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Regulatory T cells in allergic inflammation

Mehdi Benamar [a,b], Qian Chen [a,b], Monica Martinez-Blanco [a,b], Talal A. Chatila [a,b,c,*]

[a] Division of Immunology, Boston Children's Hospital, Boston, MA, USA
[b] Department of Pediatrics, Harvard Medical School, Boston, MA, USA
[c] Lead Contact, USA

A B S T R A C T

Regulatory T (Treg) cells maintain immune tolerance to allergens at the environmental interfaces in the airways, skin and gut, marshalling in the process distinct immune regulatory circuits operative in the respective tissues. Treg cells are coordinately mobilized with allergic effector mechanisms in the context of a tissue-protective allergic inflammatory response against parasites, toxins and potentially harmful allergens, serving to both limit the inflammation and promote local tissue repair. Allergic diseases are associated with subverted Treg cell responses whereby a chronic allergic inflammatory environment can skew Treg cells toward pathogenic phenotypes that both perpetuate and aggravate disease. Interruption of Treg cell subversion in chronic allergic inflammatory conditions may thus provide novel therapeutic strategies by re-establishing effective immune regulation.

1. Introduction: allergic diseases as disorders of immune regulation

Allergic diseases, including such common disorders as asthma, atopic dermatitis (AD), and food allergy (FA), arise in the context of aberrant tissue immune responses against normally innocuous environmental agents (e.g. foods and aeroallergens) [1]. The prevalence of allergic diseases has increased over the last decades in association with social and environmental changes ushered in by the industrial revolution that have profoundly altered patterns of human activity, including living arrangements, diet and infections [2]. The dramatically increased prevalence of allergic diseases is a public concern both because of the morbidity that these diseases exact and also the substantial financial costs associated with their care and therapy. While therapies for allergic disorders have steadily improved thanks to a better understanding of the underlying immune processes involved and their targeting with precision therapies, those therapies have remained, for the most part, noncurative.

Allergic diseases primarily involve dysregulated type 2 immune responses at the environmental interfaces in skin, gut and lung. While allergic (type 2) immunity plays a protective role against exposure to parasites, toxins and potentially harmful allergens [3,4], its dysregulation gives rise to pathologic responses associated with the variety of allergic diseases [5–7]. Allergic inflammation mobilizes integrated innate and adaptive immune response circuits, the former including epithelial barrier cells, innate lymphoid cells (ILC), mast cells, basophils, eosinophils, and neutrophils and the latter T helper 2 cells (Th2), T follicular cells (Tfh), regulatory T (Treg) cells and B cells [8–11]. The first line of defense against allergens encompasses the barrier epithelial cells in the skin, gut, and airways. Damage to epithelial cells will release different alarmins such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) that initiate cascading innate and adaptive immune

Abbreviations: AD, Atopic dermatitis; APCs, Antigen-presenting cells; Areg, amphiregulin; AT2, Type II alveolar cells; αVβ8, alpha-V:beta-8 integrin; α4β7, Alpha 4 beta 7 integrin; BCl6, B-cell lymphoma 6; CCR6, C-C Motif Chemokine Receptor 6; CCR9, C-C Motif Chemokine Receptor 9; CNS1, Conserved Non-coding Sequence 1; CNS2, Conserved Non-coding Sequence 2; CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells; CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; CXCL12, C-X-C motif chemokine 12; DTR, Diphtheria toxin receptor; FA, Food allergy; Foxp3, Forkhead box P3; GATA3, GATA Binding Protein 3; GDF-15, Growth/differentiation factor 15; HRV, human rhinovirus; IgE, Immunoglobulin E; ILC, Innate lymphoid cells; IL-33R, Interleukin 33 receptor; IL4R, Interleukin 4 receptor; IPEX, Immune dysregulation polyendocrinopathy enteropathy X linked; iTreg, induced regulatory T cell; LAG-3, Lymphocyte activation gene-3; LPS, Lipopolysaccharide; MHCII, Major histocompatibility complex class II; MyD88, Myeloid differentiation primary response 88; nTreg, natural regulatory T cell; OVA, Ovalbumin; PD-1, Programmed cell death protein 1; pTreg, peripheral regulatory T cell; RORα, Retinoic acid receptor-related orphan receptor alpha; RORγt, Retinoic acid receptor-related orphan receptor gamma; RSV, Respiratory syncytial virus; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; T-bet, T-box expressed in T cell; TCR, T-Cell Receptor; Tfh, T follicular helper cells; Tfr, T follicular regulatory cells; TGF-β, Transforming growth factor-β; Th, T helper cells; Th2, T helper 2 cells; TLR, Toll-like receptor; Treg, Regulatory T cells; TSLP, Thymic stromal lymphopoietin; TSLPR, Thymic stromal lymphopoietin receptor; tTreg, thymic regulatory T cell.

* Corresponding author at: Division of Immunology, Boston Children's Hospital, Boston, MA, USA.
E-mail address: talal.chatila@childrens.harvard.edu (T.A. Chatila).

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responses characteristic of type 2 immunity [12–15]. These include epithelial cell proliferation and mucus hypersecretion leading to tissue remodeling, activation and proliferation of innate lymphoid cells type 2 (ILC2), and mast cells, recruitment of eosinophils, basophils, and the initiation of adaptive T and B cell allergic immunity including Th2 and Tfh responses and IgE production.

Genetic and immunologic evidence also reinforces the idea of a pivotal role for immune regulatory mechanisms centered on Treg cells in promoting tolerance to allergens and preventing allergic disorders (see below). While it is tempting to propose that a quantitative imbalance between regulatory and effector type 2 immune responses underlies the development and persistence of allergic disorders, a more complex picture has emerged whereby a subverted immune regulatory response arising out of a disturbed barrier homeostasis actively contributes to disease [16,17]. The mechanisms underlying this subversion and its role in the breakdown of the immune regulatory mechanisms normally operating to maintain allergen tolerance are the subject of this review.

2. Regulatory T cells

2.1. Physiological functions of Treg cells in peripheral tolerance

Treg cells represent a subset of 5–15% of $CD4^+$ T cells characterized by their capacity to suppress auto-immunity and inflammation [18,19]. They are critically involved in maintaining immune homeostasis and preventing self-tolerance breakdown [20,21]. Treg cells express a specific transcription factor, Forkhead box P3 (Foxp3), essential for their differentiation and function. Foxp3 loss of function mutations in mice (Scurfy mice) or humans (IPEX: immune dysregulation polyendocrinopathy enteropathy X linked) induce a breakdown of immune homeostasis associated with intense autoimmunity and allergic dysregulation due to a deficient Treg cell function [22–25]. Several attributes of Treg cells including their immune regulatory activities, distinct metabolism, and lack of inflammatory cytokines production are under the control of Foxp3 [26,27].

Treg cells control both the innate and adaptive branches of the immune response, including different types of innate immune cells (dendritic cells, mast cells, monocytes/macrophages, and ILC) and T and B cell-dependent adaptive immunity [28–34]. The capacity of Treg cells to exercise such wide-ranging immune regulatory functions is enabled by their endowment with an array of distinct and non-redundant immunosuppressive mechanisms [35]. These include key regulatory factors such as IL-10, TGF-β, IL-35 and Fibrinogen-like protein 2, the extracellular nucleotide sensors CD39 and CD73, and cell surface receptors enforcing cell contact-mediated suppression including CTLA-4, PD-1, LAG-3 and Galactin-1 [36]. In addition to the immunosuppressive functions and capacities to restrict the intensity of immune responses, Treg cells can also promote non-immunologic processes, such as organismal metabolic regulation and tissue repair, the latter by virtue of secreting cytokines such as the epidermal growth factor receptor ligand amphiregulin (Areg) [37–40].

Several studies have identified tissue Treg cells in a wide variety of nonlymphoid organs including, relevant to allergic diseases, the environmental interfaces (skin, intestinal mucosa, and lungs) as well as visceral tissues such as muscles and fat [41]. Treg cells in those tissues acquire transcriptional and functional specializations conducive to their functions in those tissues. This is exemplified by the acquisition of tissue Treg cells in the gut and the skin of functional specialization relevant to maintaining microbial commensalism and tolerance to environmental antigens [42–46].

Treg cells are broadly subdivided into two different populations that play complementary roles in maintaining peripheral tolerance [47,48]. One population is derived from thymic precursors and is identified as natural or thymic Treg (nTreg/tTreg) cells [49,50] and the other is derived from naïve $CD4^+$ T cells post-thymic development and known as induced or peripheral Treg (iTreg/pTreg) cells [51–53]. iTreg cells arise at mucosal interfaces in response to commensal metabolites, retinoic acid, and TGF-β [53–55]. They can also be differentiated from naïve CD4 cells in vitro following TCR stimulation in presence of TGF-β and IL-2 [53]. While the two populations share common regulatory mechanisms, they are endowed with distinct TCR repertoire [56,57], an attribute that broadens Treg cell antigen specificity. Treg cells present a certain degree of plasticity, which is defined by the capacity to acquire in part the transcriptional and functional programs of other Th cell types while maintaining regulatory activity [44,58–60]. Thus, Treg cells can co-express together with Foxp3 other specific transcription factors such as T-bet, BCl6, GATA3 and RORγt relevant to ongoing Th effectors cell programs [44,58–63]. Treg plasticity is crucial to coordinately mount effector Th and immune regulatory responses by means of shared sets of chemokine receptors regulated by the respective Th cell transcription factors, leading to a more focused Th cell response and limiting potential off-target damage due to uncontrolled immune activation. Nevertheless, under pressure of chronic inflammation, Treg cells may proceed to express the full program directed by the respective Th cell-specific transcription factors, becoming in effect Th cell like. As discussed below, the devolution of Treg cells into Th2 cell-like effector T cells is relevant to pathogenesis of chronic allergic inflammation.

2.2. Treg in allergic diseases

A key role of Treg cells in allergic diseases was first gleaned from Treg cell deficiency due to mutations in the transcription factor FOXP3. Patients carrying such mutations exhibit severe allergic inflammation with elevated serum IgE and manifest allergic disorders such as FA and AD [64]. In mice, depletion of antigen-specific Treg cells by diphtheria toxin in "depletion of regulatory T cell" (DEREG) mice was sufficient to induce a breakdown of oral tolerance [65]. Moreover, a break of oral tolerance associated with increased allergy severity is induced by antibody-mediated depletion of $CD4^+CD25^+$ cells in peanut-sensitized mice [66]. Several studies support the notion that Treg cell destabilization and/or Treg cell loss of function are involved in allergic disease pathogenesis [30,40,67–69]. Deficient suppression of Th cell responses to allergens which are regulated by $CD4^+CD25^+$ Treg has been reported in patients with allergic disease [70].

Both nTreg and iTreg cells participate in maintaining mucosal tolerance, playing distinct immune regulatory roles and responding to different cues. In particular, a prominent role for iTreg cells in maintaining mucosal homeostasis has emerged especially in the gut in the context of a microbe-rich environment. Mice with a specific deletion of the Foxp3 intronic Conserved Non-coding Sequence 1 (CNS1), which is required for iTreg cell differentiation, do not develop fatal autoimmunity but present a pro-allergic phenotype [71]. The development of iTreg cells in the gut is shaped by the microbiota. Particularly relevant are the $ROR\gamma t^+$ iTreg cells which form the majority of iTreg cells in the gut and are strictly dependent on ongoing microbial stimulation. These cells expand around weaning time in conjunction with expanded microbial diversity ushered in by the introduction of solid food. Their deficiency in mice is associated with heightened susceptibility to FA. In contrast, nTreg cells seem to play a role in chronic allergic diseases by undergoing a process of Th2 cell-like reprogramming, which confers Th2 cell-like attributes on these cells.

Several studies show that allergic patients manifest defective allergen-specific Treg cell responses, which are partially or fully restored upon allergen-specific immunotherapy [72]. Indeed, peanut-allergic patients who respond to oral immunotherapy present a quantitative and qualitative increase in antigen-specific Treg cells [73]. The regulatory functions of Treg cells in allergic diseases are mediated by several non-redundant mechanisms and a defect in these functions is also associated with the development of allergic diseases. For example, Treg cell TGFβ1 expression appears to be critical for the regulation of allergic responses especially in the gut, which is relevant to oral tolerance and FA [74,75].

2.3. Role of Treg cells in Asthma

Asthma is a common chronic inflammatory disease of the airways that affects more than 350 million individuals worldwide [76]. Asthma is subdivided into two different types, allergic asthma, which constitutes the majority of cases especially in children, and non-allergic asthma, more common in adults [77]. In this review, we will focus on allergic asthma. Severity in asthma is influenced both by genetic and environmental factors [77–80]. For example, a genetic coding variant in the *IL4R* gene in which a glutamine residue at position 576 of the human IL-4Rα is changed to arginine (*IL4R*^{R576}) is associated with an increase in asthma severity in patients and in a mouse model of allergic airway inflammation [81–84]. Asthma is characterized by excessive allergen-specific CD4$^+$ T cells immune response, enhanced IgE antibodies production, and a massive release of Th2 cytokines such as IL-4, IL-5, and IL-13 [16]. Studies on asthma patients indicated that CD4$^+$ Th cell subsets play a crucial role in asthma pathogenesis. The dysregulated Th immune response, including Th2, Th17 and Tfh cells, produces inflammatory cytokines and chemokines that contribute to the immunopathogenesis of severe asthma [67,85].

Treg cells are critical to maintaining airway tolerance. At steady state, signalling via the IL-33 receptor (IL-33R, also known as ST2) found on a subpopulation of resident lung tissue Treg cells induces expression of the cytokine IL-35, which suppresses IL-17-producing lung innate γδ T cells and consequently restrains the development of allergic airway inflammation [86]. Other studies have shown that adoptive transfer of ovalbumin (OVA)-specific CD4$^+$CD25$^+$ Treg cells into the OVA-sensitized mice attenuated airway hyper-responsiveness and reduced recruitment of eosinophils, and Th2 cytokine expression in the lung following allergen challenge [87].

In addition to reinforcing tolerance in lung tissues, Treg cells act to promote tissue repair [37,38]. Depletion of Treg cells by diphtheria toxin in mice expressing the diphtheria toxin receptor (DTR) specifically in Treg cells significantly decreased epithelial proliferation and lung tissue repair after acute injury in mice [88]. When co-cultured with primary type II alveolar cells (AT2), Foxp3$^+$ Treg cells directly enhanced epithelial AT2 cell proliferation [88]. Indeed, Treg cell transfer in *Rag1*$^{-/-}$ mice decreases fibrosis after LPS injection and promotes lung tissue repair [89]. Mechanistically, Treg cells can reduce lung epithelial CXCL12 production and reduce fibrocyte recruitment [89]. Treg cells can also mediate airway tolerance and tissue repair by controlling other immune cells. For example, Treg cells can inhibit pro-inflammatory macrophage responses that will promote tissue inflammation resolution and ultimately enhance bronchioalveolar stem cell proliferation [89]. Furthermore, the epidermal growth factor family member Areg produced by Treg cells can promote lung tissue repair and regeneration to prevent permanent tissue damage [37,90–92].

2.4. Role of Treg cell subversion in asthma pathogenesis

Cumulative evidence supports the hypothesis that dysregulated Treg cells play a crucial role in the pathogenesis of allergic asthma [17]. Subversion of allergen-specific Treg cells can lead to the loss of their immune regulatory activity and their conversion into Th2 and Th17 T effector-like cells. While this mechanism may have an adaptive role in immunity to helminth infections, it has emerged as a key pathogenic mechanism of allergic diseases including asthma [83,93–95]. Studies have shown that Treg cells from patients with allergic asthma or mouse models of allergic airway inflammation present a shift toward a Th2 cell-like phenotype. For example, asthmatics patients present an increase of CRTH2$^+$ circulating Treg cells, which produce a large amount of IL-4 and show reduced suppressive function, compared to healthy controls [96]. Moreover, mouse lung Treg cells isolated following IL-33-dependent allergen-driven airway inflammation show upregulation of the canonical Th2 transcription factor GATA binding protein 3 (GATA3) and the IL-33 receptor (ST2) along with enhanced secretion of type 2 cytokines [97,98]. In addition, recruited CCR6$^+$ Treg cells are likely to differentiate into Th17-like cells, which could be associated with the pathology of allergic asthma by promoting Th17 responses [99].

The role of Treg cell subversion in allergic airway inflammation and the mechanisms by which this subversion takes effects have been recently clarified. Critical to this subversion is the induced expression of the Notch receptor Notch4 on lung tissue Treg cells in the context of allergic airway inflammation, which subverts their immune tolerance function and promotes Th2 and Th17 tissue responses [11]. Notch4 is upregulated by an IL-6 dependent mechanism, and the magnitude of the upregulation correlates with disease severity in both human subjects with asthma and mouse models of allergic airway inflammation [10,11]. Notch4 activates two main signaling branches, including the WNT/β-catenin and the Hippo pathway, to direct distinct lung tissue Th cell responses. Wnt//β-catenin directs Th2-like Treg cell skewing and promotes ILC2 responses, the latter in part by producing the cytokine GDF-15, which drives ILC2 activation. In contrast, the Hippo pathway directs Treg skewing toward a Th17 cell fate, mediated in part by destabilizing Treg cells through methylation of the *Foxp3* CNS2 element [11]. Treg cell-specific deletion of the gene encoding WNT pathway effector/β-catenin suppressed the Th2 and ILC2 cell responses in allergic airway inflammation. Reciprocally, Treg cell-specific deletion of the genes encoding the Hippo pathways effectors Yap1 and TAZ suppressed the lung tissue Th17 cell responses (Fig. 1). These findings illustrated the critical role of lung tissue Treg cells in allergic airway inflammation and the modularity of the regulatory responses in controlling distinct aspects of tissue inflammation in asthma.

2.5. Viral infections, Asthma and Treg cells

A confluence of studies now supports the hypothesis that asthma development is influenced by respiratory viral infections in early life [100]. Furthermore, asthma exacerbations can be triggered by respiratory viruses, notably human rhinovirus (HRV) and respiratory syncytial virus (RSV) [101,102]. Respiratory viral infections may potentiate airway allergic inflammation and lung eosinophilia by augmenting allergic sensitization and Th2 responses [93,103–107]. Early infection with RSV has been shown to be closely associated with the development of asthma by skewing the immune response towards a Th2 phenotype.

A role for Treg cells in virus-induced asthma has been suggested. Treg cells from healthy subjects and those with asthma displayed an anti-viral response after HRV infection and showed reduced suppressive capacity, suggesting that Treg cell function might be impaired or altered during RSV infection [108]. Novel functions for Treg cells have been identified in shaping the CD4$^+$ effector T cell response during RSV infection and promoting resolution of pathology [109]. Treg cells may also play an important role in the association between HRV and the development of asthma and asthma exacerbations [108]. Lung tissue Treg cells are subverted in the context of severe viral infections including influenza and SARS-CoV2, with heightened expression of Notch4, suggesting that common subversion mechanisms may be operative in allergic and virus-induced asthma [90]. Causal association and mechanistic studies on early-life viral infections and later asthma development will help us to better understand asthma pathogenesis and highlight a potential therapeutic target in the treatment of asthma disease.

2.6. Treg cells in AD

AD is a common chronic inflammatory skin disease that affects 15%− 20% of children and is the first step of the “atopic march” that can lead to the development of FA and asthma [110,111]. AD is characterized by a Th2-dominated skin inflammation ushered in by a defective skin barrier, with dermal infiltration by CD4$^+$ Th2 cells and eosinophils, along with increased cutaneous expression of Th2 cytokines such as IL-4

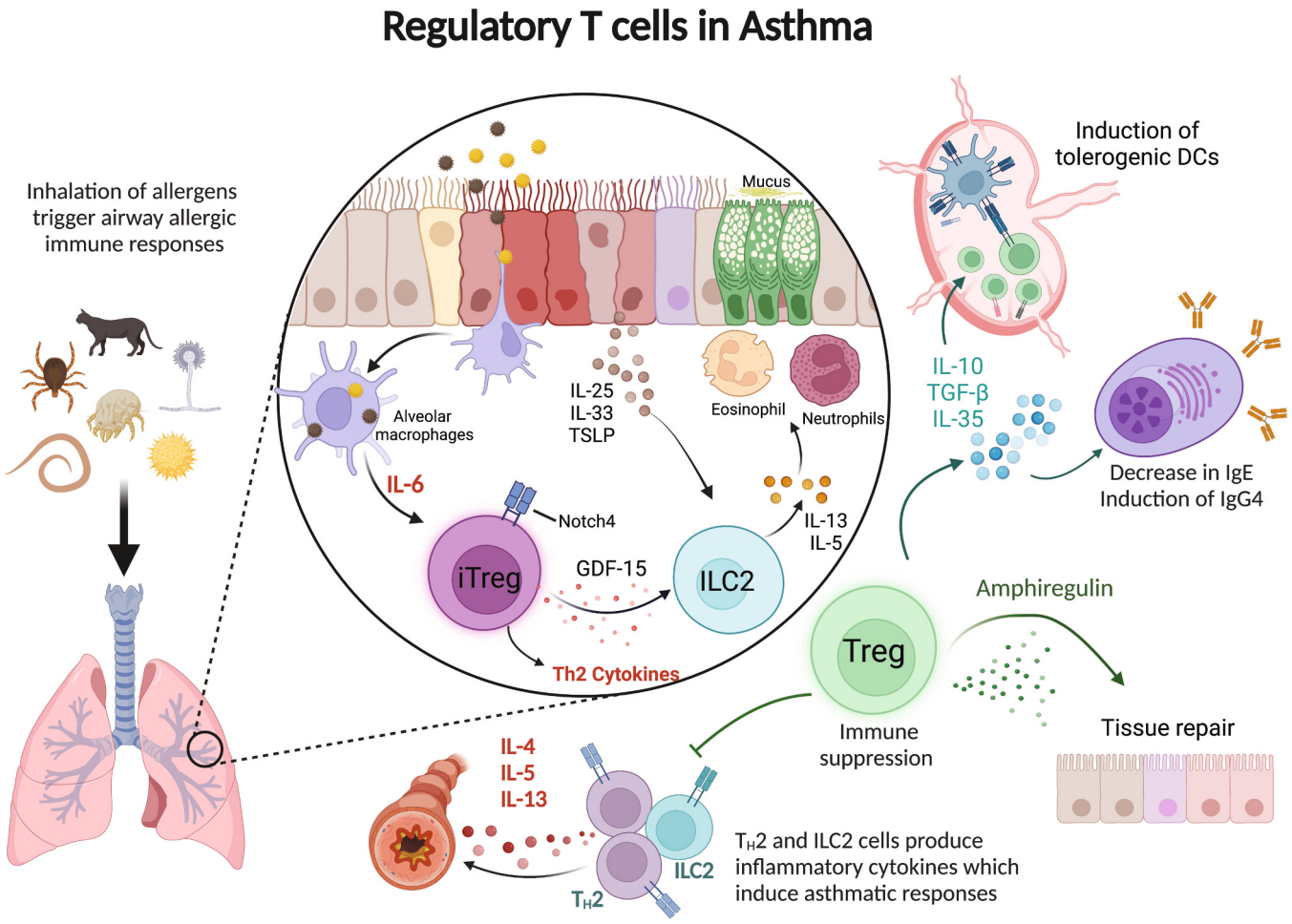

Fig. 1. Regulatory T cells in Asthma. At steady state, Treg cells control innate and adaptive airway tissue immune responses and also promote tissue repair through the secretion of cytokines such as Areg. Upon aeroallergen exposure, airway epithelial cells will produce alarmins, including IL-25, IL-33, TSLP, to activate ILC2 and other innate and adaptive immune cells. Production by alveolar macrophages of IL-6 will promote Treg destabilization through a Notch4-dependent mechanism. Notch4^{+} Treg cells will also produce Th2 cytokines and GDF-15 that will promote ILC2 activation and cytokine production. The schematics were prepared using BioRender.

and IL-13, high serum IgE production and eosinophilia [110,111]. The skin type 2 immune response, which normally plays a critical role in skin wound healing [112], is also essential for AD development and persistence as illustrated by studies in patients with eczema as a consequence of primary atopic disorders due to inborn errors of immunity and also in relevant mouse models of AD [113–115]. These observations are consistent with AD being a form of dysregulated, type 2 immunity-mediated tissue repair response instigated by a defective skin barrier function [116].

Treg cells are abundant in the skin, where they are seeded early in life to mediate tolerance to the skin microbiota [43,117]. A majority of skin Treg cells express the transcription factor GATA3 [118,119], consistent with their function in tissue repair together with other type 2 immune response components including ILC2 and Th2 cells. They also have been reported to express the retinoic acid receptor-related orphan receptor α (RORα), which may help restrain dysregulated type 2 immune responses in the skin [120]. Skin Treg cells also express alarmin receptors including IL-33R and TSLPR [121,122], which allows them to sense tissue damage and to co-mobilize with the ensuing type 2 immune response to promote damage repair, made possible by alarmin-induced Treg cell production of Areg [37].

The role of Treg cells in AD was initially suggested by the observation that patients with IPEX due to loss of function FOXP3 mutations present with AD as a key manifestation of their disease [22,123]. An increase in Foxp3^{+} Treg cells has been observed in patients with AD, in the allergen-exposed skin area and in the secondary lymphoid organs in an AD model [124,125]. Treg cells in AD have also been observed to exhibit a Th2 cell-like phenotype [126], suggesting they are co-opted in a process of Th2 cell-like reprogramming. Such a process has been previously described in FA and shown to contribute to disease pathogenesis [94]. The extent to which Th2 cell-like reprogramming of Treg cells also contributes to AD remains to be established.

Relevant to the issue of immune dysregulation in AD is the role of the changed skin microbiome in driving Treg cell dysfunction in this disease. Skin Treg cells co-localize with the commensal bacteria at the hair follicles [127,128] and are decreased in germ-free mice, consistent with a role of the microbiome in driving Treg cell skin expansion [127]. The skin microbiome is altered in AD, with near universal colonization by strains of *S. aureus* that frequently produce superantigenic toxins [129]. Patients with more severe AD exhibit *S. aureus* predominance while patients with less severe disease show *S. epidermidis* predominance [130]. *S. aureus* isolates from AD patients with more severe flares induced epidermal thickening and expansion of cutaneous Th2 and Th17 cells in a mouse skin colonization model [130]. In related studies, impaired skin Treg cell-mediated immunoregulation promotes type-2 cytokine production by commensal-specific plastic Th17 cells [118]. Overall, these findings point to a confluence of the skin dysbiotic process in AD, the skin Treg cell dysfunction, and the dysregulated Th2 immunity that merit further future studies.

2.7. Treg cells in FA

Foxp3$^+$ Treg cells in the gut mediate active tolerance to a wide and ever-changing variety of foods while simultaneously enforcing tolerance to the gut microbiota, which presents the heaviest microbial load in the body [131]. The maintenance of tolerance in the gut is further compounded by the different anatomical regions involved, each endowed with a distinct microbial community, and by nutritional and microbial changes occurring during development. These include the early life seeding of the gut microbiota with the dominance of milk-dependent microbial taxa such as *Bifidobacteria* followed by a shift towards blooming Clostridiales and Bacteroidetes taxa promoted by the introduction of solid food during the peri-weaning period [132]. The complexity of these changes is reflected by the diversity of Foxp3$^+$ Treg cells populations in the gut and their respective effector mechanisms. In particular, a large proportion of Treg cells in the gut are iTreg cells derived from naïve CD4$^+$ T cells that differentiate extrathymically in the mesenteric draining lymph nodes and are particularly enriched in the lamina propria [133,131,44,45]. These cells are critically required for maintaining oral tolerance to gut microbiota and food antigens and are preferentially imprinted with gut-homing molecules such as integrin α4β7 and the chemokine receptor CCR9, allowing them to localize in the intestinal lamina propria [134].

A majority of the gut iTreg cells express the RAR-related orphan receptor gamma t (RORγt) [44–46]. These cells differentiate under the direct influence of the microbiota and become particularly enriched in the gut at around the weaning time [135]. Studies in mice indicate that these cells are long-lived and mediate tolerance into adulthood [136]. The differentiation of RORγt $^+$ Treg cells results from the confluence of three distinct sets of signals. The first involves antigen presentation by MHCII$^+$ antigen-presenting cells (APCs) that also express RORγt$^+$, including ILC3 and the newly described Thetis cells, the latter being dominant in early life [137–139] (reviewed in [140]). The second signal involves a TGFβ1-dependent mechanism that is mediated by αVβ8 integrin on the APCs [137–139], with differentiating iTreg cells likely providing the latent TGFβ1 source [131,132]. Finally, the differentiation of RORγt$^+$ is further directed by microbial metabolites including but not limited to secondary bile acids [136–138].

Defects in the microbiota/RORγt$^+$ Treg cell axis have been implicated in the pathogenesis of FA. First, Treg cell-specific deletion of *Rorc*, encoding RORγt, exhibits increased serum IgE and heightened susceptibility to FA [38,133]. In several mouse models of FA, including one with a gain of function mutation in the IL-4Ra chain (*Il4ra*^{F709}) and another with Treg cell-specific deletion of *Tgfb1*, susceptibility to FA is associated with deficient RORγt$^+$ Treg cells in the gut. In both mouse models, both the susceptibility to FA and the RORγt$^+$ Treg cell deficiency could be corrected by treatment with immunomodulatory commensal *Clostridia* and *Bacteroidetes* species. However, the capacity of commensal bacteria to rescue FA in these mice is strictly contingent on the competency of RORγt expression in Treg cells. The capacity of the immunomodulatory *Clostridia* and *Bacteroidetes* bacteria to upregulate RORγt$^+$ Treg cell differentiation was dependent on Treg cell-intrinsic signaling via the toll-like receptor (TLR) coupled adaptor MyD88 [38,133]. Treg cell-specific MyD88 deletion impaired RORγt$^+$ Treg cell differentiation in the gut, indicative of a role for TLR/MyD88 signaling in the induction of this Treg cell subset in the gut.

The importance of the microbiota/ RORγt$^+$ Treg cell axis in FA can also be inferred from human studies. Thus, patients with FA exhibit decreased frequency of RORγt$^+$ Treg cell in circulation [141]. Analyses of the gut microbiota of human subjects with FA reveal the presence of dysbiosis associated with alterations in immunomodulatory bacteria. The functional significance of this dysbiosis was revealed in studies whereby the microbiota of human subjects with FA but not those of control subjects failed to support effective RORγt$^+$ Treg cell differentiation or provide protection from FA when transplanted into germ-free mice. Collectively, the mouse and human data give rise to the concept of a microbial origin of FA, whereby dysbiosis in human subjects with FA results in failure of effective microbiota-directed differentiation of RORγt$^+$ Treg cells, resulting in susceptibility to FA [131,135]. Such a dysbiosis may occur early in life due to diverse factors, including among others antibiotic treatment or cesarian delivery, or may emerge later in life due to insults that impact the integrity of the gut microbiota.

In addition to RORγt$^+$ Treg cell deficiency, FA is associated with the expansion of Helios$^+$ Treg cells the exhibit heightened expression of the transcription factor GATA3 and otherwise manifest attributes associated with Th2 cell-skewing including increased expression of the cytokines IL-4 and IL-13 [142]. This pathogenic process, which was also observed in human FA subjects, appears critical in promoting disease susceptibility as Treg cell-specific deletion of a genetic cassette encompassing the *Il4* and *Il13* genes greatly attenuated disease severity in mice [94,142]. The expansion of pathogenic Th2 cell-like reprogrammed Treg cells coincident with the contraction of the RORγt$^+$ Treg cell population suggests that the two populations may compete for the same niche. This could involve competition for IL-2 produced by antigen-specific T cells [143] and ILC3 cells [144]. The emergence of pathogenic Th2 cell-like reprogrammed Treg cells may be abetted by dysbiosis-driven activation of innate immune cells driving type 2 (allergic) skewing including Tuft cells and ILC2. The former may sense changes in luminal metabolites including succinate to drive ILC2 expansion by secreting IL-25 [145–149].

The Treg cell disturbances in FA have direct bearing on the regulation of allergy-promoting innate immune cells. RORγt$^+$ Treg cells are critical in restraining mast cell expansion and activation by a TGFβ1-dependent mechanism [46,74]. Reciprocally, Th2 cell-like reprograming impairs the capacity of Treg cells to suppress ILC2 activation in FA [150]. Yet another instance where Treg cell disturbances impact FA is at the level of the IgE response. A subpopulation of Th2-skewed T follicular helper (Tfh) cells is critical for the development of pathogenic high-affinity IgE responses relevant to anaphylaxis to foods and also allergic airway inflammation. This population, termed T follicular helper cells 13 (Tfh13), co-expresses GATA3 and Bcl6, has Th2 cytokine profile (IL-4^{hi}IL-13^{hi}IL-5^{hi}IL-21^{lo}), and activates IgE class switching in B cells by virtue of IL-4 secretion [151–153]. The capacity of Tfh13 cells to promote IgE responses is restrained by Foxp3$^+$ T follicular regulatory cells (Tfr). These cells develop from Foxp3$^+$ Tregs residing in the B cell follicles and have a context-dependent function in allergic diseases, acting as repressors or helpers of the IgE response [154,155] (Fig. 2). Importantly, the balance between Tfr and Tfh dictates B cell activation and antibody production. Depletion of Tfr cells exacerbates the Tfh13 response and potentiates high-affinity allergen-specific IgE production [151]. Treg cell-intrinsic microbial signaling acting via the TLR adaptor MyD88 may also shape the differentiation and function of Tfr cells in the gut relevant to allergic diseases [42].

Seeking to use the capacity of some bacteria to induce tolerance-promoting RORγt$^+$ Treg cells, therapeutic strategies using targeted mono- or poly- bacteriotherapy for re-establishing oral tolerance in mouse models have been developed [141,156]. The capacity to manipulate the regulatory response induced by the microbiota through the production of different metabolites and the implication for engineered bacteriotherapy further expands the horizon for novel therapies, but additional and in-depth investigations are required. Overall, microbiota-based, Treg cell-targeted approaches could be an efficient strategy for restoring oral tolerance in FA.

3. Conclusion

While Treg cells play a key role in suppressing responses to allergens in different allergic diseases, cumulative evidence suggests that their function may be subverted in the context of chronic allergic inflammation, leading to their reprogramming into pathogenic pro-inflammatory cells. The dual nature of Treg cells in suppressing or promoting allergic diseases in a context-dependent manner provides novel opportunities for

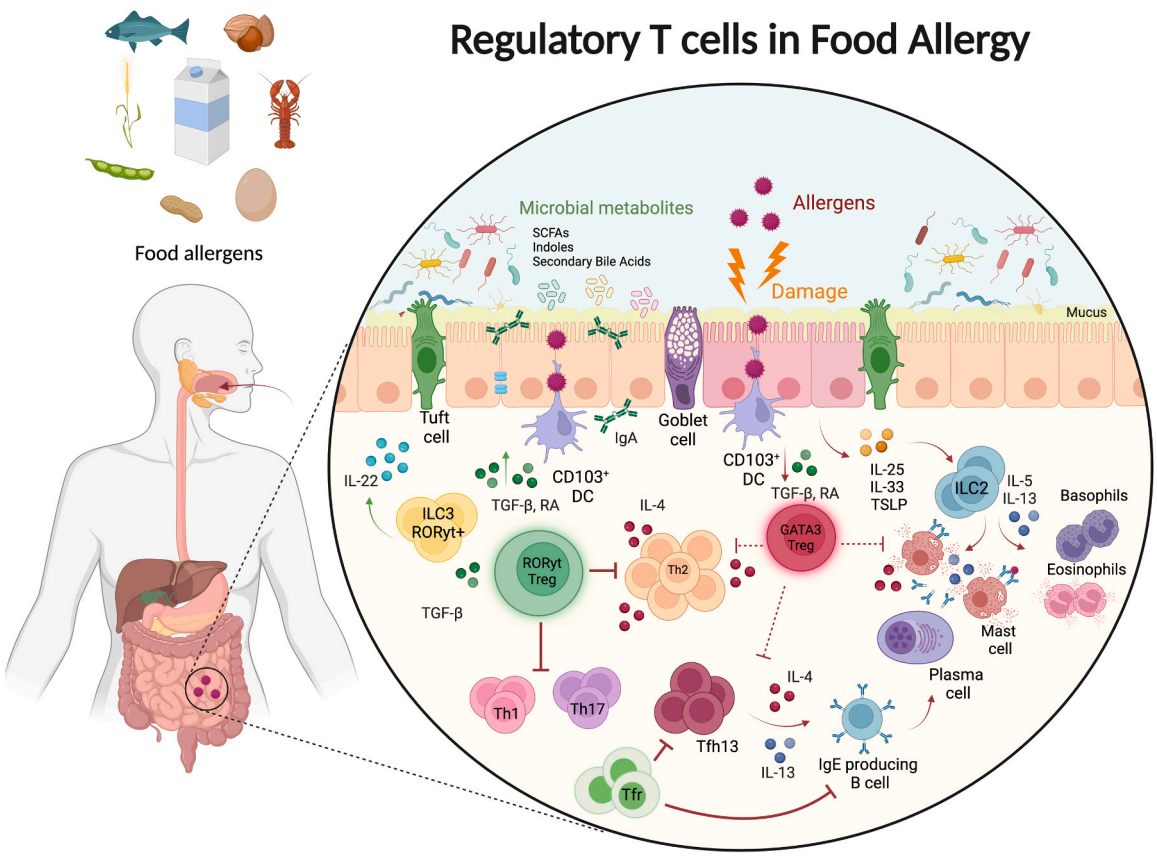

Fig. 2. Role of Treg in FA. Under homeostatic conditions, antigen presenting cells (APCs) like CD103$^+$ dendritic cells (DCs) and RORγt$^+$ innate lymphoid cells type 3 (ILC3s) sample the gut lumen and promote the expansion of RORγt$^+$ iTreg cells. Commensal bacteria and derived metabolites promote barrier integrity and contribute to the development of nascent iTreg cells and their differentiation into RORγt$^+$ by MyD88 signaling-dependent mechanisms. RORγt$^+$ Treg cells suppress allergen-specific Th2 cell responses and mast cell activation. Treg cells also suppress ILC2 activation, while Tfr cells constrain Tfh13 differentiation. Defects in the microbiota/RORγt$^+$ Treg cells axis have been implicated in the pathogenesis of FA by disrupting the barrier integrity and impairing the differentiation of RORγt$^+$ Treg cells in favor of Treg cells with a Th2-cell-like phenotype. These Th2-reprogrammed Treg cells express GATA3 and produce IL-4 and IL-13, leading to exaggerated tissue ILC2 and Th2 responses, mast cell expansion, dysregulated Tfh13 activation and specific IgE antibody responses. The schematics were prepared using BioRender.

targeted precision therapies to restore tissue tolerance in these disorders.

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References

[1] S.J. Galli, M. Tsai, A.M. Piliponsky, The development of allergic inflammation, Nature 454 (7203) (2008) 445–454.
[2] T.A. Platts-Mills, The allergy epidemics: 1870-2010, J. Allergy Clin. Immunol. 136 (1) (2015) 3–13.
[3] N.W. Palm, R.K. Rosenstein, R. Medzhitov, Allergic host defences, Nature 484 (7395) (2012) 465–472.
[4] W.C. Gause, T.A. Wynn, J.E. Allen, Type 2 immunity and wound healing: evolutionary refinement of adaptive immunity by helminths, Nat. Rev. Immunol. 13 (8) (2013) 607–614.
[5] L. Tordesillas, M.C. Berin, H.A. Sampson, Immunology of Food Allergy, Immunity 47 (1) (2017) 32–50.
[6] E.B. Florsheim, et al., Food allergy as a biological food quality control system, Cell 184 (6) (2021) 1440–1454.
[7] L.E. Cheng, R.M. Locksley, Allergic inflammation–innately homeostatic, Cold Spring Harb. Perspect. Biol. 7 (3) (2014), a016352.
[8] C.A. Akdis, et al., Type 2 immunity in the skin and lungs, Allergy 75 (7) (2020) 1582–1605.
[9] Q. Chen, et al., Development of allergen-specific IgE in a food-allergy model requires precisely timed B cell stimulation and is inhibited by Fgl2, Cell Rep. 39 (13) (2022), 110990.
[10] M. Benamar, et al., A common IL-4 receptor variant promotes asthma severity via a T(reg) cell GRB2-IL-6-Notch4 circuit, Allergy 77 (11) (2022) 3377–3387.
[11] H. Harb, et al., A regulatory T cell Notch4-GDF15 axis licenses tissue inflammation in asthma, Nat. Immunol. 21 (11) (2020) 1359–1370.
[12] R. Ebina-Shibuya, W.J. Leonard, Role of thymic stromal lymphopoietin in allergy and beyond, Nat. Rev. Immunol. 23 (1) (2023) 24–37.
[13] F.Y. Liew, J.P. Girard, H.R. Turnquist, Interleukin-33 in health and disease, Nat. Rev. Immunol. 16 (11) (2016) 676–689.
[14] M. Xu, C. Dong, IL-25 in allergic inflammation, Immunol. Rev. 278 (1) (2017) 185–191.
[15] F. Roan, K. Obata-Ninomiya, S.F. Ziegler, Epithelial cell-derived cytokines: more than just signaling the alarm, J. Clin. Invest 129 (4) (2019) 1441–1451.
[16] M. Noval Rivas, T.A. Chatila, Regulatory T cells in allergic diseases, J. Allergy Clin. Immunol. 138 (3) (2016) 639–652.
[17] H. Harb, T.A. Chatila, Regulatory T-cells in asthma, Curr. Opin. Allergy Clin. Immunol. (2023).
[18] S. Sakaguchi, et al., Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases, J. Immunol. 155 (3) (1995) 1151–1164.
[19] S. Sakaguchi, Naturally arising Foxp3-expressing CD25+CD4+ regulatory T cells in immunological tolerance to self and non-self, Nat. Immunol. 6 (4) (2005) 345–352.
[20] S.Z. Josefowicz, L.F. Lu, A.Y. Rudensky, Regulatory T cells: mechanisms of differentiation and function, Annu Rev. Immunol. 30 (2012) 531–564.
[21] C. Benoist, D. Mathis, Treg cells, life history, and diversity, Cold Spring Harb. Perspect. Biol. 4 (9) (2012), a007021.
[22] T.A. Chatila, et al., JM2, encoding a fork head-related protein, is mutated in X-linked autoimmunity-allergic disregulation syndrome, J. Clin. Invest 106 (12) (2000) R75–R81.

[23] C.L. Bennett, et al., The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3, Nat. Genet 27 (1) (2001) 20–21.
[24] M.E. Brunkow, et al., Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse, Nat. Genet 27 (1) (2001) 68–73.
[25] W. Lin, et al., Regulatory T cell development in the absence of functional Foxp3, Nat. Immunol. 8 (4) (2007) 359–368.
[26] L.M. Charbonnier, et al., Functional reprogramming of regulatory T cells in the absence of Foxp3, Nat. Immunol. 20 (9) (2019) 1208–1219.
[27] J.D. Fontenot, M.A. Gavin, A.Y. Rudensky, Foxp3 programs the development and function of CD4+CD25+ regulatory T cells, Nat. Immunol. 4 (4) (2003) 330–336.
[28] M. Larche, Regulatory T cells in allergy and asthma, Chest 132 (3) (2007) 1007–1014.
[29] M.A. Khan, Regulatory T cells mediated immunomodulation during asthma: a therapeutic standpoint, J. Transl. Med 18 (1) (2020) 456.
[30] O. Palomares, et al., Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells, Immunol. Rev. 278 (1) (2017) 219–236.
[31] T. Boonpiyathad, et al., Il-10 producing T and B cells in allergy, Semin Immunol. 44 (2019), 101326.
[32] J. Zhang, et al., Regulatory T Cells, a Viable Target Against Airway Allergic Inflammatory Responses in Asthma, Front Immunol. 13 (2022), 902318.
[33] C.E. Tadokoro, et al., Regulatory T cells inhibit stable contacts between CD4+ T cells and dendritic cells in vivo, J. Exp. Med 203 (3) (2006) 505–511.
[34] A. Schmidt, N. Oberle, P.H. Krammer, Molecular mechanisms of treg-mediated T cell suppression, Front Immunol. 3 (2012) 51.
[35] D.K. Sojka, Y.H. Huang, D.J. Fowell, Mechanisms of regulatory T-cell suppression - a diverse arsenal for a moving target, Immunology 124 (1) (2008) 13–22.
[36] A.N. Thorburn, P.M. Hansbro, Harnessing regulatory T cells to suppress asthma: from potential to therapy, Am. J. Respir. Cell Mol. Biol. 43 (5) (2010) 511–519.
[37] N. Arpaia, et al., A Distinct Function of Regulatory T Cells in Tissue Protection, Cell 162 (5) (2015) 1078–1089.
[38] J. Wu, et al., Regulatory T cells in skeletal muscle repair and regeneration: recent insights, Cell Death Dis. 13 (8) (2022) 680.
[39] P. de Candia, et al., Regulatory T cells as metabolic sensors, Immunity 55 (11) (2022) 1981–1992.
[40] C. Campbell, A. Rudensky, Roles of Regulatory T Cells in Tissue Pathophysiology and Metabolism, Cell Metab. 31 (1) (2020) 18–25.
[41] M. Panduro, C. Benoist, D. Mathis, Tissue Tregs, Annu Rev. Immunol. 34 (2016) 609–633.
[42] S. Wang, et al., MyD88 Adaptor-Dependent Microbial Sensing by Regulatory T Cells Promotes Mucosal Tolerance and Enforces Commensalism, Immunity 43 (2) (2015) 289–303.
[43] T.C. Scharschmidt, et al., A Wave of Regulatory T Cells into Neonatal Skin Mediates Tolerance to Commensal Microbes, Immunity 43 (5) (2015) 1011–1021.
[44] E. Sefik, et al., MUCOSAL IMMUNOLOGY. Individual intestinal symbionts induce a distinct population of RORgamma(+) regulatory T cells, Science 349 (6251) (2015) 993–997.
[45] C. Ohnmacht, et al., MUCOSAL IMMUNOLOGY. The microbiota regulates type 2 immunity through RORgammat(+) T cells, Science 349 (6251) (2015) 989–993.
[46] J. van der Veeken, et al., Genetic tracing reveals transcription factor Foxp3-dependent and Foxp3-independent functionality of peripherally induced Treg cells, Immunity 55 (7) (2022) 1173–1184 e7.
[47] M.A. Curotto de Lafaille, J.J. Lafaille, Natural and adaptive foxp3+ regulatory T cells: more of the same or a division of labor? Immunity 30 (5) (2009) 626–635.
[48] A.M. Bilate, J.J. Lafaille, Induced CD4+Foxp3+ regulatory T cells in immune tolerance, Annu Rev. Immunol. 30 (2012) 733–758.
[49] M. Asano, et al., Autoimmune disease as a consequence of developmental abnormality of a T cell subpopulation, J. Exp. Med 184 (2) (1996) 387–396.
[50] N. Ohkura, Y. Kitagawa, S. Sakaguchi, Development and maintenance of regulatory T cells, Immunity 38 (3) (2013) 414–423.
[51] E.G. Schmitt, C.B. Williams, Generation and function of induced regulatory T cells, Front Immunol. 4 (2013) 152.
[52] W. Chen, et al., Conversion of peripheral CD4+CD25- naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3, J. Exp. Med 198 (12) (2003) 1875–1886.
[53] T.S. Davidson, et al., Cutting Edge: IL-2 is essential for TGF-beta-mediated induction of Foxp3+ T regulatory cells, J. Immunol. 178 (7) (2007) 4022–4026.
[54] S. Xiao, et al., Retinoic acid increases Foxp3+ regulatory T cells and inhibits development of Th17 cells by enhancing TGF-beta-driven Smad3 signaling and inhibiting IL-6 and IL-23 receptor expression, J. Immunol. 181 (4) (2008) 2277–2284.
[55] M. Martinez-Blanco, et al., Retinoic Acid Induces Functionally Suppressive Foxp3(+)RORgammat(+) T Cells In Vitro, Front Immunol. 12 (2021), 675733.
[56] C.S. Hsieh, et al., Recognition of the peripheral self by naturally arising CD25+ CD4+ T cell receptors, Immunity 21 (2) (2004) 267–277.
[57] D. Haribhai, et al., A requisite role for induced regulatory T cells in tolerance based on expanding antigen receptor diversity, Immunity 35 (1) (2011) 109–122.
[58] S. Sakaguchi, et al., The plasticity and stability of regulatory T cells, Nat. Rev. Immunol. 13 (6) (2013) 461–467.
[59] M.A. Koch, et al., The transcription factor T-bet controls regulatory T cell homeostasis and function during type 1 inflammation, Nat. Immunol. 10 (6) (2009) 595–602.
[60] B.H. Yang, et al., Foxp3(+) T cells expressing RORgammat represent a stable regulatory T-cell effector lineage with enhanced suppressive capacity during intestinal inflammation, Mucosal Immunol. 9 (2) (2016) 444–457.
[61] Y. Chung, et al., Follicular regulatory T cells expressing Foxp3 and Bcl-6 suppress germinal center reactions, Nat. Med 17 (8) (2011) 983–988.
[62] E.A. Wohlfert, et al., GATA3 controls Foxp3(+) regulatory T cell fate during inflammation in mice, J. Clin. Invest 121 (11) (2011) 4503–4515.
[63] Y. Wang, M.A. Su, Y.Y. Wan, An essential role of the transcription factor GATA-3 for the function of regulatory T cells, Immunity 35 (3) (2011) 337–348.
[64] W. Lin, et al., Allergic dysregulation and hyperimmunoglobulinemia E in Foxp3 mutant mice, J. Allergy Clin. Immunol. 116 (5) (2005) 1106–1115.
[65] U. Hadis, et al., Intestinal tolerance requires gut homing and expansion of FoxP3 + regulatory T cells in the lamina propria, Immunity 34 (2) (2011) 237–246.
[66] F. van Wijk, et al., CD4+CD25+ T cells regulate the intensity of hypersensitivity responses to peanut, but are not decisive in the induction of oral sensitization, Clin. Exp. Allergy 37 (4) (2007) 572–581.
[67] W. Chen, et al., The mechanisms of effector Th cell responses contribute to treg cell function: new insights into pathogenesis and therapy of asthma, Front. Immunol. 13 (2022), 862866.
[68] Y.E. Yao, et al., gammadeltaT17/gammadeltaTreg cell subsets: a new paradigm for asthma treatment, J. Asthma 59 (10) (2022) 2028–2038.
[69] H. Sbihi, et al., Thinking bigger: How early-life environmental exposures shape the gut microbiome and influence the development of asthma and allergic disease, Allergy 74 (11) (2019) 2103–2115.
[70] Y.H. Shi, et al., An increased ratio of Th2/Treg cells in patients with moderate to severe asthma, Chin. Med J. (Engl.) 126 (12) (2013) 2248–2253.
[71] S.Z. Josefowicz, et al., Extrathymically generated regulatory T cells control mucosal TH2 inflammation, Nature 482 (7385) (2012) 395–399.
[72] A. Abdel-Gadir, A.H. Massoud, T.A. Chatila, Antigen-specific Treg cells in immunological tolerance: implications for allergic diseases, F1000Res 7 (2018) 38.
[73] A. Syed, et al., Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3), J. Allergy Clin. Immunol. 133 (2) (2014) 500–510.
[74] J.A. Turner, et al., Regulatory T cell-derived TGF-beta1 controls multiple checkpoints governing allergy and autoimmunity, Immunity 53 (6) (2020) 1202–1214 e6.
[75] E. Stephen-Victor, et al., Essential functions of regulatory T cell TGF-beta1 revealed by differential gene-targeting approaches, Immunity 54 (3) (2021) 397–398.
[76] Z.I. Komlosi, et al., Cellular and molecular mechanisms of allergic asthma, Mol. Asp. Med. 85 (2022), 100995.
[77] H. Hammad, B.N. Lambrecht, The basic immunology of asthma, Cell 184 (6) (2021) 1469–1485.
[78] E. von Mutius, D. Vercelli, Farm living: effects on childhood asthma and allergy, Nat. Rev. Immunol. 10 (12) (2010) 861–868.
[79] D. Vercelli, Discovering susceptibility genes for asthma and allergy, Nat. Rev. Immunol. 8 (3) (2008) 169–182.
[80] F.D. Martinez, D. Vercelli, Asthma, Lancet 382 (9901) (2013) 1360–1372.
[81] M. Benamar, et al., A common IL-4 receptor variant promotes asthma severity via a Treg cell GRB2-IL-6-Notch4 circuit, Allergy (2022).
[82] G.K. Hershey, et al., The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor, N. Engl. J. Med 337 (24) (1997) 1720–1725.
[83] A.H. Massoud, et al., An asthma-associated IL4R variant exacerbates airway inflammation by promoting conversion of regulatory T cells to TH17-like cells, Nat. Med 22 (9) (2016) 1013–1022.
[84] R. Tachdjian, et al., Pathogenicity of a disease-associated human IL-4 receptor allele in experimental asthma, J. Exp. Med 206 (10) (2009) 2191–2204.
[85] J. Jeong, H.K. Lee, The Role of CD4(+) T Cells and Microbiota in the Pathogenesis of Asthma, Int J. Mol. Sci. 22 (2021) 21.
[86] L.D. Faustino, et al., Interleukin-33 activates regulatory T cells to suppress innate gammadelta T cell responses in the lung, Nat. Immunol. 21 (11) (2020) 1371–1383.
[87] J. Kearley, et al., Resolution of airway inflammation and hyperreactivity after in vivo transfer of CD4+CD25+ regulatory T cells is interleukin 10 dependent, J. Exp. Med 202 (11) (2005) 1539–1547.
[88] J.R. Mock, et al., Foxp3+ regulatory T cells promote lung epithelial proliferation, Mucosal Immunol. 7 (6) (2014) 1440–1451.
[89] B.T. Garibaldi, et al., Regulatory T cells reduce acute lung injury fibroproliferation by decreasing fibrocyte recruitment, Am. J. Respir. Cell Mol. Biol. 48 (1) (2013) 35–43.
[90] H. Harb, et al., Notch4 signaling limits regulatory T-cell-mediated tissue repair and promotes severe lung inflammation in viral infections, Immunity 54 (6) (2021) 1186–1199 e7.
[91] D. Burzyn, et al., A special population of regulatory T cells potentiates muscle repair, Cell 155 (6) (2013) 1282–1295.
[92] K.A. Kaiser, et al., Regulation of the alveolar regenerative niche by amphiregulin-producing regulatory T cells, J. Exp. Med 220 (2023) 3.
[93] N. Krishnamoorthy, et al., Early infection with respiratory syncytial virus impairs regulatory T cell function and increases susceptibility to allergic asthma, Nat. Med 18 (10) (2012) 1525–1530.
[94] M. Noval Rivas, et al., Regulatory T cell reprogramming toward a Th2-cell-like lineage impairs oral tolerance and promotes food allergy. Immunity 42 (3) (2015) 512–523.
[95] V.S. Pelly, et al., Interleukin 4 promotes the development of ex-Foxp3 Th2 cells during immunity to intestinal helminths, J. Exp. Med 214 (6) (2017) 1809–1826.
[96] T. Boonpiyathad, et al., Impact of high-altitude therapy on type-2 immune responses in asthma patients, Allergy 75 (1) (2020) 84–94.

[97] T. Boonpiyathad, et al., Der p 1-specific regulatory T-cell response during house dust mite allergen immunotherapy, Allergy 74 (5) (2019) 976–985.
[98] C.C. Chen, et al., IL-33 dysregulates regulatory T cells and impairs established immunologic tolerance in the lungs, J. Allergy Clin. Immunol. 140 (5) (2017) 1351–1363 e7.
[99] X. Shen, et al., Reduced CCR6(+)IL-17A(+)Treg Cells in Blood and CCR6-Dependent Accumulation of IL-17A(+)Treg Cells in Lungs of Patients With Allergic Asthma, Front Immunol. 12 (2021), 710750.
[100] T. Jartti, J.E. Gern, Role of viral infections in the development and exacerbation of asthma in children, J. Allergy Clin. Immunol. 140 (4) (2017) 895–906.
[101] D.J. Jackson, et al., Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children, Am. J. Respir. Crit. Care Med 178 (7) (2008) 667–672.
[102] M. Caliskan, et al., Rhinovirus wheezing illness and genetic risk of childhood-onset asthma, N. Engl. J. Med 368 (15) (2013) 1398–1407.
[103] P.W. Tebbey, M. Hagen, G.E. Hancock, Atypical pulmonary eosinophilia is mediated by a specific amino acid sequence of the attachment (G) protein of respiratory syncytial virus, J. Exp. Med 188 (10) (1998) 1967–1972.
[104] J. Schwarze, et al., Respiratory syncytial virus infection results in airway hyperresponsiveness and enhanced airway sensitization to allergen, J. Clin. Invest 100 (1) (1997) 226–233.
[105] M. Roman, et al., Respiratory syncytial virus infection in infants is associated with predominant Th-2-like response, Am. J. Respir. Crit. Care Med 156 (1) (1997) 190–195.
[106] N. Sigurs, et al., Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7, Am. J. Respir. Crit. Care Med 161 (5) (2000) 1501–1507.
[107] X. Hu, et al., Respiratory Syncytial Virus Exacerbates OVA-mediated asthma in mice through C5a-C5aR regulating CD4(+)T cells Immune Responses, Sci. Rep. 7 (1) (2017) 15207.
[108] K. Jansen, et al., Loss of regulatory capacity in Treg cells following rhinovirus infection, J. Allergy Clin. Immunol. 148 (4) (2021) 1016–1029 e16.
[109] L.R. Durant, et al., Regulatory T cells prevent Th2 immune responses and pulmonary eosinophilia during respiratory syncytial virus infection in mice, J. Virol. 87 (20) (2013) 10946–10954.
[110] S. Stander, Atopic Dermatitis, N. Engl. J. Med 384 (12) (2021) 1136–1143.
[111] C.Ft Schuler, et al., Novel insights into atopic dermatitis, J. Allergy Clin. Immunol. (2022).
[112] I.C. Boothby, J.N. Cohen, M.D. Rosenblum, Regulatory T cells in skin injury: At the crossroads of tolerance and tissue repair, Sci. Immunol. 5 (2020) 47.
[113] J.D. Milner, Primary Atopic Disorders, Annu Rev. Immunol. 38 (2020) 785–808.
[114] S. Nakajima, et al., Insights into atopic dermatitis gained from genetically defined mouse models, J. Allergy Clin. Immunol. 143 (1) (2019) 13–25.
[115] S. Baris, et al., Severe allergic dysregulation due to a gain of function mutation in the transcription factor STAT6, J. Allergy Clin. Immunol. (2023).
[116] T. Dainichi, et al., The epithelial immune microenvironment (EIME) in atopic dermatitis and psoriasis, Nat. Immunol. 19 (12) (2018) 1286–1298.
[117] T.C. Scharschmidt, et al., Commensal microbes and hair follicle morphogenesis coordinately drive treg migration into neonatal skin, Cell Host Microbe 21 (4) (2017) 467–477 e5.
[118] O.J. Harrison, et al., Commensal-specific T cell plasticity promotes rapid tissue adaptation to injury, Science 363 (2019) 6422.
[119] L.A. Kalekar, et al., Regulatory T cells in skin are uniquely poised to suppress profibrotic immune responses, Sci. Immunol. 4 (2019) 39.
[120] N. Malhotra, et al., RORalpha-expressing T regulatory cells restrain allergic skin inflammation, Sci. Immunol. 3 (2018) 21.
[121] M. Kashiwagi, et al., Direct control of regulatory T cells by keratinocytes, Nat. Immunol. 18 (3) (2017) 334–343.
[122] M. Delacher, et al., Genome-wide DNA-methylation landscape defines specialization of regulatory T cells in tissues, Nat. Immunol. 18 (10) (2017) 1160–1172.
[123] M. Halabi-Tawil, et al., Cutaneous manifestations of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, Br. J. Dermatol. 160 (3) (2009) 645–651.
[124] N. Fyhrquist, et al., Foxp3+ cells control Th2 responses in a murine model of atopic dermatitis, J. Invest Dermatol. 132 (6) (2012) 1672–1680.
[125] Y. Ito, et al., Expansion of FOXP3-positive CD4+CD25+ T cells associated with disease activity in atopic dermatitis, Ann. Allergy Asthma Immunol. 103 (2) (2009) 160–165.
[126] A.J. Reefer, et al., Analysis of CD25hiCD4+ "regulatory" T-cell subtypes in atopic dermatitis reveals a novel T(H)2-like population, J. Allergy Clin. Immunol. 121 (2) (2008) 415–422 e3.
[127] N. Ali, et al., Regulatory T Cells in Skin Facilitate Epithelial Stem Cell Differentiation, Cell 169 (6) (2017) 1119–1129 e11.
[128] R. Sanchez Rodriguez, et al., Memory regulatory T cells reside in human skin, J. Clin. Invest 124 (3) (2014) 1027–1036.
[129] P. Ogonowska, et al., Colonization With Staphylococcus aureus in Atopic Dermatitis Patients: Attempts to Reveal the Unknown, Front Microbiol 11 (2020), 567090.
[130] A.L. Byrd, et al., Staphylococcus aureus and Staphylococcus epidermidis strain diversity underlying pediatric atopic dermatitis, Sci. Transl. Med 9 (2017) 397.
[131] E. Stephen-Victor, E. Crestani, T.A. Chatila, Dietary and Microbial Determinants in Food Allergy, Immunity 53 (2) (2020) 277–289.
[132] Z. Al Nabhani, et al., A Weaning Reaction to Microbiota Is Required for Resistance to Immunopathologies in the Adult, Immunity 50 (5) (2019) 1276–1288 e5.
[133] L. Kreft, C. Hoffmann, C. Ohnmacht, Therapeutic Potential of the Intestinal Microbiota for Immunomodulation of Food Allergies, Front Immunol. 11 (2020) 1853.
[134] L.T. Yokanovich, R.D. Newberry, K.A. Knoop, Regulation of oral antigen delivery early in life: Implications for oral tolerance and food allergy, Clin. Exp. Allergy 51 (4) (2021) 518–526.
[135] R. Rachid, E. Stephen-Victor, T.A. Chatila, The microbial origins of food allergy, J. Allergy Clin. Immunol. 147 (3) (2021) 808–813.
[136] K.A. Knoop, et al., Regulatory T cells developing peri-weaning are continually required to restrain Th2 systemic responses later in life, Front. Immunol. 11 (2020), 603059.
[137] M. Lyu, et al., ILC3s select microbiota-specific regulatory T cells to establish tolerance in the gut, Nature (2022).
[138] R. Kedmi, et al., A RORγt+ cell instructs gut microbiota-specific Treg cell differentiation, Nature (2022).
[139] B. Akagbosu, et al., Novel antigen presenting cell imparts Treg-dependent tolerance to gut microbiota, Nature (2022).
[140] E. Stephen-Victor, T.A. Chatila, An embarrassment of riches: RORgt+ antigen presenting cells in peripheral tolerance, Immunity (2022).
[141] A. Abdel-Gadir, et al., Microbiota therapy acts via a regulatory T cell MyD88/RORgammat pathway to suppress food allergy, Nat. Med. 25 (7) (2019) 1164–1174.
[142] A. Abdel-Gadir, et al., Oral immunotherapy with omalizumab reverses the Th2 cell-like programme of regulatory T cells and restores their function, Clin. Exp. Allergy 48 (7) (2018) 825–836.
[143] D. Lozano-Ojalvo, et al., Allergen recognition by specific effector Th2 cells enables IL-2-dependent activation of regulatory T-cell responses in humans, Allergy (2022).
[144] L. Zhou, et al., Innate lymphoid cells support regulatory T cells in the intestine through interleukin-2, Nature 568 (7752) (2019) 405–409.
[145] J. von Moltke, et al., Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit, Nature 529 (7585) (2016) 221–225.
[146] M.R. Howitt, et al., Tuft cells, taste-chemosensory cells, orchestrate parasite type 2 immunity in the gut, Science 351 (6279) (2016) 1329–1333.
[147] A. Banerjee, et al., Succinate Produced by Intestinal Microbes Promotes Specification of Tuft Cells to Suppress Ileal Inflammation, Gastroenterology 159 (6) (2020) 2101–2115 e5.
[148] F. Gerbe, et al., Intestinal epithelial tuft cells initiate type 2 mucosal immunity to helminth parasites, Nature 529 (7585) (2016) 226–230.
[149] M.S. Nadjsombati, et al., Detection of Succinate by Intestinal Tuft Cells Triggers a Type 2 Innate Immune Circuit, Immunity 49 (1) (2018) 33–41 e7.
[150] M. Noval Rivas, et al., IL-4 production by group 2 innate lymphoid cells promotes food allergy by blocking regulatory T-cell function, J. Allergy Clin. Immunol. 138 (3) (2016) 801–811 e9.
[151] R.L. Clement, et al., Follicular regulatory T cells control humoral and allergic immunity by restraining early B cell responses, Nat. Immunol. 20 (10) (2019) 1360–1371.
[152] U. Gowthaman, et al., Identification of a T follicular helper cell subset that drives anaphylactic IgE, Science 365 (6456) (2019) eaaw6433.
[153] U. Gowthaman, J.S. Chen, S.C. Eisenbarth, Regulation of IgE by T follicular helper cells, J. Leukoc. Biol. 107 (3) (2020) 409–418.
[154] Q. Chen, A.L. Dent, Regulation of the IgE response by T follicular regulatory cells, J. Allergy Clin. Immunol. 150 (5) (2022) 1048–1049.
[155] Y. Yao, et al., Roles of follicular helper and regulatory T cells in allergic diseases and allergen immunotherapy, Allergy 76 (2) (2021) 456–470.
[156] T. Feehley, et al., Healthy infants harbor intestinal bacteria that protect against food allergy, Nat. Med 25 (3) (2019) 448–453.