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REVIEW ARTICLE

Regulatory T cells and their role in allergic disease

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Abstract

The incidence of allergic diseases has been rising over the past decades, and this troubling trend coincides with environmental changes such as shifts in diet and increased antibiotic use, both of which can impact our immune system. Allergic reactions occur when the immune system overreacts to normally harmless substances, and it is known that regulatory T cells (Tregs) play a major role in immune system suppression and the generation of tolerance. However, new research suggests that Tregs can malfunction in environments that promote allergies. This review delves into Treg function, and how environmental factors can influence their ability to maintain immune homeostasis. Specifically, we explore the origins of Treg cells, as well as the mechanisms used for suppression of inflammation and tissue healing, with a concentration on food allergies, atopic dermatitis and asthma. Understanding Treg function in the context of a changing environment is crucial for developing new strategies to prevent and treat allergies.

Abbreviations: AD, Atopic dermatitis; Ahr, Aryl hydrocarbon receptor; APC, Antigen presenting cells; Areg, Amphiregulin; CagA, cytotoxin-associated gene A; CRTH2, Chemoattractant receptor-homologous molecule expressed on Th2 cells; CTLA-4, Cytotoxic T lymphocyte antigen 4; DC, Dendritic cell; DEREG, DEpletion of REGulatory T cells; FA, Food allergy; FOXP3, Forkhead box P3; GATA3, GATA-binding protein 3; GGT, γ-glutamyl transferase (GGT); HDM, House dust mite; IgE, Immunoglobulin E; IL, Interleukin; ILC, Innate lymphoid cell; IPEX, Immunodysregulation, polyendocrinopathy, enteropathy, X-linked; iTreg, Induced T regulatory cell; LAG-3, Lymphocyte activation gene 3; MI, Myocardial infarction; mLN, Mesenteric lymph nodes; nTreg, Natural T regulatory cell; PAH, Polycyclic aromatic hydrocarbons; PM, Particulate matter; PSA, Polysaccharide A; RALDH2, Retinoic acid catalysing enzyme; RORγt, RAR-related orphan receptor gamma t; RyR2, Ryanodine receptor; SAG, Staphylococcal enterotoxin B; SCFA, Short chain fatty acid; SNP, Single nucleotide polymorphism; Tbet, T-box transcription factor; TCR, T-cell receptor; Teff, Effector T cell; Tfh, T follicular helper; Tfr, Follicular T regulatory; TGF-β, Transforming growth factor beta 1; Th, T helper; Th2, Type 2T helper cell; Tr1, T regulatory 1; Treg, Regulatory T cell; VacA, vacuolating cytotoxin A.

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KEYWORDS
allergy, asthma, atopic dermatitis, food allergy, T regulatory cell

1 | INTRODUCTION

The escalating incidence of allergic disorders has become a pressing health issue in affluent and rapidly developing societies.[1,2] Furthermore, the Industrial Revolution's transformative social and environmental changes, significantly impacting human behaviour, lifestyle, diet and infectious exposures over the past 150 years, have contributed to the rise and severity of allergic diseases.[2–5] In the United States, food allergy prevalence is 8% in children and 5% in adults, while asthma affects 8.6% of children and 7.4% of adults.[6] Additionally, in the context of early childhood, there is evidence of the allergic march, which begins with atopic dermatitis, then progresses to food allergies, allergic rhinitis and asthma.[7] This amplified burden of allergic diseases has led to considerable morbidity and substantial financial burden for individuals and healthcare systems.[8] While therapeutic advancements have targeted inflammatory processes and provided symptomatic relief, these therapies are, for the most part, non-curative.

The dramatic surge in allergic disease prevalence in recent decades strongly suggests an influence of environmental factors that interact with genetically predisposed individuals to promote disease development.[9] Recent studies emphasize a dynamic interplay of environmental factors including: diet,[10] pollutants,[11] nonpathogenic bacterial exposure[12,13] and antibiotic use[14–16] on immune system development and function.[17,18] These findings also support the central role of commensal bacteria in regulating allergic diseases, through dynamic interaction with the host's genetic background and environmental inputs that either foster or disrupt tolerance mechanisms.[12,19–23]

Considering immune tolerance, it is well known that regulatory T (Treg) cells play a crucial role in promoting tolerance to allergens and preventing allergic disease.[24,25] This review will delve into recent advancements highlighting the 'dual potential' of Tregs in allergic disease, namely their ability to either promote tolerance in a healthy environment or contribute to disease exacerbation when exposed to a pro-allergic inflammatory milieu.

2 | TREGS—ORIGIN AND MECHANISM OF ACTION

Treg cells are divided into two major categories: the natural (nTregs) (also called thymic Tregs) and the induced (iTreg) (also called peripheral Tregs),[26–28] shown in Figure 1. nTregs are thymus-derived and mainly mediate self-antigen tolerance, whereas iTregs (derived from naïve CD4 T cells in the peripheral blood) become tissue resident cells that play a crucial role in homeostasis and the regulation immune responses within particular organs.[26,27] For example, iTreg cells in the gut and the lung can be induced via microbially derived metabolites,[29] TGF-β and retinoic acid,[30,31] shown in Figure 1. Additionally, iTreg cells can also be induced in the gut, to protect from food allergy.[32,33] Though both nTregs and iTregs use similar immune suppressive mechanisms, major differences are observed in their T-cell receptor (TCR) repertoire. iTregs recognize a much wider array of antigens and thus have better ability to engage pathogens, allergens and other factors encountered in the peripheral tissues.[34]

Tregs play an important suppressive role in the immune response, by acting at sites of inflammation to control T effector (Teff) cell function through humoral factors or via direct cell–cell interactions. In the case of humoral suppression, IL-10 secretion inhibits Teff activation, while TGF-β and IL-35 promote Treg differentiation and enhance function. Additionally, secretion of cytolytic factors such as granzyme A and B induce apoptosis in Teff cells[35–38]; however, it was also shown that granzymes can be self-damaging to the cells that secrete them, as Tregs as cells producing granzyme B were shown to be more apoptotic.[39] Considering cell–cell interactions, IL2/CD25, as well as several immune checkpoint receptors including: cytotoxic T lymphocyte antigen 4 (CTLA-4), lymphocyte activation gene 3 (LAG-3), CD73, CD39 and ST2, participate in the Treg mechanism of action, illustrated in Figure 2A. IL2/CD25 interaction promotes the suppression of antigen presenting cells (APCs) by depriving them of their trophic cytokines IL-4, IL-10 and IFNγ.[40] Additionally, the transcription factor Helios (a repressor of Treg IL-2 expression) has been identified as a pivotal component for the suppressive capacity and stabilization of Treg cells during inflammatory processes.[41] Considering checkpoint inhibitors, binding of CTLA-4 on Tregs to the B7 ligands (CD80 and CD86) on Teff cells inhibits their activation and proliferation,[42] whereas binding of LAG-3 to MHCII molecules causes cell exhaustion.[43] Both CTLA-4 and LAG-3 expression on Tregs also down-modulate APCs in a similar fashion.[42,44] Tregs also exert their function through membrane bound enzymes such as CD39 and CD73 which act together to convert extracellular ATP to immunosuppressive adenosine. The binding of adenosine to receptors on Teff cells reduces T-cell proliferation and dampens the production of pro-inflammatory cytokines. Notably, generation of adenosine by these enzymes can also lead to loss of Treg suppressive ability.[45] Finally, the IL-33 receptor (ST2) acts as an activator of Treg cells. Upon release by epithelial cells, IL-33 binds to ST2, magnifying the regulatory and suppressive capacity of Treg cells both in the lungs and the colon.[22,46]

The suppressive function of Treg cells is not the only component of their regulatory profile. These cells also participate in tissue repair mechanisms, which are crucial to orchestrate the healing response after severe inflammatory responses. For

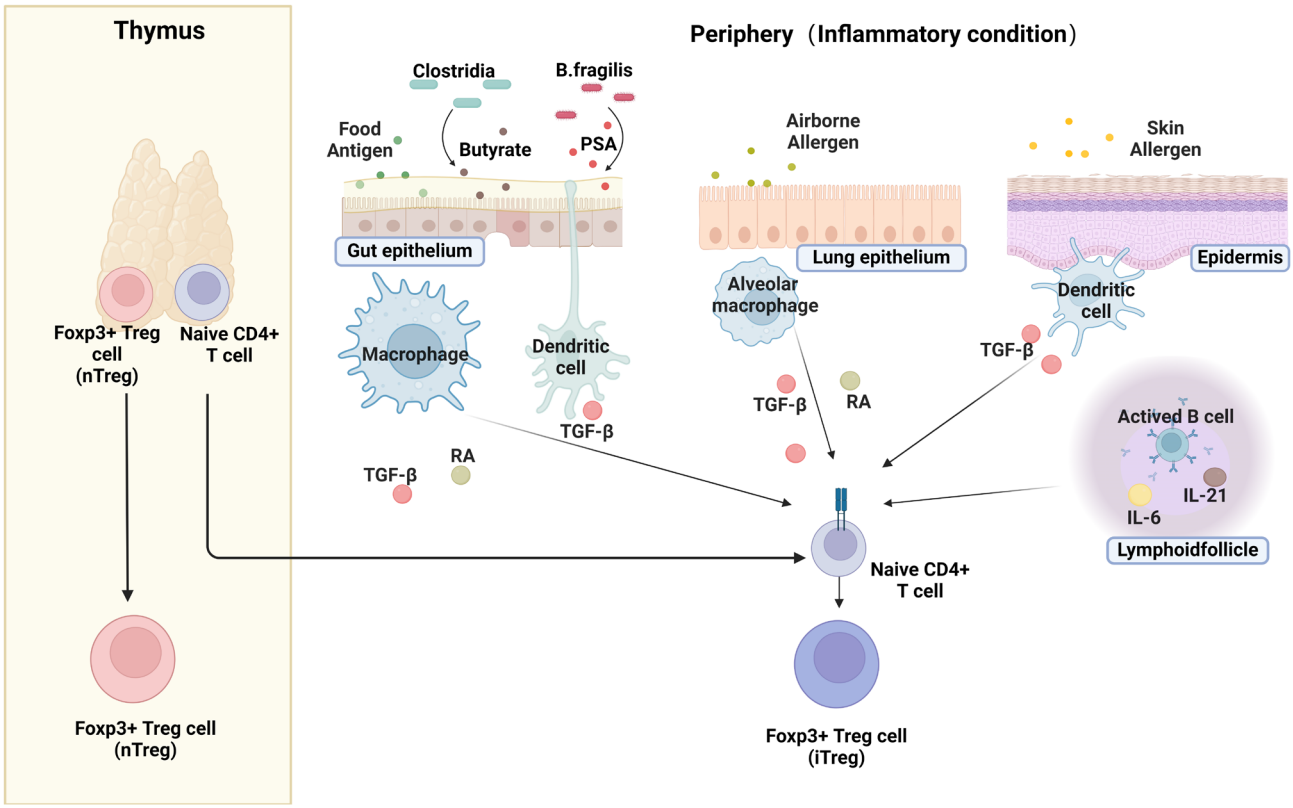

FIGURE 1 Origins of Treg cells. Treg cells originate either from the thymus (called natural Tregs (nTreg)) or develop in the periphery from naïve CD4+ T cells into induced Tregs (iTreg). nTregs mediate self-antigen tolerance, whereas iTregs develop in peripheral tissues and play an important role in maintaining tolerance at mucosal surfaces. iTregs differentiate in the gut via: Stimulation by TGF-β and retinoic acid, exposure food allergens and contact with bacterially produced SCFAs or bacterial components such as *Bacteroides*-derived polysaccharide A (PSA). In the lungs, iTregs can be induced by airborne allergens as well as TGF-β and retinoic acid secreted by alveolar macrophages. Finally, in the skin, iTregs can be activated by contact with skin allergens and through dendritic cell (DC) TGF-β production.

instance, injured muscles produce IL-33, which subsequently stimulate Tregs to produce amphiregulin (Areg), a molecule which stimulates tissue repair and proliferation of satellite cells through the epidermal growth factor receptor pathway.[47] It is known that Areg, expressed on cytotoxic CD4+ and CD8+ T cells, plays a protective role in the pathogenesis of fibrotic disorders[48] and bacterial infections.[49] In allergic disease, Areg expression on CCR10+ ILC2 cells also plays an important role protecting against allergic asthma.[50] Additionally, in the lungs, Treg cells produce Areg in response to lung injury following viral lung infection.[51] Nevertheless, Areg is not always a protector. There have been reports that Areg induction in the skin of mice with mutated keratin (and defective barrier function) promoted itching through thymic stromal lymphopoietin (TSLP) production by keratinocytes.[52] In other types of tissue damage, such as in myocardial infarction (MI), Treg cells play an important role in repair processes though CD39-mediated adenosine formation, which stimulates switching of M1 macrophages towards an anti-inflammatory M2 phenotype.[53–55] The recruitment of Treg cells into the heart tissues is CCR5 dependent, as shown in knocking down CCR5 in mice, which led to impaired healing due to impaired Treg infiltration.[56,57] Tissue repair processes of Treg cells are shown in Figure 2B.

3 | TREG PLASTICITY AND EPIGENETICS

Tregs display a great deal of plasticity, using their cytokine and chemokine profiles to control inflammatory processes via the suppression of various immune cell subtypes. For instance, in Peyer's patches in the murine gut, expression of IL-6 and IL-21 can stimulate the transformation of Tregs into follicular Th (Tfh)-like cells called follicular Tregs (Tfr).[58–60] These regulatory Tfr migrate to the germinal centre, promoting germinal centre formation and inhibiting Tfh-mediated B-cell activation and antibody production,[61–63] shown in Table 1. Moreover, in addition to FOXP3, Tregs can also co-express T-box transcription factors (T-bet), forming Th1-like Tregs. These cells can help suppress excessive Type 2 response associated with allergy through the secretion of IFNγ and their maintenance of suppressive function[64–67] (Table 1).

Although Treg plasticity underpins a well-regulated immune response, exposure to chronic inflammation can also shift these responses from a suppressive to an inflammatory phenotype. For instance, gut resident Tregs that co-express the RAR-related orphan receptor gamma t receptor (RORγt), known as Th17-like Tregs, suppress food allergic responses, but in contrast promote allergic asthma in the lungs via IL-17 production.[19,68–71] Tregs co-expressing

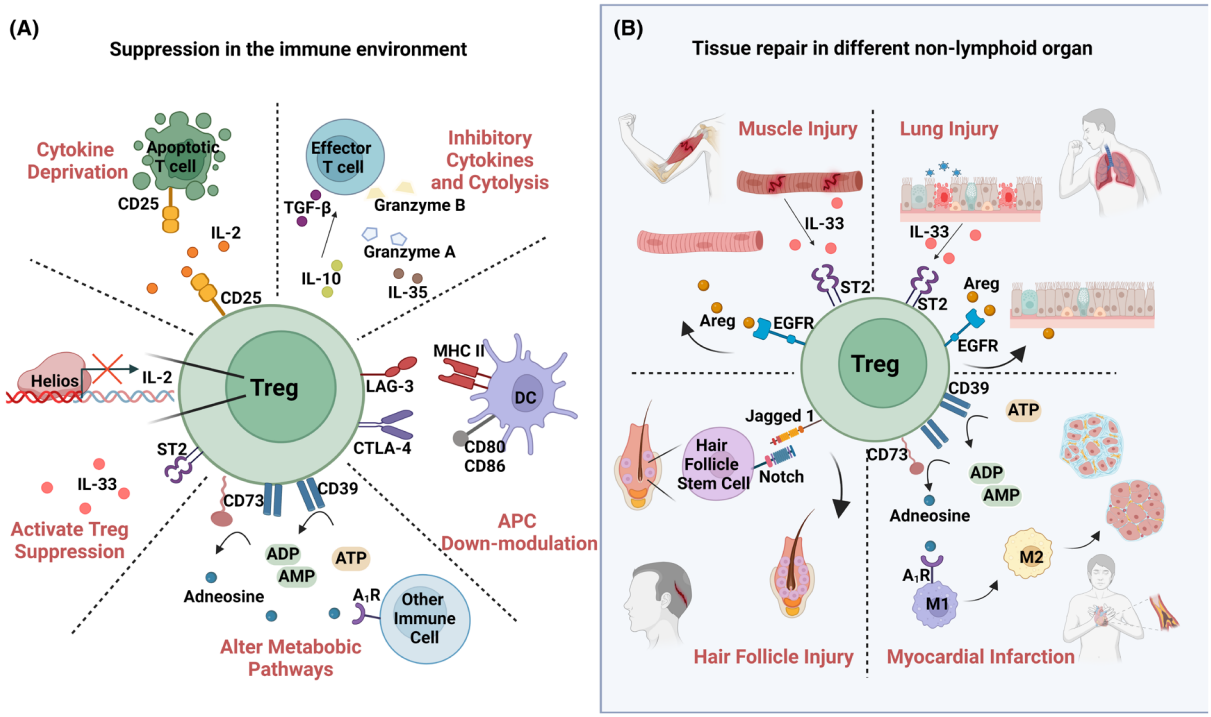

FIGURE 2 Mechanisms of action in Treg cells. (A) Treg cells suppress immune responses through multiple mechanisms. Tregs can secrete cytokines such as IL-10, TGF-β and IL-35, as well as cytolytic factors such as granzyme A and B to mediate suppressive function. Regarding cell–cell contact, binding of CTLA-4 and LAG-3 on Tregs to B7 and MHCII molecules on APCs results in inhibition of APC activation. Tregs convert ATP to adenosine via CD39 and CD73, reducing Teff cell proliferation and pro-inflammatory cytokine production. IL-33 binds to ST2 on Tregs, enhancing their regulatory and suppressive functions in the lungs and colon. The transcription factor Helios inhibits IL-2 expression in Tregs. Additionally, IL2/CD25 on Tregs suppress APCs by depriving them of essential cytokines. (B) Tissue repair mechanisms in Treg cells. Treg cells aid tissue repair by producing Areg in response to IL-33 from muscle or lung injury, promoting repair and cell proliferation. In myocardial infarction, Tregs convert ATP to adenosine, transforming M1 macrophages to an anti-inflammatory M2 phenotype which produces IL-10. Tregs also promote hair growth in skin via the Notch pathway.

TABLE 1 Treg subtypes.

Name	Cellular markers	Role in the immune response
Follicular Tregs (Tfr)	FoxP3+ CD25+ CXCR5+ BCL6+ PD1+ CTLA4+ ICOS+	Migration to germinal centre, inhibition of Tfh-mediated B-cell activation and antibody production
Th1-like Tregs	FoxP3+ CD25+ CD127low T-bet+ CCR5+ CXCR3+	Increased IFNγ secretion that may help suppress excessive Type 2 responses
Th17-like Tregs	FoxP3+ CD25low CD127low RORγt+ CCR6+	Enhance Th17 responses in the lung that aggravates allergic asthma. In contrast in the gut, they suppress food allergy
Th2-like Tregs	FoxP3+ CD25+ CD127low GATA3+ CCR4+	Expression of IL-4, IL-5 and IL-13 exacerbates allergic asthma and food allergy
exTregs	FoxP3low CD25− CD127+	Transition from FoxP3 expressing suppressive cell to inflammatory effector T cell. Worsens allergic inflammation

FoxP3, GATA-binding protein 3 (GATA3) and a receptor known as 'chemoattractant receptor-homologous molecule expressed on Th2 cells' (CRTH2) participate in ILC2 recruitment to the lungs.[72] This influx of ILC2 cells combined with the production of IL-4, IL-5 and IL-13 from these Th2-like Tregs worsens allergic asthma and food allergy.[72–76] Finally, continued exposure to a chronic inflammatory

milieu can lead to loss of FoxP3 expression, in a process that is not yet completely understood. This results in a cell type called exTregs, consisting of former Tregs that have lost their suppressive capabilities and effectively transitioned into conventional T effector cells that participate in pathogenic immune reactions and exacerbate allergic inflammation.[77]

Epigenetic mechanisms, such as DNA methylation and histone modification, play a crucial role in regulating Treg plasticity at key genomic loci. For instance, nTregs can be distinguished from iTregs by a significant DNA hypomethylation at the Foxp3 promotor and Foxp3-associated enhancer regions such as the Treg cell-specific demethylated region (TSDR—also known as conserved noncoding DNA sequence 2 (CNS2)).[78,79] Furthermore, maintenance of DNA methylation by DNA methyltransferase DNMT1 and Ten-Eleven Translocation (TET) enzymes is required to control the stability of Foxp3 in nTregs in thymus, as deletion of this gene results in diminished numbers and suppressive function of Treg cells.[80] Thus, nTreg cells require both a canonical hypomethylation pattern and maintenance methylation to stabilize their lineage identity and function. In addition to methylation, the FoxP3 locus is also acetylated during T-cell development. Histone acetyltransferases (HATs) interact with the FoxP3 locus during this time to promote sustained FoxP3 expression in Treg cells.[81,82]

A chronic inflammatory milieu is also a strong environmental driver of epigenetic changes, and modifications to the FoxP3 locus directly influence T reg plasticity. For example, if TET or HAT enzyme activity is lost, due to an infection or a metabolic change, Tregs lose Foxp3 expression and gain a Th17-like phenotype.[82] In addition to this, a sustained level of IL-6 can lead to loss of Foxp3 by promoting DNMT1-mediated DNA methylation and histone deacetylase (HDAC) activity.[83] The substantial epigenetic regulation involved in Treg plasticity opens up promising avenues for future therapeutic interventions, where targeting these epigenetic mechanisms could potentially modulate Treg function in allergic diseases. Descriptions of epigenetic modifiers of Treg plasticity are shown in Table 2.

4 | TREG CELLS AT BARRIER SITES

The epithelial barrier is an important component to consider in the pathogenesis of allergic disease.[84,85] The epithelium of the skin, gastrointestinal tract and lungs engage in intricate interactions with the environment, microbiota and immune system, and disruption at barrier sites is associated with altered immune homeostasis[86–89] and the development of allergic diseases such as asthma,[90] atopic dermatitis,[91] allergic rhinitis,[92] chronic rhinosinusitis[93] and eosinophilic esophagitis.[94] Interestingly, disrupted barrier function in specific organs can also influence the development of allergic diseases in different sites. The gut–lung axis provides an excellent example of such barrier dysfunction wherein early-life gut microbial dysbiosis has been linked to increased asthma severity.[21] Tregs play a pivotal role in maintaining epithelial barrier homeostasis through several different pathways.[95] In the intestine, Tregs can promote intestinal barrier integrity via the secretion of IL-10,[96] suppression of neutrophil infiltration[97] and inhibition of type 2 immune responses in food allergies.[98] Finally, in the lung, Tregs promote epithelial proliferation in a CD103-depdendent manner.[99]

5 | TREG CELLS IN SKIN DISEASE

Atopic dermatitis (AD) or eczema is a prevalent inflammatory skin disease, characterized by abnormalities in the skin barrier, cellular immune deviations and increased sensitization to environmental allergens, that can affect both children and adults.[100] AD lesions are characterized by the infiltration of activated Th2 cells and eosinophils, expansion of ILC2 cells, production of IL-4 and IL-13 as well as elevated levels of total and allergen-specific IgE, all of which are directly associated with disease severity.[101–104] Regarding Tregs, these cells are highly enriched in the skin of humans and mice and are important for the control of allergic inflammation and repair.

The most striking evidence for Tregs in protection against AD is observed in the IPEX disease, in humans (associated with FOXP3

TABLE 2 The mechanism and the role of epigenetic modifiers in Treg cells.

Epigenetic modifier	Mechanism	Role in Treg cells
TET enzymes	DNA demethylases	Induce and maintain Foxp3 expression
HATs	Histone acetylation enzymes	Induce and maintain Foxp3 expression
Satb1	Genome organizer	Stabilizes the Treg cell-defining gene regulatory network
CoREST	Epigenetic repressor complex	Disrupts Foxp3-driven repression of Th1 cytokines
UHRF1	DNA methytransferase adapter protein	Controls stability of Foxp3 in nTregs in the thymus
DNMT1	Maintenance DNA methyltransferase	Stabilizes lineage identity and function of Tregs
EZH2	Histone methytransferase	Binds to Foxp3 containing domains and deposits a repressive chromatin modification

gene mutations)[105] and in scurfy mice (which lack Treg cells), which is characterized by severe allergic skin inflammation, mimicking the skin lesions observed in AD. In addition to this, CARMIL2 deficiency (capping protein regulator and myosin 1 linker 2) is an autosomal recessive inborn error of immunity (IEI) that causes dysfunction in T-cell activation and decrease in the Treg population, which is also associated with AD.[106] Tregs have been shown to attenuate skin inflammation in several mouse models of AD, for instance, Nidhi et al. showed that RORα-expressing skin Tregs were important in suppressing type 2 cytokines in an ILC2 model of AD.[107] Furthermore, sonic Hedgehog (Shh) signalling in skin reduced AD pathology by increasing Treg-mediated immune suppression.[108] Moreover, defective Treg function underlies the exaggerated contact hypersensitivity exhibited by *Dock8*$^{-/-}$ mice in response to the hapten oxazolone, and increases their susceptibility to allergic skin inflammation elicited by skin sensitization with antigen or by cutaneous exposure to *Staphylococcus aureus*,[109–111] shown in Figure 3.

Despite the well-established presence of Tregs in AD skin, the recruitment of these cells and their potential dysfunction in AD remain perplexing. It is known that an elevation of Treg cells significantly correlates with AD severity, however while some studies show Treg accumulation in skin lesions, but no increase in the number of circulating cells[112] others showed increased Treg presence in both the blood and skin of AD patients[113–117] or decreased frequency of circulating T regs.[118] Furthermore, a recent meta-analysis study showed increased Th17/Th22 cells and decreased Treg cells in blood of AD patients.[119] These discrepancies could be due to the plasticity of Treg cells and the markers employed for cell identification. Importantly, FOXP3 expression does not occur exclusively in Tregs, it can also be transiently induced in activated skin Teff cells.[120–122]

Treg expresses a variety of skin-homing addressins including CCR4, CCR5, CCR6 and cutaneous lymphocyte-associated antigen (CLA),[105,123–125] and several reports have identified increased expression of these molecules on skin Treg cells in AD.[115,124,126] Additionally, there is a subpopulation of skin Treg cells that lack expression of CCR6 and promote the Th2 immune response.[105,125,127,128] Despite the augmented number of Treg cells in the skin of AD patients, a decreased Treg/Teff ratio still results in higher levels of IL-4 and IL-13,[129] shown in Figure 3. In addition to quality and quantity impairments, Treg cells also exhibit high plasticity. Treg cells able to differentiate

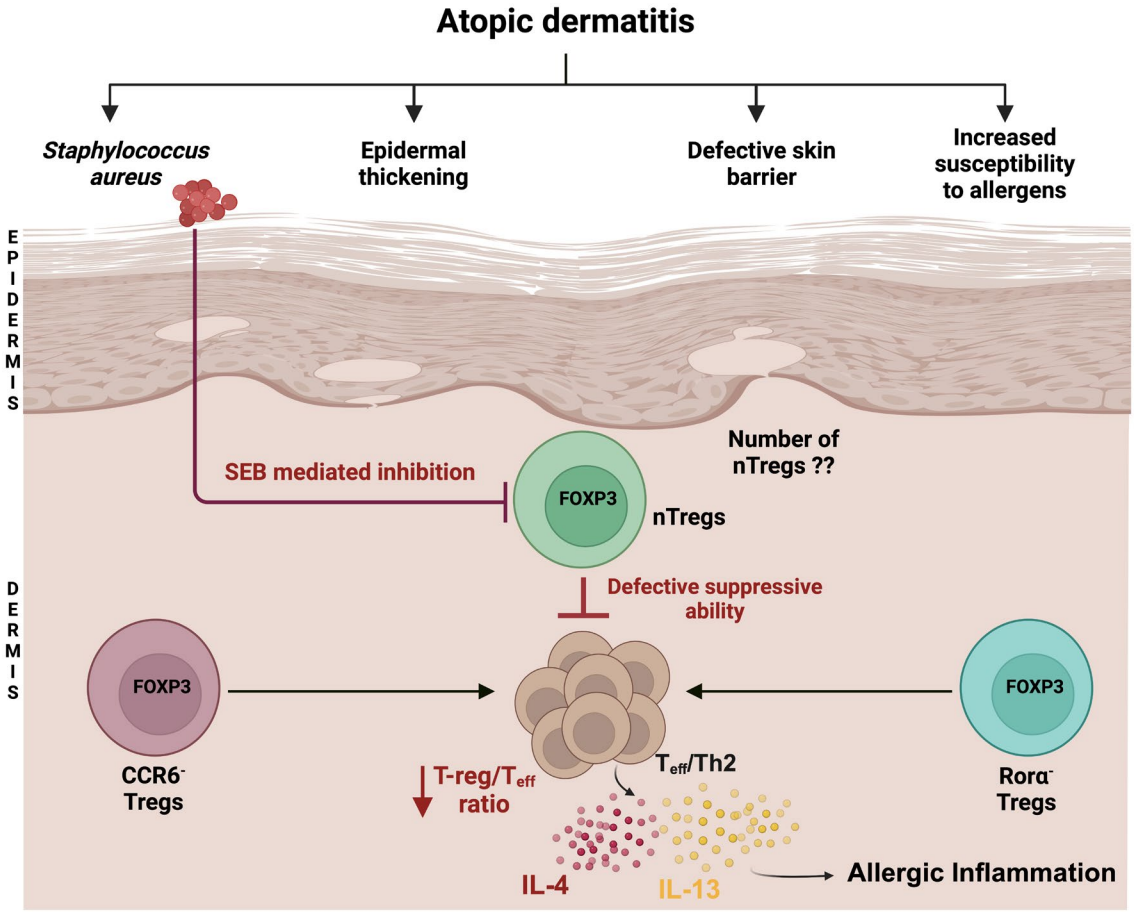

FIGURE 3 Dysregulation of Tregs in atopic dermatitis. AD is characterized by epidermal thickening, skin barrier defects and increased susceptibility to allergen. Though the number of Tregs residing in the skin during AD patients is not clear, it is known that the suppressive ability of Tregs is defective due to a lower ratio of Tregs to Teff cells (Treg/Teff). Subpopulations of Rorα- and CCR6-Tregs are also involved in AD and through expression of IL-4 and IL-13 can promote Th2 immune responses in the skin. Additionally, colonization of the skin by *S. aureus* is highly prevalent in AD patients, inhibiting Treg activity through the production of superantigens such as SEB.

into Th1, Th2 or Th17 under the influence of specific cytokines and by epigenetic reprogramming,[105,130,131] thus repressing their suppressive functions and contributing to AD pathogenesis.

Regarding bacterial colonization, increased Th2 cytokines and decreased antimicrobial peptide synthesis facilitates *S. aureus* skin colonization in AD patients compared to healthy controls, and the load of *S. aureus* correlates with disease severity.[132] *S. aureus* strains produce superantigens such as staphylococcal enterotoxin B (SEB), and several reports have shown that these superantigens inhibit Treg suppressive function and promote Th2 like functions.[133] This SEB-mediated Treg inhibition was shown to be modulated through the glucocorticoid-induced tumour necrosis factor receptor family-related protein (GITR/GITRL) pathway and upregulation of the GITR ligand on monocytes.[134] Thus, Treg impairment may be more prominent in AD patients with *S. aureus* colonization. In contrast, the presence of the commensal bacterium *Lactobacillus rhamnosus* activates Treg function and suppresses Th1, Th17 and thymic stromal lymphopoietin-mediated responses in AD patients.[126] Several treatments have been developed for AD patients that either generate or modulate Treg cell function. Low-dose IL-2 treatment, which has the potential to increase Treg number and function, showed an improvement of clinical symptoms and signs in eczema in AD patients.[135] Treatment with allergen immunotherapy (AIT) and vitamin D supplements, both of which have the potential promote Treg cell development, also showed a significant reduction in the severity of AD.[136]

In summary, the role of Tregs in the pathogenesis of AD is complex and remains an area of investigation. Comprehensive phenotypic and mechanistic studies investigating Tregs during AD skin flares are required to better illuminate their role in this disease, and additionally, to develop therapeutics harnessing Tregs for AD treatment. From a clinical standpoint, the mechanisms by which Treg cells contribute to AD initiation are an important issue to be addressed.

6 | TREG CELLS IN FOOD ALLERGY

The gastrointestinal tract is continuously exposed to foreign antigenic material derived from the diet, and more than 100 g of food protein from plant and animal sources is consumed every day. Despite this enormous load of foreign antigens, in most individuals the immune system does not mount an adverse immune reaction to food proteins, primarily due to the induction of oral tolerance. Oral tolerance is the default physiological mechanism that is actively induced in response to orally ingested foreign antigens, and it is the underlying basis through which large amounts of food antigens can be consumed every day. However, breakdown of oral tolerance triggers a pathogenic type 2 immune response characterized by the generation of high-affinity IgE responses to food antigens. In individuals sensitized to food proteins, subsequent exposure to the sensitized food results in mast cell and basophil activation and in rare cases such a response results in anaphylaxis, an acute life-threatening systemic allergic response to food.[137–140] Consequently, the diagnosis of food allergy (FA) is carried out through an allergen skin prick test and the detection of food allergen-specific IgE levels in the serum.[141–143] Several mechanisms have been described in regulating oral tolerance including the induction of T-cell anergy, clonal deletion of effector T cells, induction of IgG and IgA responses and the generation of iTreg cells.[19,144,145]

Immune exposure to large doses of food antigens has been shown to induce T-cell anergy and clonal deletion of antigen reactive T cells via apoptosis.[146] Conversely, low and sustained doses of food antigens induce antigen-specific Treg cells.[146] A recent study explored the fate of the CD4 T-cell response to gliadin,[78] a major wheat protein that harbours IgE epitopes and is known to cause a spectrum of allergies such as atopic eczema and food allergy.[147] Mice fed with gliadin induced a small proportion of T follicular helper (Tfh) like cells that expressed CXCR5 and promoted a weak anti-gliadin IgG1 response.[148] Gliadin exposure also induced a significant non-canonical anergic T helper cell subset that expressed the folate receptor and CD73. These anergic T helper cells lacked inflammatory functions and were incapable of inducing gut pathology, eventually differentiating to Treg cells (under the influence of IL2).[148] Allergen exposure in general has also been shown to induce IL2 production in effector Th2 cells, subsequently promoting the maintenance and survival of Treg cell responses which in turn suppresses pathogenic allergen-specific Th2 cells.[149] Therefore, low-dose IL2 has been proposed as a key therapeutic strategy in controlling FA.[150,151] Finally, the role of iTregs in regulating tolerance to food antigens has also been described using DEREG mice (DEpletion of REGulatory T cells), which express the diphtheria toxin receptor driven by the FOXP3 promoter. Depletion of Treg cells with diphtheria toxin after the induction of oral tolerance to food antigens resulted in mice developing antigen-specific IgE responses and food allergy,[152] corroborating a necessary role for iTregs cells in controlling tolerance to food antigens.[153]

Tregs specific for food antigens are induced in the gut-draining mesenteric lymph nodes (mLN).[154] Intestinal phagocytes such as macrophages and DCs extend dendrites through enterocytes to sample luminal antigen. Non-migratory CX3CR1^{+} macrophages capture soluble antigens from the lumen and transfer them to migratory CD103+ DCs via connexin 43 gap junctions.[155] The small intestine contains different DC subsets, with CD103+ DCs residing in the lamina propria (LP), and exhibiting a mature yet tolerogenic phenotype through the expression of the immunoregulatory cytokines IL-10, IL-27, TGF-β1 and the M2 catalysing enzyme RALDH2. CD103+ DCs migrate to mLN in a CCR7 dependent manner to induce antigen-specific Treg cells,[154] shown in Figure 4A. Food-derived retinoic acid also orchestrates the transmigration of cDC2s from the LP to intraepithelial sites, programming a tolerogenic milieu under the influence of environmental cues and mucin.[156] Indeed, DCs differentiated in the presence of retinoic acid efficiently suppress allergen-specific Th2 responses in vitro and in vivo.[157,158] In addition to regulating the phenotype and functionality of DCs, retinoic acid also plays a critical role in imprinting the gut homing markers CCR9 and integrin α4β7 on Treg cells, which guides them back to the intestine where they proliferate and promote oral tolerance.[159] Perturbation of this trafficking axis is associated with failure to

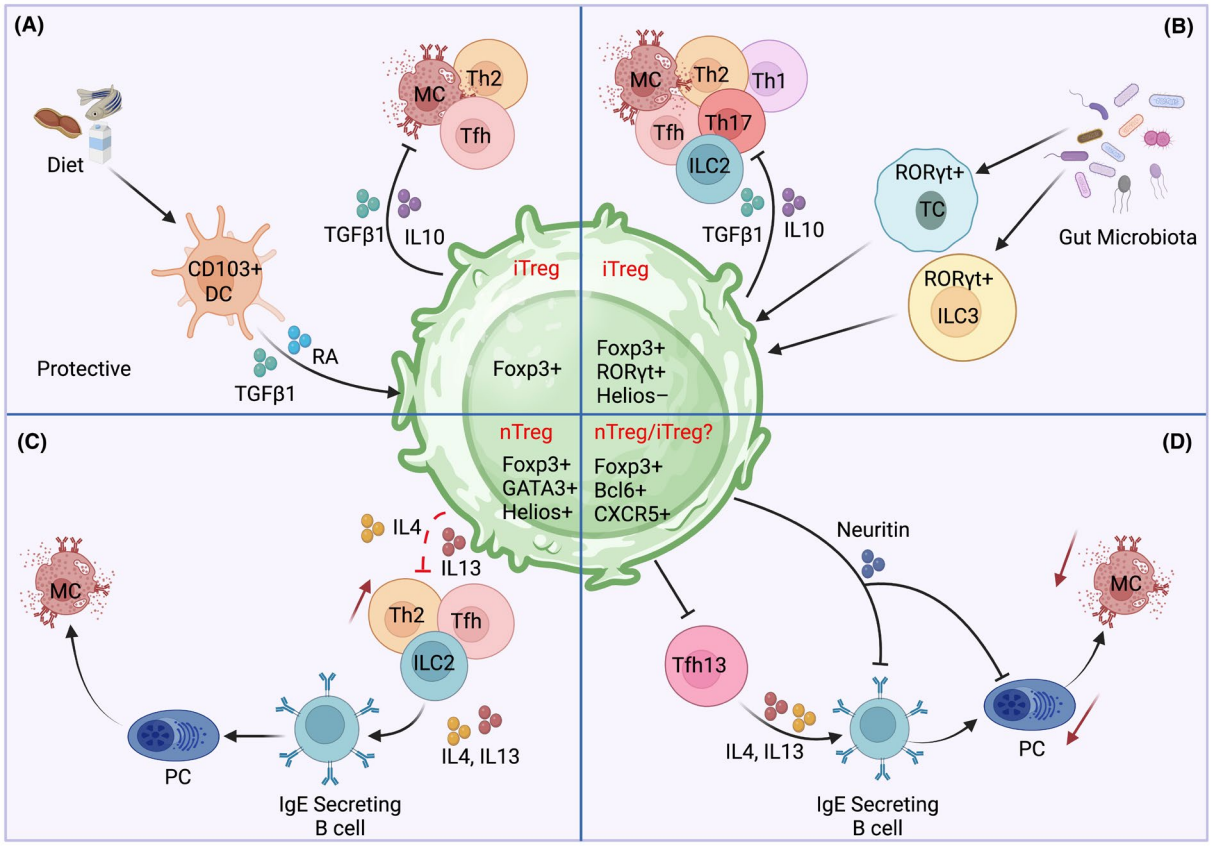

FIGURE 4 Treg cell subsets in food allergy (FA). (A) Classical antigen presenting cells (APCs) such as CD103+ dendritic cells (DCs) capture food antigens and induce the differentiation of antigen-specific Treg cells under the influence of TGF-β1 and retinoic acid. iTreg cells secrete IL-10 and TGF-β1 and suppress Th2 responses to food antigens. (B) RORγt+APCs, including type 3 innate lymphoid cells (ILC3s) and Thetis cells (TC), sample commensal antigens in the gut lumen and induce RORγt+ iTreg cells. Commensal-induced RORγt+Treg cells suppresses allergen-specific Th2 responses and mast cell activation through a TGF-β1 dependent mechanism. (C) Impairment in the microbiota-food-antigen-Treg axis disrupts the tolerogenic balance in the gut and promotes the expansion of Th2-cell-like Tregs which express GATA3 and secrete IL-4 and IL-13. These Th2-reprogrammed Treg cells fail to curtail allergen-specific immune responses leading to a dysregulated Th2 and Tfh responses that promote IgE antibody production and mast cell activation to food. (D) Tfr cells limit the pathogenic activity of Tfh cells and secrete neuritin which repress IgE class switching and plasma cell formation in B cells.

induce oral tolerance to food antigens, as mice deficient in integrin beta 7 or CCR7 are associated with loss of tolerance to orally administered antigens.[152,154] Furthermore, eosinophils migrating along the crypt-villus axis need retinoic acid for their maintenance.[160] In addition to eosinophils, ILC2 require retinoic acid for a better adaptation to the small intestine environment.[161]

In addition to antigens derived from the diet, the intestinal immune system is constantly interacting with the antigens and immunogenic components derived from the commensal microbiota residing in the gut mucosa. Gut microbial composition is highly dynamic, specifically during the early life where nutritional demands dictate the succession of microbial communities.[162] Interaction with the gut microbiota in early life influences immune system development, and Treg cell imprinting during this crucial time period is hypothesized to play a role in the suppression of allergic reactions to food antigens.[19] *Bifidobacteria* and *Lactobacillus* species predominantly colonize the neonatal gut and secrete diverse neurotransmitters that induce Tregs early in life, licensing long-term tolerance to food antigens later in life.[163] Then, the introduction of solid foods during the weaning period promotes the expansion of *Clostridia* and Bacteroidetes clades which subsequently induce a highly specialized subset of Treg cells expressing RORγt.[74,75]

RORγt Tregs are induced early in life under the direct influence of the gut microbiota and stably persist to adulthood, promoting tolerance to food and commensal antigens by actively suppressing pathogenic Th1, Th2 and Th17 responses,[164,165] shown in Figure 4B. Interestingly, RORγt Treg differentiation was found to be governed by MHCII^{+}RORγt^{+} APCs that were distinct from DCs.[166–168] These RORγt^{+} APCs were characterized as ILC3s, and a newly described cell type named as Thetis cell. Both ILC3s and Thetis cells induced RORγt Tregs through TGF-β1 signalling pathways involving αVβ integrin dependent mechanisms, with Thetis cells playing a dominant role early in life.[166,168] Finally, immunogenic cues such as polysaccharide and secondary bile acids derived from the microbiota instruct the development of RORγt Treg cells.[169,170]

Over the last decade, a growing body of evidence has indicated a role for gut dysbiosis in the pathogenesis of FA in both human subjects and animal models.[171,172] A healthy microbiota is

constituted by the presence of microbial communities that programme tolerogenic responses, and conversely, FA is associated with microbial signatures that fail to curtail allergic responses to food antigens. Faecal analysis of the early-life microbiota in babies with FA has identified a dynamic change in microbial communities associated with the loss of Clostridial species.[68,173] Administration of immunomodulatory *Clostridia* and Bacteroidetes species to FA prone mice suppressed the antigen-specific IgE response and protected mice from anaphylaxis.[68] This mechanism was contingent on the capacity of these bacteria to induce RORγt Treg cells, deletion of Rorc in Treg cells abrogated the protective response mediated by bacteriotherapy.[68]

In addition to the RORγt Treg cells, food antigens also drive a Th2 cell like programming in a distinct subset of Helios$^+$ Treg cells in the gut mucosa. These cells express the transcription factor GATA3 and have the capacity to secrete IL4 and IL13 upon antigen exposure,[174] shown in Figure 4C. Th2 reprogramming in Treg cells impairs their tolerogenic function by suppressing TGF-β1 expression in a *Stat6*-dependent manner.[69] This pathogenic Treg subset has also been identified in human FA patients. Oral immunotherapy with omalizumab reversed the Th2 reprograming of Tregs and improved Treg cell function.[175] Notably, RORγt$^+$ Tregs and GATA3$^+$ Tregs are reciprocally regulated in a balance that is largely monitored by Treg-derived TGF-β1. In mice, deletion of TGF-β1 in Tregs impaired RORγt Treg cell differentiation and reciprocally expanded the pool of Th2 skewed Treg cells. Consequently, these animals had mast cell expansion in the gut and were susceptible to the development of FA.[19,69]

Cross linking of high-affinity antigen-specific IgE present on mast cells with cognate food antigens results in mast cell degranulation and in some cases systemic anaphylaxis. Generation of antigen-specific IgE responses is supported by Tfh cells, and a rare subset Tfh subset termed Tfh13 cells that were recently was described in mice and humans.[176] Expressing the transcription factors BCL6 and GATA3 and characterized by high expression of the Th2 cytokines IL13, IL4 and IL5, this subset of Tfh cells controlled the induction of high-affinity anaphylactic IgE responses to food and environmental allergens,[176] shown in Figure 4D. The pathogenic responses of Tfh13 and IgE secreting B cells are monitored by FOXP3$^+$ follicular regulatory T cells (Tfr). Tfr deficient mice are associated with higher autoantibody responses including IgG1 and IgE levels.[177,178] Ablation of Tfr cells in a mouse model of allergic house dust mite (HDM) heightened Tfh13 activity and resulted in increased production of HDM-specific IgE and exacerbated lung inflammation.[178] Tfr cells are endowed with the expression of the neuropeptide neuritin which represses IgE class switching and plasma cell formation of B cells.[177] The role of Tfr cells in food allergy and the mechanism though which they control Tfh13 responses remains to be elucidated. Research over the past decade has advanced our understanding on the specific roles played by Treg cells in regulating tolerance to food antigens. Distinct subsets of Tregs and Tfh cells have now been identified that are implicated in the pathophysiology of FA. Future studies translating this knowledge to clinics will be pertinent in quelling the rise of FA.

7 | TREG CELLS IN ASTHMA

Asthma is a heterogenous chronic inflammatory condition of the airways affecting up to 30% of the population in different countries. It is characterized by diverse respiratory symptoms including cough, wheeze, shortness of breath and chest tightness; which are driven by the inflammation of the airways and trigger processes such as mucus production, airway remodelling and bronchial hyperreactivity.[179] Asthma manifests as different phenotypes and endotypes with specific etiopathogenic mechanisms, broadly classified as type-2 immune-mediated or non-type 2 immune-mediated, and based on blood and tissue eosinophilia, exhaled nitric oxide levels and total and specific IgE.[180] Allergic / type-2 asthma is usually triggered by sensitization in early life to environmental allergens such as HDM, pollen, animal dander or cockroach.[181] Upon recognition of these triggers, allergen-specific Th2 cells release type-2 cytokines (IL-4, IL-5, IL-9, IL-13) that lead to airway eosinophilia, mucus oversecretion and priming of B cells for allergen-specific IgE synthesis.

Treg dysfunction plays an essential role in asthma pathogenesis, as these cells are key regulators of tolerance mechanisms. In the lung, immune tolerance is mainly controlled by three Treg subsets: FOXP3 iTregs, T regulatory 1 (Tr1) cells and follicular Tregs (Tfr).[182] These cell types promote the differentiation of regulatory B cells and prime DC towards a tolerogenic profile, hence inhibiting the proximal pathways of sensitization and IgE production triggered upon allergen exposure.[183] By producing IL-10, IL-35, TGF-β, CTLA-4, PD1 and other tolerogenic mediators, Treg subsets in the lung restrain the function of Th2 cells, eosinophils, ILC2s, mast cells and basophils, the most essential cells involved in the allergic asthma reaction.[182] Early studies in murine allergic asthma models have shown that depletion of CD4+CD25+ Tregs enhances neutrophil and T-cell recruitment to the airways, IL-4 and IL-5 production, and airway hyperreactivity.[184]

Patients with severe asthma show reduced numbers of FOXP3+ Tregs in the bronchoalveolar fluid compared to healthy controls, and decreased levels of circulating Tregs with impaired migration to the lung epithelium.[185–187] In these patients, FOXP3+ Tregs display reduced expression levels of CCR5, indicating an impaired suppressive activity correlating with worsened lung function parameters.[185] In addition, Tregs in asthma show high expression levels of CRTH2, a type 2 receptor for prostaglandin D2, associated with asthma control and exacerbation.[188] Thus, allergic asthma is characterized by decreased Treg numbers, with low CCR5 and high CRTH2 expression indicating an impaired functionality and a Th2-biased phenotype.

7.1 | Intrinsic and extrinsic influences on Treg function affecting asthma development and exacerbation

A strong genetic component underlies asthma susceptibility, as shown by multiple studies (reviewed in[189]). With recent advances in sequencing technologies, a plethora of genome-wide association studies (GWAS) have identified various loci associated with asthma,[190]

including several single nucleotide polymorphisms (SNPs) associated with the type-2 endotype.[191,192] Recently, a large meta-analysis combining GWAS results from Iceland and UK biobanks reported 88 independent associations at 56 loci, the majority involved in the regulation of CD4+ T-cell activation, responses and physiology.[193] Regarding Tregs, it is known that monogenic mutations affecting FOXP3 (i.e. IPEX syndrome in humans or scurfy mice) cause severe immune dysregulation with autoimmunity and allergic manifestations, including elevated serum IgE and peripheral eosinophilia.[194] Another loci controlling Treg function which shows a strong association with asthma is the Ryanodine receptor 2 (RyR2),[195] a calcium channel that mediates the contractile response in airway smooth muscle cells.[196,197] Recently, it was shown that FOXP3 blocks the expression of RyR2 in Tregs, reducing the m-calpain activity necessary for their disengagement from DC, thereby enhancing contact-dependent suppressive activity.[198] Interestingly, the authors showed that shRNA-mediated depletion of RyR2 in conventional CD4+ T cells strengthened their interaction with DC, rendering them immunosuppressive and making them capable of improving ovalbumin-induced airway inflammation and autoimmunity in Scurfy mice.[198]

The influence of environmental factors on asthma exacerbations is well established. Among such factors, rhinoviral infections are strongly associated with severe exacerbations.[199] Rhinovirus infection has been shown to directly affect the suppressive activity of Tregs, rendering them less able to inhibit type 2 immune responses,[200] shown in Figure 5. Another important risk factor responsible for asthma exacerbation is exposure to high levels of ambient air pollution,[201] which is associated with epigenetic changes affecting Treg function. Common environmental pollutants (i.e. polycyclic aromatic hydrocarbons (PAHs), CO, NO_2 and particulate matter (PM)) induce alterations in CpG methylation of the FOXP3 locus, impairing Treg activity and worsening the asthma phenotype.[201,202] Further studies indicate a strong correlation between childhood exposure to air pollutants and FOXP3 methylation levels, further associated with Treg dysfunction and increased plasma IgE levels,[203] Figure 5. Additionally, PM exposure has been shown to alter the Treg/Th17 cell balance, aggravating asthma manifestations in an aryl hydrocarbon receptor (Ahr)-dependent manner.[204] PM-triggered activation of Ahr, in turn, induces the expression of the Notch ligand JAG1, driving iTreg destabilization and promoting allergic airway inflammation.[11,205] In recent studies, we have identified Notch4 as the receptor on Tregs involved in these interactions, which is upregulated in circulating Tregs of asthma subjects in an IL-6-dependent manner.[72,206] Interestingly, targeting IL-6R signalling can enhance the immunosuppressive properties of Tregs in association with inhibition of Notch4 expression, which may represent a therapeutic opportunity for patients with severe asthma.[207–209]

Finally, the important role of the microbiome in shaping immune responses along the gut–lung axis is being increasingly recognized, as recently reviewed in.[210] Gut commensal bacteria can control T-cell homeostasis by modulating the Treg/Th17 cell balance,[21] shown in Figure 5. For instance, *Bacteroides fragilis* and several *Clostridium* strains are known inducers of Tregs, driven by microbial byproducts like *Bacteroides*-derived polysaccharide A (PSA)[211] or short chain

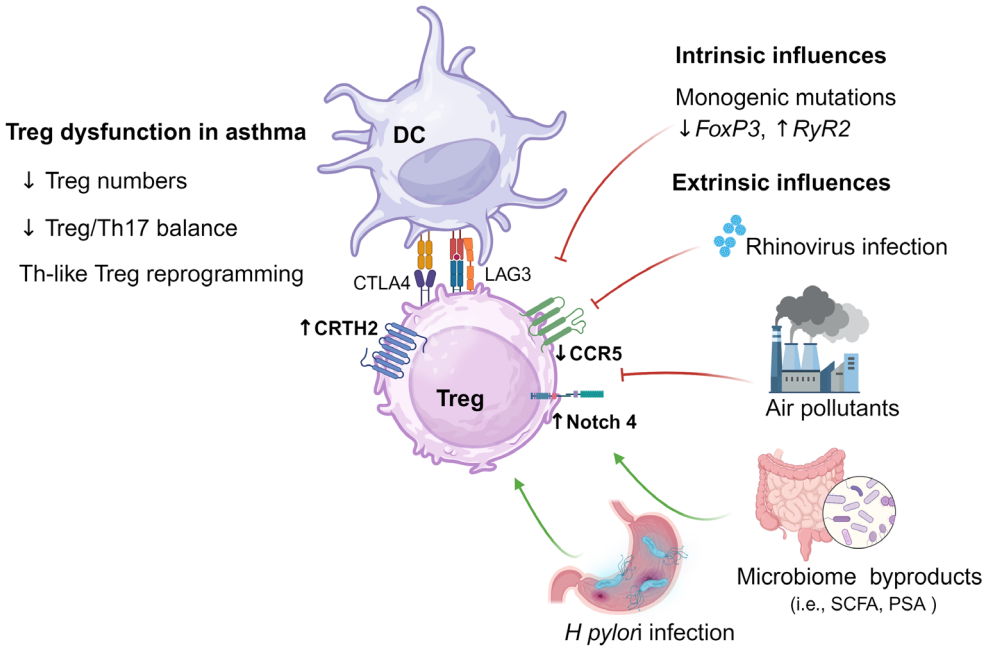

FIGURE 5 Intrinsic and extrinsic factors contributing to Treg dysfunction in asthma. Asthma patients exhibit decreased Treg counts and Treg/Th17 balance as well as reprogramming of Tregs towards a Th2-like phenotype. Monogenic mutations and SNPs, as revealed by GWAS studies, represent the main intrinsic factor influencing Treg function in asthma. As for extrinsic influences, rhinoviral infections and environmental pollutants are important negative modulators of Treg function contributing to asthma exacerbations. On the other hand, microbial byproducts derived from gut commensals and also pathogenic bacteria (i.e. *H. pylori*) are important Treg inducers with potential therapeutic application.

fatty acids (SCFA).[212,213] Butyrate and propionate, in particular, are strong Treg inducers through the inhibition of histone deacetylases that affect the FOXP3 promoter, thereby promoting Treg induction and stability.[214,215] Indeed, oral administration of PSA induced IL-10-producing Tregs and attenuated the asthmatic phenotype in a murine model, suggesting that these bacterial metabolites may provide opportunities for therapeutic interventions.[216]

Another important Treg inducer in the gastrointestinal tract is the gram-negative bacteria *Helicobacter pylori*, which currently affects approximately 50% of the world population.[217] Interestingly, several epidemiological studies highlight the beneficial role of this—once commensal—bacteria in the development of asthma.[218–220] This association likely stems from the Treg inducing ability of *H. Pylori*,[221,222] which depends on bacterial virulence factors like cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA) and γ-glutamyl transferase (GGT).[223] More recently, animal studies confirmed the epidemiological data by showing that neonatal infection with *H. pylori* led to an attenuated asthma phenotype in later life through the induction of Tregs.[224] Further studies showed that *H. pylori* reprograms DC towards a tolerogenic IL-18-producing phenotype that promotes the development of immunoprotective Tregs.[225] Therapeutic applications of *H. pylori* in asthma have also been envisioned, using bacterial extracts or purified virulence proteins. For instance, prophylactic application of *H. pylori*-derived extracts modulated DC and Treg responses via IL-10 signalling, attenuating allergic airway disease in later life.[226] Likewise, recent animal studies highlighted the potential prophylactic and therapeutic effects of applying purified VacA in acute and chronic allergic airway disease.[226–229]

8 | CONCLUSION

In the last decade, we have deepened our knowledge of the immune mechanisms driving allergic diseases and their treatment. Tolerance to environmental and food allergens is core to a healthy immune response, and in this context, allergen-specific Tregs are crucial players in the prevention of allergic diseases and for successful immunotherapy. To date, allergen immunotherapy remains the only intervention with the potential to restore immune function in allergic diseases, being the subject of intensive research to provide mechanistic insights into its protective effects. Treg dysfunction is central to the pathogenesis of allergic disorders and is characterized by loss of peripheral tolerance and the generation of chronic inflammation. Hence, a better understanding of the mechanisms driving FOXP3 expression and Treg stabilization will contribute to the development of novel therapeutic strategies for these disorders.

AUTHOR CONTRIBUTIONS

M.L.C and G.B wrote the asthma section. S.M and M. D wrote the skin section. E.S.V wrote the food allergy section. X.C and H.H wrote the introduction and the main Treg section. M.L.C and H.H revised, edited and finalized the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors declare that there was no conflict of interest when writing this manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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