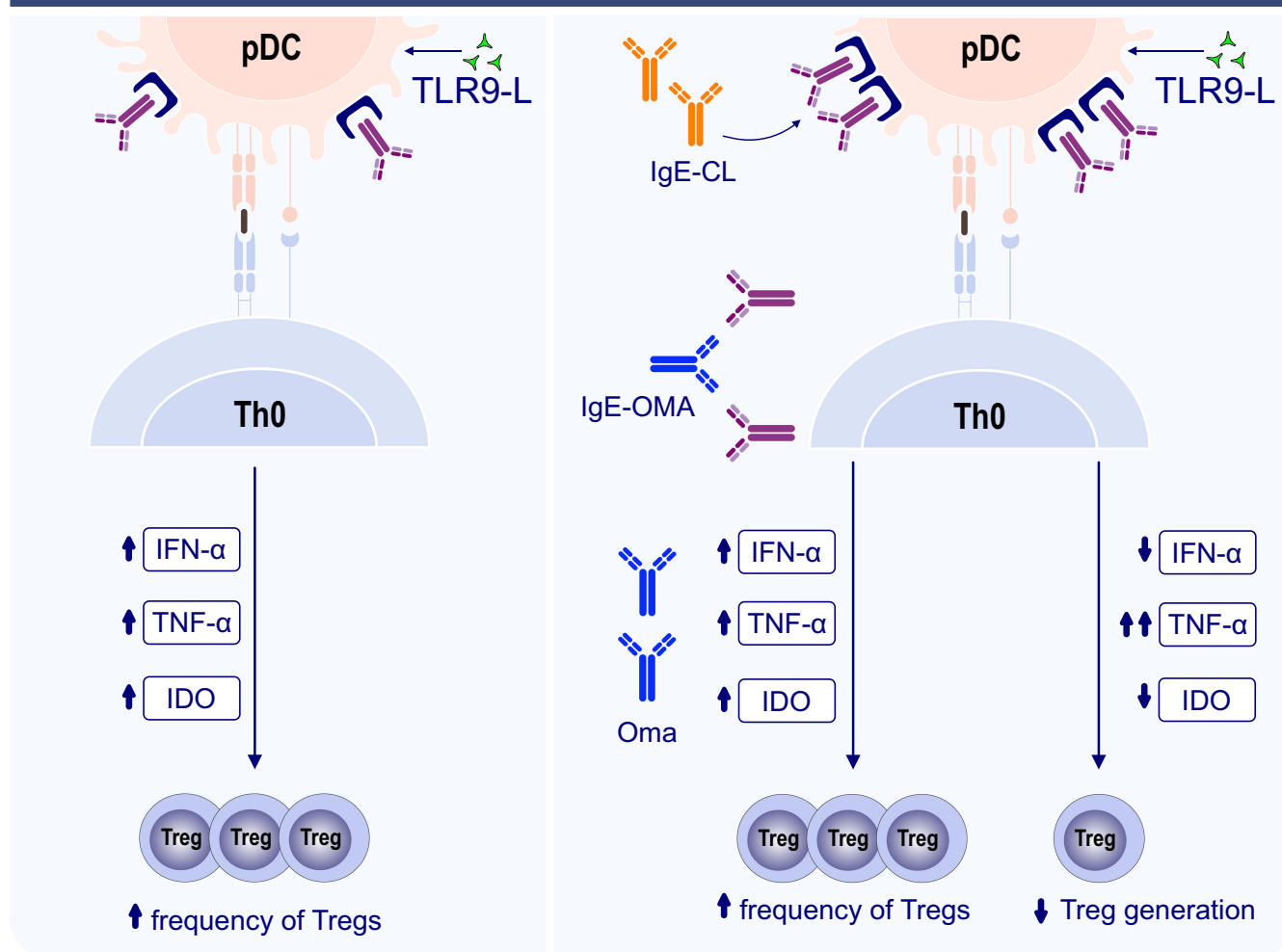


**FIGURE 5** Role immune cells of IgE in autoimmunity. Many immune cells are involved in the pathophysiology of autoimmune diseases through IgE-mediated or non-IgE-dependent mechanisms. Cells expressing the high-affinity receptor, FcεRI, and responsiveness to autoreactive IgE have been linked to the pathogenesis of diseases such as SLE, CSU, BP and AD. FcεRI-expressing cells contribute to other autoimmune diseases, such as MS, RA and GD, although IgE-mediated activation has not been clearly established. Mast cells and basophils are the main FcεRI-bearing cells, and they contribute to antibody-mediated autoimmune diseases (AAID) involving autoreactive IgE and FcεRI-aggregating antibodies. pDCs, eosinophils and Langerhans cells also express FcεRI and contribute to AAID through IgE-dependent or IgE-independent mechanisms. Activation of mast cells through FcεRI contributes to the pathophysiology of CSU, BP and AD. Mast cells are also involved in pathophysiology of RA, GD, SSc, MS and EGPA although FcεRI-mediated activation has not been demonstrated. Basophils contribute to pathophysiology of SLE, CSU, AD and MCTD in an IgE-dependent manner; however, their role in BP and MS has not been linked to IgE-dependence. A clear role for pDCs in the pathophysiology of SLE has been established through IgE-mediated activation, whereas their contribution to GS and RA may be regulated by FcεRI-targeting self-antibodies. Eosinophils expressing-FcεRI are linked to CSU, AD and BP pathophysiology. Contribution of eosinophils to EGPA and MS but IgE-mediated activation has not been clearly demonstrated. Langerhans cells contribute to BP and MS pathophysiology through the expression of FcεRI, yet their role on SLE by FcεRI-mediated activation is unknown. AD, atopic dermatitis; BP, Bullous pemphigoid; CSU, Chronic spontaneous urticaria; EGPA, Eosinophilic Granulomatosis with Polyangiitis; GD, Graves's disease; GS, Gougerot-Sjogren syndrome; MCTD, Mixed Connective Tissue Disease; MS, Multiple Sclerosis; RA, Rheumatoid Arthritis; SLE, Systemic lupus erythematosus; SSc, Systemic Sclerosis

Anti-IgE treatment restores the capacity of pDCs impaired by IgE-FcεRI cross-linking to induce Tregs in vitro in atopic patients. The mechanism for this is believed to be via pDC activity modulation. Omalizumab removes IgE from the surface of pDCs, which diminishes the negative effects of IgE-mediated FcεRI cross-linking on pDCs and restores Treg homeostasis: specifically, purified pDCs stimulated with the Toll-like receptor 9-ligand type B CpG ODN2006 (TLR9-L) induced increased numbers of CD4+CD127lowCD25+Foxp3+ Tregs compared with unstimulated

pDCs, which was impaired by IgE-FcεRI cross-linking (IgE-CL) in TLR9-L-activated pDCs. Pretreatment of pDCs with omalizumab restored the capacity of TLR9-L-activated pDCs under IgE-CL to generate CD4+CD127lowCD25+Foxp3+ Tregs (Figure 6). While this study provides interesting preliminary evidence for a role for anti-IgE therapy in autoimmune disease, the study is limited in that it was carried out in vitro; to confirm the findings in vivo, a controlled clinical study needs to be carried out in future with a large patient cohort.

## Tregs and IgE - potential implications in autoimmunity



**FIGURE 6** Regulatory T cells and IgE interactions: Potential implications in autoimmunity. Purified pDCs stimulated with the Toll-like receptor 9-ligand type B CpG ODN2006 (TLR9-L) induced increased numbers of  $CD4^+CD127^{\text{low}}CD25^+Foxp3^+$  Tregs compared to unstimulated pDCs, which was impaired by IgE-FcεR1 cross-linking (IgE-CL) in TLR9-L-activated pDCs. Pretreatment of pDCs with omalizumab restored the capacity of TLR9-L-activated pDCs under IgE-CL to generate  $CD4^+CD127^{\text{low}}CD25^+Foxp3^+$  Tregs. IDO, indoleamine 2,3-dioxygenase; IFNα, interferon alpha; IgE-CL, IgE-FcεR1 cross-linking; Oma, omalizumab; pDC, plasmacytoid DC; TLR9-L, toll-like receptor 9 ligand; TNFα, tumour necrosis factor alpha

Anti-IgE treatment with omalizumab is effective for severe allergic asthma as shown both in clinical trials<sup>134</sup> and in long-term, real-life studies.<sup>139</sup> It is also indicated in CSU and has shown effectiveness in nasal polyposis,<sup>140,141</sup> bullous pemphigoid,<sup>142</sup> virally induced asthma exacerbations and mastocytosis<sup>143</sup> and food allergy.<sup>144</sup> In food allergy, supplementation of oral immunotherapy by omalizumab promotes allergen desensitization through an initial omalizumab-dependent step that acutely depletes allergen-reactive T cells, followed by an increase in allergen-specific Treg activity due to the reversal of their Th2 cell-like programme. Improved Treg function may be a key mechanism by which oral immunotherapy (OIT) ameliorates food allergy.<sup>145</sup>

There is good evidence for Treg involvement in SLE,<sup>90</sup> and there have been reports of IgE anti-dsDNA autoantibodies; however, there are technical challenges to accurately detect IgE autoantibodies in

the presence of a vast excess of IgG. While therapies for SLE exist, the disease remains uncontrolled; therefore, SLE may be a potential candidate for anti-IgE treatment. An initial clinical trial showed that patients treated with omalizumab showed significant improvement in disease activity scores and that it was well tolerated with mostly mild adverse events comparable to those experienced with placebo treatment.<sup>146</sup>

The finding that anti-IgE therapy restores Treg homeostasis, and that this mechanism is associated with clinical improvement in asthma, suggests that anti-IgE therapy may also have a potential role in the management of autoimmune diseases with Treg cell involvement.

In theory, Treg-based therapies could be important for re-establishing immune homeostasis in progressive MS, especially in

relapsing remitting MS (RRMS), although it could be argued that there is limited remaining medical need in RRMS with the advent of anti-CD20 monoclonal antibodies.<sup>147</sup> Regarding IgE, an initial study suggested that serum IgE levels were slightly lower in patients with MS than those of a control group with other neurologic disorders than MS.<sup>148</sup> Further studies elucidated differences in specific IgEs in patients with MS. Patients with MS and mite-specific anti-IgE were different to those without this IgE with a younger age of onset, more likely to be male, with a lower expanded disability status scale (EDSS) and a predisposition to atopy.<sup>149</sup> Neither serum total IgE nor the frequency of hyperIgEaemia differed significantly between groups. Another study showed that serum from patients with MS has higher levels of IgE against myelin protein-derived peptides potential targets of an autoimmune attack on the central nervous system, regardless of clinical subtype.<sup>150</sup>

While it is known that the suppressive capacity of Tregs is reduced in MG, the association of type 2 responses and IgE with the development of MG is yet to be explored. Current therapy options are focused on antigen-specific therapies including immunoadsorption and induction of immune tolerance against AChR, MuSK and LRP4.<sup>151</sup>

Interestingly, anti-IgE therapy has been shown to induce a short-term clinical improvement in osteoarthritis,<sup>152</sup> although the finding that IgE-dependent mast cell activation has a role in osteoarthritis suggests that this may be mediated through mast cells rather than Tregs.<sup>153</sup>

Our belief is that at present IBD might well represent an interesting area for anti-IgE therapy. Increased incidence of food allergy and IgE levels are seen in patients with Crohn's disease, especially in patients with Crohn's disease and orofacial granulomatosis.<sup>17-19</sup>

## 6 | CONCLUSIONS AND FUTURE PERSPECTIVES

Tregs ensure a balanced immune response to foreign and self-antigens; Treg dysfunction is critical in the pathogenesis of allergic, autoimmune and chronic inflammatory disorders. Overall, data suggest IgE autoantibodies can contribute to symptoms of autoimmune diseases, mainly through the activation of FcεRI on mast cells and basophils.

The capacity of activated pDCs to induce functional Tregs is significantly impaired by IgE-cross-linking, which may be restored by anti-IgE therapy, suggesting a potential role for this approach in the treatment of inflammatory and autoimmune diseases involving Treg dysfunction. The advent of these novel discoveries together with cutting-edge technologies such as a CRISPR-based techniques to identify novel gene regulators involved in *FOXP3* expression<sup>154</sup> and harnessing of epigenetic mechanisms<sup>155</sup> should significantly contribute to paving the way for novel Treg-based therapeutic strategies in the near future. More basic and clinical translational research is required, however, to determine whether these strategies might represent a viable approach.

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## CONFLICT OF INTEREST

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