

REVIEW

Type 2 immunity in the skin and lungs

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Abstract

There has been extensive progress in understanding the cellular and molecular mechanisms of inflammation and immune regulation in allergic diseases of the skin and lungs during the last few years. Asthma and atopic dermatitis (AD) are typical diseases of type 2 immune responses. Interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin are essential cytokines of epithelial cells that are activated by allergens, pollutants, viruses, bacteria, and toxins that derive type 2 responses. Th2 cells and innate lymphoid cells (ILC) produce and secrete type 2 cytokines such as IL-4, IL-5, IL-9, and IL-13. IL-4 and IL-13 activate B cells to class-switch to IgE and also play a role in T-cell and eosinophil migration to allergic inflammatory tissues. IL-13 contributes to maturation, activation, nitric oxide production and differentiation of epithelia, production of mucus as well as smooth muscle contraction, and extracellular matrix generation. IL-4 and IL-13 open tight junction barrier and cause barrier leakiness in the skin and lungs. IL-5 acts on activation, recruitment, and survival of eosinophils. IL-9 contributes to general allergic phenotype by enhancing all of the aspects, such as IgE and eosinophilia. Type 2 ILC contribute to inflammation in AD and asthma by enhancing the activity of Th2 cells, eosinophils, and their cytokines. Currently, five biologics are licensed to suppress type 2 inflammation via IgE, IL-5 and

its receptor, and IL-4 receptor alpha. Some patients with severe atopic disease have little evidence of type 2 hyperactivity and do not respond to biologics which target this pathway. Studies in responder and nonresponder patients demonstrate the complexity of these diseases. In addition, primary immune deficiency diseases related to T-cell maturation, regulatory T-cell development, and T-cell signaling, such as Omenn syndrome, severe combined immune deficiencies, immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, and DOCK8, STAT3, and CARD11 deficiencies, help in our understanding of the importance and redundancy of various type 2 immune components. The present review aims to highlight recent advances in type 2 immunity and discuss the cellular sources, targets, and roles of type 2 mechanisms in asthma and AD.

KEYWORDS

asthma, atopic dermatitis, biologics, ILC2, type 2 immunity

1 | INTRODUCTION

Allergic diseases cause significant morbidity and mortality with almost one billion cases, accounting for a significant portion of overall healthcare costs. The dysregulated immune response, chronic inflammation, and remodeling in the affected tissues define a dynamic and heterogeneous spectrum of anaphylaxis, food allergy, asthma, allergic rhinitis, chronic rhinosinusitis with nasal polyposis (CRSwNP), and atopic dermatitis (AD). Two main subtypes of immune responses driving asthma and AD have been defined, namely type 2-high and type 2-low.¹⁻⁴ Precision medicine and biomarker discovery is important for the management of asthma and AD in the context of a better selection of good responders to treatment, prediction of outcomes, and design of disease-modifying strategies. Progress has been made in profiling the type 2 immune response-driven diseases. In contrast, the non-type 2 immune response in asthma and AD is insufficiently understood.

The majority of patients with AD, CRS and asthma involve, or result from, an overexpression of type 2 inflammatory pathways (Figure 1).⁵⁻⁷ A specific type 2 set of cytokines are produced during the induction and maintenance of allergic immune response with the contribution of epithelial cells, dendritic cells (DC), T cells, innate lymphoid cells (ILC), eosinophils, mast cells (MC), and basophils. Activation of Th2 and ILC2 pathways is at the core of type 2 inflammation. Th2 cytokines include interleukin (IL)-4, IL-5, IL-9, IL-13, and IL-31, and main type 2 cytokines of ILC2 are IL-5, IL-9, and IL-13.^{8,9} IL-4 induces Th2 cell differentiation and induces isotype switching to IgE production in B cells. IL-5 is mainly responsible for the maturation and recruitment of eosinophils.¹⁰ IL-9, secreted by Th9 cells, induces eosinophilic inflammation, MC growth, mucus hypersecretion, and airway hyperresponsiveness (AHR).¹¹ IL-13 regulates the proliferation of IgE-producing B cells, mucus hypersecretion and AHR and opens the epithelial tight junction (TJ) barrier.^{12,13} Epithelial cells of airways and skin are the first line of defense against allergens. Upon

exposure to allergens, infectious agents and toxins, epithelial cells release alarmins, such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP).^{14,15} These cytokines can directly induce type 2 cytokine production in ILC2.¹⁶ IL-33 and TSLP directly activate MC.¹¹ TSLP stimulates Th0 cells and DC to induce a Th2-like response. TSLP also promotes B-cell proliferation.¹⁷ A default role for these cytokines can be suggested in immunity against helminth infections with IgE production, and eosinophilia as well as type 1 hypersensitivity reactions and allergic form of delayed type hypersensitivity (type 4) reactions.¹⁸

Type 2 immunity and inflammation underlie asthma and AD. This review article focuses on how type 2 inflammation and immunity induces IgE synthesis, eosinophil involvement and airway remodeling, and how these factors relate to skin and lung allergy.¹⁹⁻²¹

2 | TYPE 2 IMMUNITY IN THE LUNG AND SKIN

2.1 | Type 2 response and asthma

One of the main clinical characteristics of asthma is reversible airflow obstruction: it can be variable in its presence, intensity, and reversibility with bronchodilators or anti-inflammatory therapy. Many factors contribute to airflow obstruction. These include bronchospasm, inflammation, edema, neovascularization, mucus formation, and remodeling. Remodeling, a more recently recognized contributor to asthma, refers to the injury/repair cycle that can occur in severe or long-standing chronic disease.²²⁻²⁴ Historically, remodeling was defined as airway basement membrane thickening, which compromises the lumen of the airway and airflow. It is proposed that this thickening arises from chronic and persistent inflammation.²⁵ However, the components of remodeling have expanded to include chronic airway inflammation, goblet cell hyperplasia, hypertrophy of

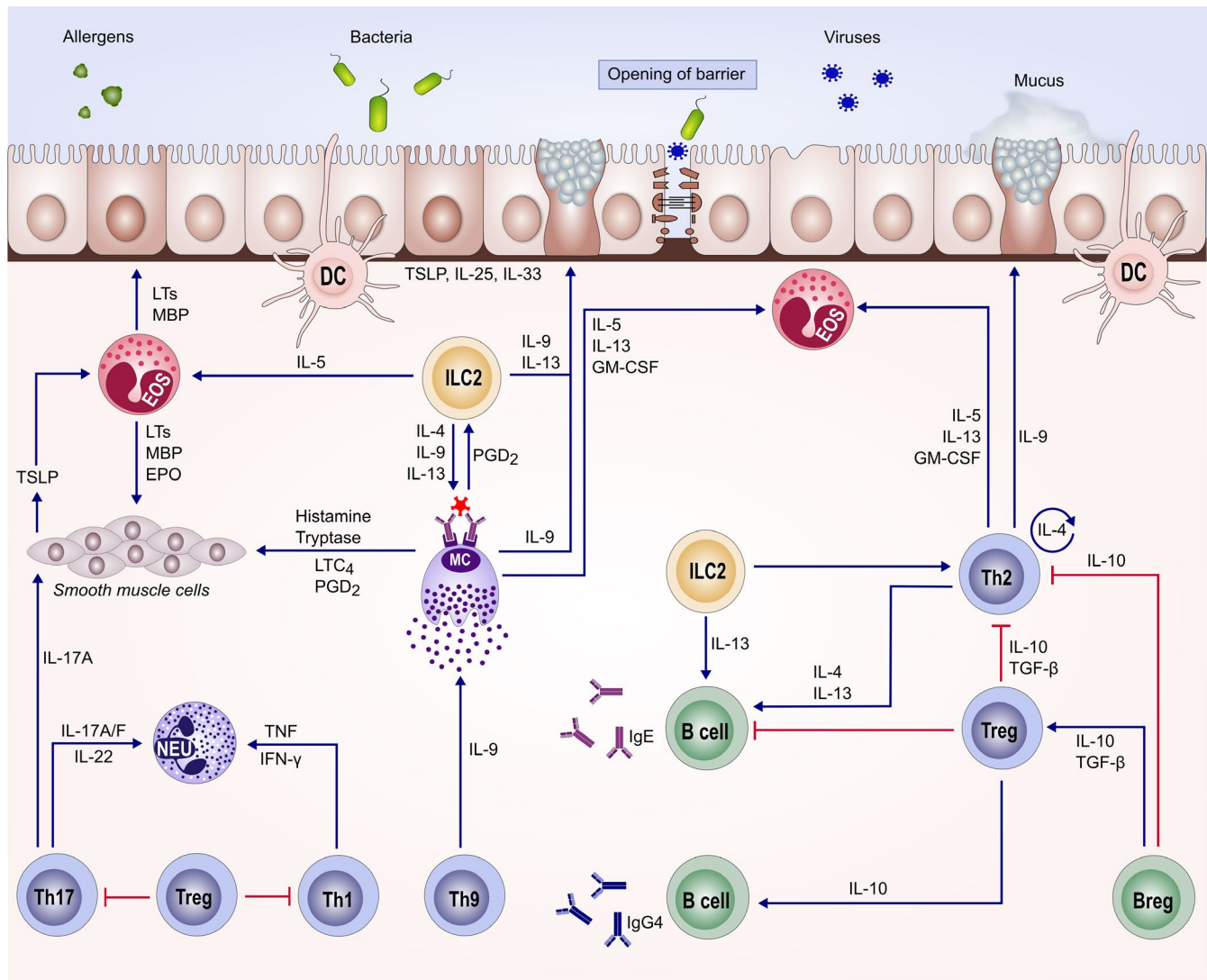


FIGURE 1 Overview on the mechanisms of type 2 immune responses. Epithelial barrier impairment during exposure to bacteria, viruses, and inflammation can lead to opening of epithelial barriers and allow penetration of allergens through the tissues. Allergens with protease activity can disrupt epithelial cell tight junction proteins and gain access to submucosal dendritic cells (DC). Damaged epithelial cells release alarmin (TSLP, IL-25, and IL-33), which activate innate lymphoid cells (ILC) and DC. Matured DC migrate to local lymph nodes and present processed allergen peptides to naive T cells through MHC class II molecules. Naive T cells in the presence of IL-4 differentiate into Th2 cells. The type 2 cytokines IL-4, IL-5, IL-9, and IL-13 are produced not only by Th2 cells but also by ILC2. IL-4 and IL-13 are involved in IgE class-switch in B cells. IgE binds to FcεRI on the surface of mast cells (MC) and sensitizes them. Subsequent release of mast cell-associated mediators, such as histamine, tryptase, prostaglandins, leukotrienes, and cytokines, induces goblet cell hyperplasia, smooth muscle contraction, and increased vascular permeability. IL-5 induces eosinophilia. Immunoregulatory cytokines, such as IL-10 and TGF-β, released by T-regulatory (Treg) cells can suppress type 2 as well as Th1 and Th17 response. IL-10-producing B regulatory cell (Breg) cells also inhibit effector T cells. EPO, eosinophil peroxidase; IL, interleukin; LT, leukotrienes; LTC4, leukotriene C4; MBP, major basic protein; PGD2, prostaglandin D2; TGF-β, transforming growth factor-β; TSLP, thymic stromal lymphopoietin

airway smooth muscle, and edema.²⁵ These changes lead to persistent airflow obstruction which is not responsive to bronchodilation or anti-inflammatory actions of corticosteroids. Persistent airflow obstruction is associated with a lack of asthma control and an increase in susceptibility for exacerbations.

Type 2 inflammation with IL-4 and IL-13 at its core creates a vicious cycle. Environmental triggers activate type 2 inflammation through alarmins, which include the production of IL-4, IL-5, and IL-13.^{14,26,27} Epithelial injury sets into motion inflammation and

remodeling if these processes are sustained such as in severe asthma and the further generation of pro-inflammatory mediators to establish a vicious cycle (Figure 2). IL-4 and IL-13 have pivotal roles in many aspects of airway changes in asthma and are serving as important targets for effective treatment, whereas IL-5 supports tissue and systemic eosinophilia. These changes in inflammation and remodeling further increase the susceptibility for exacerbations, which become further stimulus for airway injury and subsequent remodeling. Three epithelial-derived cytokines, IL-25, IL-33, and TSLP, are

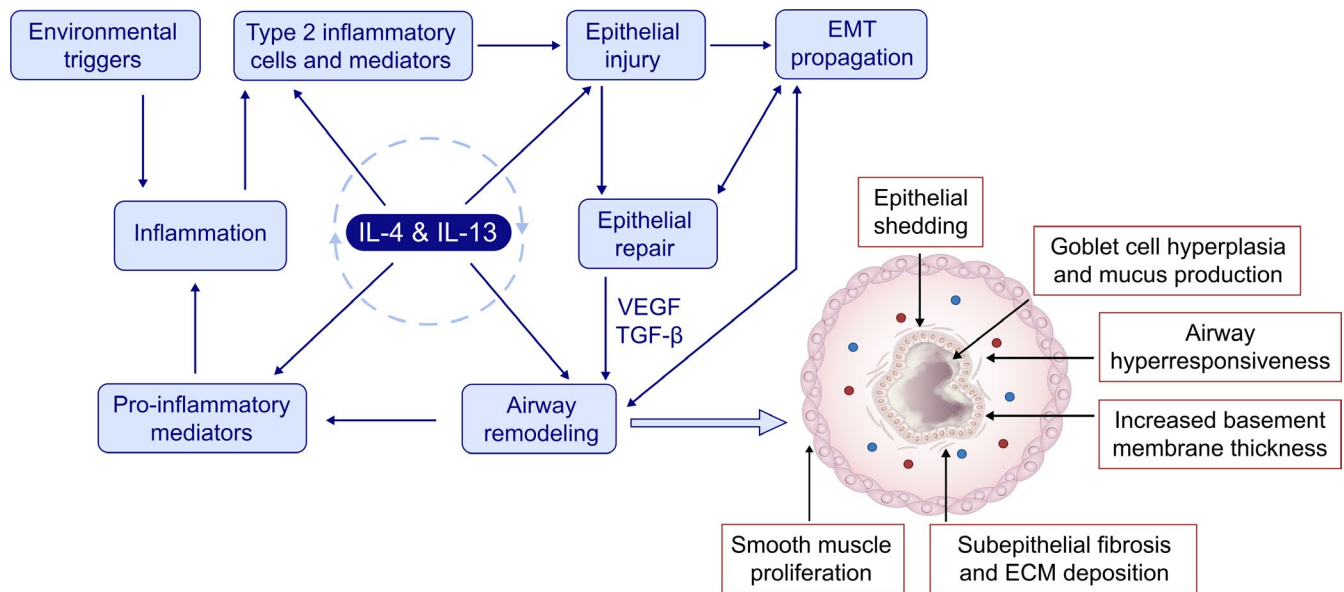


FIGURE 2 The vicious cycle in the pathogenesis of asthma. Exposure to environmental triggers can lead to airway damage and induce alarmin (IL-25, IL-33, TSLP) production, followed by type 2 inflammation. Impaired airway and its repair may go on to develop tissue remodeling and sustained inflammation. Increased activation of the epithelium leads to signaling to inflammatory cells and also activation of the underlying mesenchymal cells, such as smooth muscle cells and fibroblasts. It leads the epithelial-mesenchymal transition (EMT) propagation. Both structural and inflammatory cell produce growth factors, such as transforming growth factor (TGF)-superfamily, vascular endothelial growth factor (VEGF), and interleukin (IL)-13. Progressive structural changes include proliferation of fibroblasts and airway smooth muscle and vascular remodeling together with excessive and dysregulated extracellular matrix (ECM) deposition, which may lead to an airway hyperresponsiveness and airway obstruction. In turn, the pro-inflammatory environment generated by airway remodeling sustains the inflammatory response. IL, interleukin; TSLP, thymic stromal lymphopoietin

initiators of this process. This is demonstrated by findings in murine asthma models showing that isolated blockade of IL-25, IL-33, and TSLP reduces airway inflammation and hyperresponsiveness^{14,26} and that blocking all three cytokines this effect is more potent.²⁷ This has implications for the treatment of human asthma. IL-4 and IL-13 are mainly generated by Th2 lymphocytes and ILC2. Both of these cytokines contribute to a variety of pathological changes underlying airway obstruction. At the beginning of this cascade, type 2 cytokines disrupt epithelial barrier function in the lungs, much like in the skin in AD.^{12,13,28} In addition, they act on other airway structures such as the basement membrane, causing thickening and increased airway rigidity, and smooth muscle, in which it induces hyperplasia, enhanced constriction and diminished relaxation. Stimulation of goblet cell hyperplasia and subsequent excessive mucus production are another effect of IL-4 and IL-13, which is of particular interest and importance: IL-13R α 2 has a potential role in IL-13-induced MUC5AC and ciliary changes through ERK1/2 signal pathway in the nasal epithelium. IL-13R α 2 may contribute to airway inflammation and aberrant remodeling which are the main pathological features of CRSwNP.²⁹ Finally, by affecting expression of vascular adhesion molecule (VCAM), for example, VCAM-1, eosinophil recruitment to the airway occurs with their participation in eosinophilic inflammation and eventual remodeling.

The development of remodeling is further enhanced by the presence of other inflammatory cells, such as MC and eosinophils, which generate growth factors such as transforming growth factor- β

(TGF- β) to further promote fibrosis. The role of other TGF- β family member cytokines such as bone morphogenic proteins and activin in remodeling remains to be elucidated.³⁰ Overall, remodeling is a complex issue and many other molecules are involved. These act as agonists or antagonists of type 2 immune response, for example, LIGHT, a tumor necrosis factor (TNF) family member, which acts together with TGF- β to promote airway remodeling.³¹

2.2 | Type 2 response and AD

AD and asthma are both type 2 immune diseases.⁴ Although they share common pathomechanistic elements, there are important differences between AD and asthma translating to different therapeutic targets. AD begins early, often in the first year of life, whereas asthma usually starts later in childhood or adolescence.³² Both diseases are characterized by type 2 immune signatures, as evidenced by increased protein expression of IL-4 receptor (IL-4R), IL-4, IL-13, TSLP, and IL-33 in the skin and lung, respectively. In contrast, leukocytic infiltrates in lesional tissue differs between these diseases.^{4,33-35} Whereas asthma has a large B-cell component, and prominent eosinophil infiltrates, AD is primarily a T cell-driven disease, with variable numbers of eosinophils.^{4,34,36} Treatments targeting eosinophils using anti-IL-5³⁷ or IL-5 receptor α (IL-5RA)³⁸ strategies are effective in asthma. Meanwhile, there is no data supporting these treatment approaches in AD, although so far only short (2 weeks), small

studies have been conducted.³⁹ IgE is thought to be pathogenic in asthma. In line with this idea, therapeutic targeting of IgE is an effective approach in asthma.⁴ In contrast, IgE is considered to play a bystander role in AD. Dupilumab, an antibody directed against the IL-4R subunit α shows similar efficacy in AD patients regardless of their IgE status.^{40,41} Similarly, recent studies suggest that the IL-13 antagonist lebrikizumab has similar effects.⁴² This may indicate that IL-13 is the key cytokine inducing skin inflammation in AD. However, while dupilumab is approved for the treatment of asthma,⁴³ IL-13 antagonists (lebrikizumab and tralokinumab) did not show significant efficacy in asthma.^{44,45} One must keep in mind that the IL-13 studies in asthma did not differentiate between eosinophil-rich asthma and other subtypes, which may at least partially explain these different effects. It seems that the epithelial cytokines TSLP and IL-33 have different roles in asthma and AD. Whereas both mediators have been successfully targeted in asthma,^{46,47} AD studies have not shown any effects yet.^{48,49} A large phase 2 study with the anti-IL-33 antibody etokimab did not ameliorate AD,⁴⁸ while showing promising data in asthma.⁵⁰ Targeting the OX40 pathway, which is involved in both Th2 skewing and T-regulatory cell induction,⁵¹ seems to have early signs of efficacy in AD,⁵² but did not show efficacy in earlier asthma studies.⁵³

Thus, when considering a treatment approach for a given patient, we need to take into account potential comorbidities for optimal management across the atopic spectrum.

2.3 | IgE

IgE is responsible for allergic sensitization and the eventual contribution of MC- and basophil-driven inflammation. In the development of allergic sensitization, a first step is the regulation of B-cell generation of IgE. IL-4 and IL-13 direct and regulate B-cell immunoglobulin antibody class-switching from IgM to IgE, which then leads to the production of IgE antibodies.⁵⁴ IgE⁺ cells have a unique differentiation program consisting of isotype switching to a germinal-center IgG1⁺ B-cell intermediate.⁵⁵ Cellular IgE memory resides in very rare IgE memory B cells and mainly in IgG1⁺ memory B cells that undergo a sequential switch to IgE after re-exposure to antigen. With the development of antigen-specific IgE antibodies, MC and basophils become sensitized and can recognize environmental allergens. In asthma, the key allergens of importance include house dust mites, animal dander, and mold.^{56,57}

Recognition of inhaled allergens by IgE-specific antibodies on the MC membrane results in bridging of IgE molecules and a signaling in MC to release and generate a wide variety of products.⁵⁸ Although the traditional view has focused on the release and synthesis of bioamines, for example, histamine, and lipid products, such as leukotrienes, MC and basophils generate and release a large profile of cytokines and chemokines.⁵⁸

The release of histamine and generated leukotrienes lead to immediate airway smooth muscle contraction—bronchospasm—as well as changes in vascular permeability, which affect exudation fluid and

facilitate inflammatory cell egress to affected tissues. MC also generate a wide variety of cytokines and chemokines including IL-4, IL-5, and IL-13, along with TSLP, TNF- α , and TGF- β 1.¹¹ It is this profile of inflammation-promoting cytokines that perpetuates and sustains airway inflammation; IgE is a key component in the induction of this inflammatory cascade.

IgE is also a biomarker for the presence of a type 2 immune pattern in asthma.⁵⁹ Along with elevated eosinophils, both in sputum and the peripheral blood, and an increased fractional exhaled nitric oxide (FeNO), elevated IgE reflects the presence of a type 2 phenotype. In contrast to eosinophils and FeNO, IgE levels have not been predictive to identify those patients likely to respond to treatment with type 2 monoclonal antibodies, including omalizumab. Serum IgE concentrations are used to determine an appropriate weight/volume-based dose for anti-IgE (omalizumab) treatment, but IgE values are not necessarily predictive of a favorable response to omalizumab.⁶⁰ Recent findings in local allergic rhinitis in some of the patients suffering from both allergic rhinitis and asthma suggest an effect of omalizumab on not only circulating IgE, but also locally produced and tissue expressed IgE.⁶¹

2.4 | Eosinophilia

The role and contribution of eosinophils have been more fully delineated with the advent of biological treatments in severe asthma, particularly the IL-5 targeting therapeutics.^{62,63} Eosinophils are generated in the bone marrow and arise from CD34⁺ progenitor cells. The development, maturation, terminal differentiation, and release of eosinophils is controlled by IL-5, and to some extent by IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Figure 3).⁶⁴ An understanding of the role and contribution of eosinophils to asthma pathophysiology is evolving.

Eosinophils are biologically well equipped to participate in allergic inflammation and airway injury/repair, or remodeling, processes. When activated, eosinophils release granule proteins, which are basic in nature and may have profound inflammatory and functional effects on airway tissues. The granule proteins include major basic protein (MBP) and eosinophil peroxidase (EPO) along with others. MBP and EPO appear to be the most central granule proteins in initiating airway injury.⁶⁴ Like MC and basophils, eosinophils are capable of generating a wide variety of cytokines and growth factors, including IL-5, which can perpetuate the eosinophils involvement in inflammation and set up a vicious cycle.⁶⁵

An initial step in the eosinophils' contribution to airway inflammation, and hence asthma severity, occurs as these cells migrate to the airways. Eosinophil trafficking is complex and mediated by a number of important type 2 inflammatory cytokines.⁶⁶ A first step in this process is an adhesion of eosinophils to blood vessels via VCAMs, a main one being VCAM-1. VCAM-1 expression is regulated by IL-4. Upon binding of very late antigen-4 to VCAM-1, eosinophils diapedise from the blood vessel and are guided toward the lung and airway. The chemokines eotaxin I, II, and III, macrophage-derived

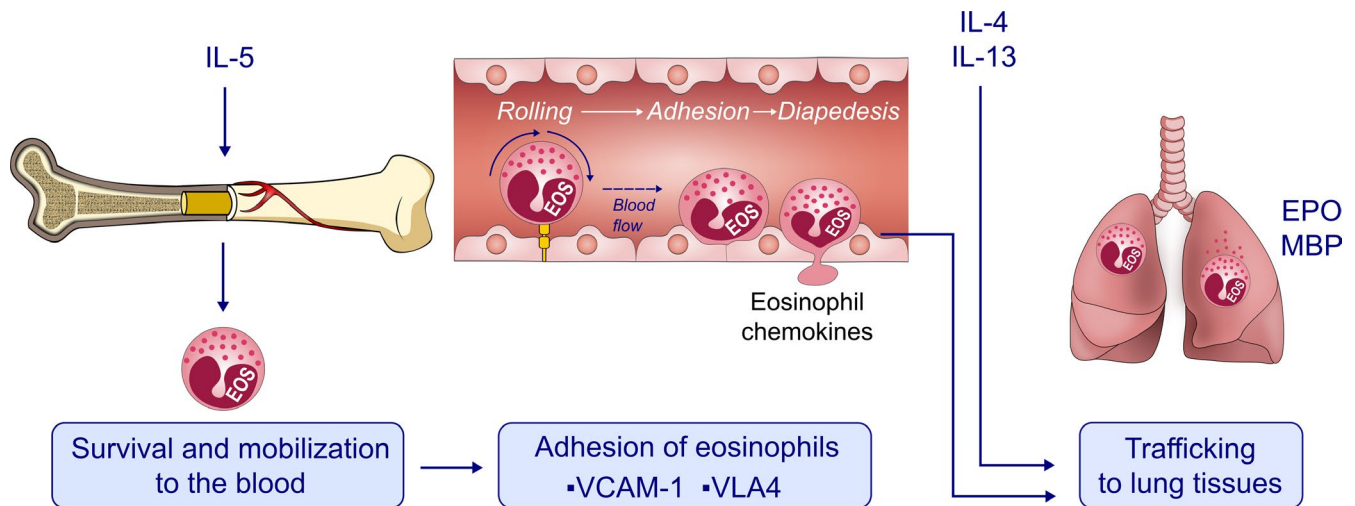


FIGURE 3 Eosinophil trafficking to tissues. The development, maturation, terminal differentiation, and release of eosinophils are controlled by IL-5, and to some extent by IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF). Eosinophils develop in the bone marrow, where they differentiate from hematopoietic progenitor cells into mature eosinophils. Eosinophil migration out of the bone marrow into the circulation is primarily regulated by IL-5. Circulating eosinophils subsequently interact with the endothelium by a process involving rolling, adhesion, and diapedesis. Depending on the target organ, eosinophils cross the endothelium into tissues by a regulated process involving coordinated interaction between networks of chemokines (CCL5/RANTES, CCL11/Eotaxin-1, CCL24/Eotaxin-2, CCL26/Eotaxin-3, CCL22/macrophage-derived chemokine, CCL17/thymus and activation-regulated chemokine), eosinophil adhesion molecules (eg, VLA-4 [integrin $\alpha 4 \beta 1$]), and adhesion receptors on the endothelium (eg, VCAM-1). When activated, eosinophils release granule proteins, such as major basic protein (MBP) and eosinophil peroxidase (EPO), which have profound inflammatory effects on airway tissues. IL, interleukin; VCAM, vascular adhesion molecule; VLA, very late antigen

chemokine (MDC), thymus and activation-regulated chemokine (TARC), as well as the cytokines IL-13 and IL-5 promote this eosinophil migration. The processes, however, by which eosinophils are activated are not fully established.⁶⁷⁻⁶⁹ In mouse models and human cell cultures, IL-4 and IL-13 act together as key drivers of type 2 inflammation and blocking of both of them through IL-4R α is superior to blocking either IL-4 or IL-13 alone.⁷⁰

Elevation of eosinophils in peripheral blood (>150 cells/ μ L) and sputum (>2%) suggests a type 2 inflammation phenotype and marks an increased risk for asthma exacerbations. The mechanisms by which increased airway eosinophils create a risk factor for exacerbations are not fully established, but may arise, at least partially, as a consequence of altered Toll-like receptor (TLR) 7 function and interferon-gamma (IFN- γ) generation.⁷¹ Eosinophil activation is the key step of type 2 inflammatory cascade, mostly in the late stage of allergic response, and exerts a central role in the pathogenesis of asthma through the release of cytoplasmic granule mediators and the production of cytokines (mainly IL-1 β , IL-6, IL-8 and IL-4), lipid mediators and oxygen radicals (Figure 1). Eosinophil activation results in DC chemotactic activity, endothelial cell damage, inhibition of muscarinic receptors, altered repair processes, and induction of fibrosis, leading to airway hyperactivity and wall remodeling.⁷²⁻⁷⁴ All of these effects have direct implications in exacerbation of asthmatic symptoms. The differentiation, maturation, and survival of eosinophils depend on several cytokines, mainly IL-5, IL-3 and GM-CSF. Eosinophils moreover promote the synthesis and release of IL-2, IL-3, IL-4, IL-10, IL-12, IL-13, IL-16, IL-25, and TGF- β as well as chemokines such as RANTES/CCL5, Eotaxin/CCL11, and MCP-4/CCL13.^{75,76}

Recent work has shown that accumulation of eosinophils in the airways is associated with persistent airflow obstruction.⁷⁷ Based on in vitro studies, it has been hypothesized that activation of eosinophils generates EPO, which in turn promotes mucus plug formation. As pointed out by EAACI Systematic Reviews for Biological Guidelines, all biologicals currently approved for severe eosinophilic asthma (benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab) reduce the rate of severe asthma exacerbations and, for benralizumab, dupilumab, and mepolizumab, diminish the use of oral corticosteroids (Figure 4).⁷⁸⁻⁸⁰ There is moderate certainty for improving asthma control, quality of life, forced expiratory volume 1, and cost-effectiveness. More data on long-term safety are needed together with more efficacy data in the pediatric population.⁷⁸

2.5 | DC in type 2 immunity

Type 2 immune responses are in charge of defending the body against parasites, venoms and toxins.⁸¹⁻⁸³ Aberrant type 2 immune responses underlie different diseases such as asthma, allergic rhinitis, CRSwNP, AD, eosinophilic esophagitis (EoE), and food allergy.⁸⁴ The initiation and perpetuation of type 2 immune responses require the coordination of different innate and adaptive cell subsets both locally and systemically at the time of antigen/allergen presentation.^{85,86} DC, macrophages, and B cells represent the best-characterized professional antigen-presenting cells (APC).⁸⁷ In humans, blood DC are broadly classified into two main groups according to

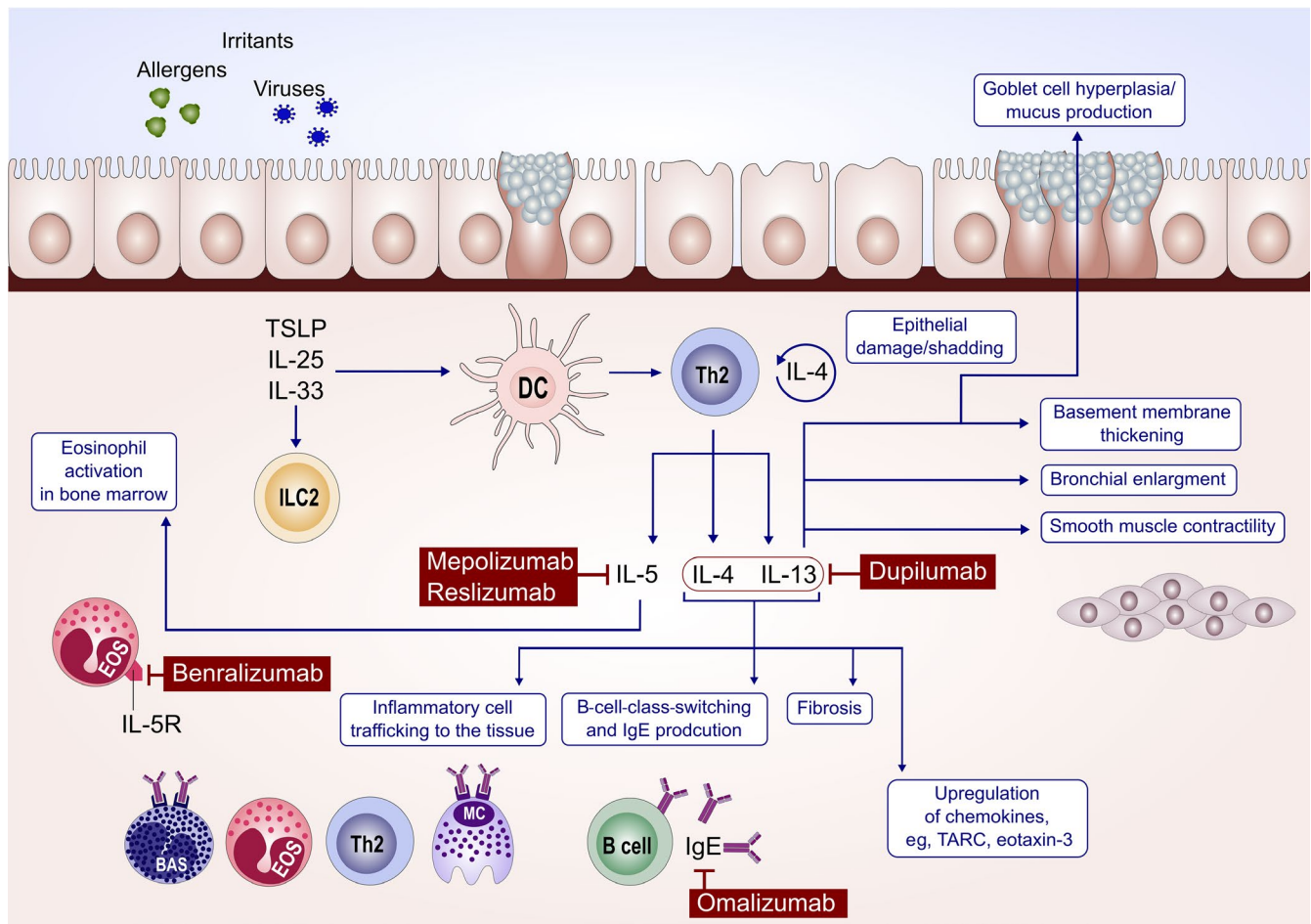


FIGURE 4 Overview of currently used biologics in asthma. Mepolizumab and reslizumab are anti-IL-5 antibodies. Benralizumab binds to the α chain of IL-5 receptor α . Omalizumab is an antibody against IgE. Dupilumab binds to the alpha subunit of the interleukin-4 receptor, interleukin

their expression of specific surface markers: (a) myeloid DC (mDC) and (b) plasmacytoid DC (pDC).⁸⁸ mDC can be further categorized into type 1 and type 2 mDC (DC1 and DC2), which correspond to their mouse counterparts of Interferon regulatory factor (IRF)8-expressing conventional DC (cDC)1 and IRF4-expressing cDC2, respectively.⁸⁸ DC2, both in humans and in mice, are the main DC subset involved in the induction and expansion of Th2 cells in the airways, gut and skin.^{84,89-93}

Immature or mature DC in the presence of different stimuli such as neurotransmitters, adenosine, flavonoids, vitamin D3 metabolites, retinoic acid, or mannan might also promote the generation of functional regulatory T (Treg) cells, thus promoting tolerance and tissue homeostasis (Figure 5).^{84,94,95} For example, fully mature pDC are able to generate functional, allergen-specific Treg cells in human tonsils,⁹⁶ which could be disrupted by pro-inflammatory cytokines and specific TLR ligands.⁹⁷ Similarly, allergoids conjugated to mannan endorse human DC with the capacity to generate functional FOXP3⁺ Tregs through mechanisms depending on programmed cell death 1 ligand 1,^{98,99} which can be broken by aluminum hydroxide by promoting metabolic reprogramming in DC.¹⁰⁰ Collectively,

DC are key in initiation, amplification and chronification of type 2 immune responses. Depending on the holistic integration of micro-environmental surrounding signals and encountering antigens, DC might promote potent inflammatory type 2 immune responses underlying asthma, AD, CRSwNP, EoE, and food allergy, or Treg cells leading to tolerance and tissue homeostasis.

In the periphery, DC take-up antigens and migrate to the draining lymph nodes (Figure 6). This migration might be significantly increased by IL-13 and TNF- α produced by ILC2 and MC, respectively.⁸⁷ In the lymph node, DC present the processed peptides associated with MHC class II molecules to naïve CD4⁺ T cells, thus inducing their activation, expansion and polarization. The precise mechanisms leading to Th2 polarization are not yet fully elucidated, but recent findings demonstrated that DC conditioned by epithelial cell-derived alarmins (TSLP, IL-33, IL-25, GM-CSF)¹⁰¹⁻¹⁰⁴ produce less IL-12 and increase the expression of specific costimulatory molecules such as OX40L or Notch receptor ligands, which in turn favor Th2 polarization.^{87,93,103,105} Different Th2 subsets can be generated, including effector Th2 cells (T_{eff}) homing back to tissues, but also central memory T (T_{CM}) and tissue-resident memory

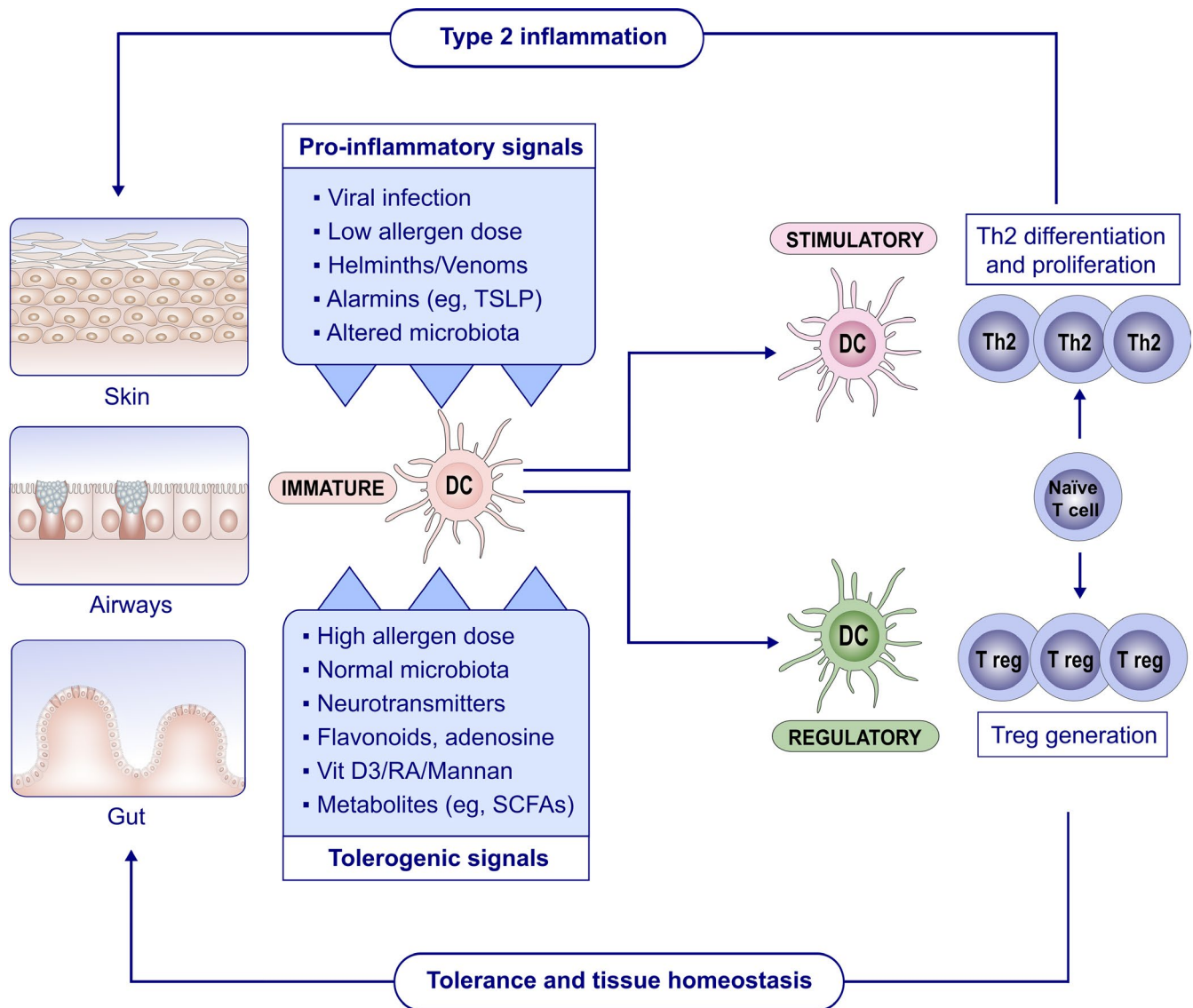


FIGURE 5 Type 2 inflammation versus immune tolerance and tissue homeostasis by dendritic cells. Dendritic cells (DC) are antigen-presenting cells able to process and integrate signals from the microenvironment. Under pro-inflammatory conditions immature DC develop into stimulatory DC and promote an effector immune response by stimulating T-cell proliferation and shaping T-cell responses toward Th1, Th2, or Th17 phenotypes. Once antigen is taken up by DC, they present them to specific CD4⁺ T cells. Low-allergen dose interactions between CD4⁺ T cells and DC result in the priming of Th2 cells, whereas high-dose interactions and tolerogenic signals (eg, vitamin D3) can lead to tolerance induction. Under a tolerogenic environment, DC acquire regulatory functions suppressing T-cell activation and proliferation and providing signals that enable regulatory T-cell (Treg) differentiation and expansion. This function maintains immune tolerance and tissue homeostasis. TSLP, thymic stromal lymphopoietin; RA, Retinoic acid; SCFAs, Short-chain fatty acids

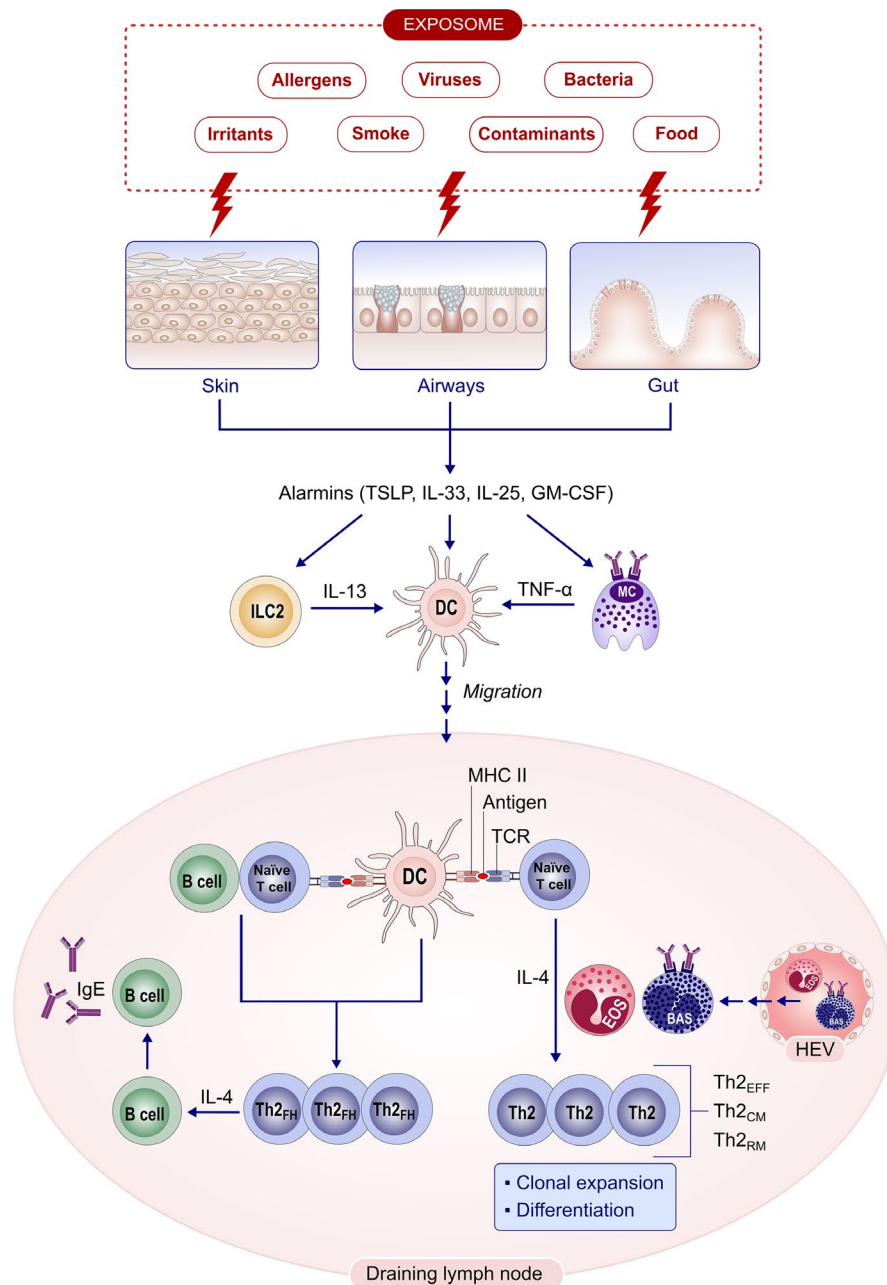
T (T_{RM}) cells, which might contribute to the initiation, propagation, and chronicity of type 2 immune responses upon persistent antigen encounter. DC in cooperation with B cells also promote the generation of IL-4- and IL-13-producing type 2 follicular Th (T_{FH}) cells, which play a significant role in the IgE class-switching at the B-cell level.^{106,107} DC also contribute to the amplification and chronicity of type 2 immune responses by activating memory antigen-specific T_{CM} and T_{RM} cells through mechanisms partially depending on IgE-facilitated presentation.⁸⁴ Other type 2 innate immune cells such as basophils, MC, eosinophils, and ILC2 could also act as APC and cooperate with DC to the perpetuation of type 2 immune responses.⁸⁷

3 | OTHER CELLS THAT CONTRIBUTE TO TYPE 2 IMMUNITY

3.1 | ILC

The classical simplistic vision that DC sample antigen before migrating to lymph nodes to elicit a type 2 CD4⁺ T-cell response has over the past few years been displaced by evidence of a more complex network of multicellular cooperation and tissue microenvironmental cues. Innate immune system cells that lack rearranged antigen receptors and markers for myeloid and lymphoid lineages,

FIGURE 6 Exposure to exposome and cellular and molecular interactions in local lymphatic tissues for the development of allergic inflammation. During sensitization to allergens, dendritic cells (DC) in the tissue first engulf antigen and then become activated. The human exposome represents the totality of all environmental exposures over a lifetime, which induces alarmins such as IL-33, IL-25, and TSLP from epithelial cells. Alarmins activate DC and innate lymphoid cells 2 (ILC2), which produce IL-13 in an antigen-nonspecific manner. Activated DC migrate rapidly into draining lymph nodes (LN). In the draining LN, antigen-presenting DC stimulate antigen-specific naïve CD4 T cells to differentiate into type 2 effector T helper (Th2) cells. Different Th2 subsets can be generated, including effector Th2 cells (Th2_{EFF}) homing back to tissues, but also central memory (Th2_{CM}) and tissue-resident memory (Th2_{RM}) cells. DC in cooperation with B cells also promote the generation of IL-4- and IL-13-producing type 2 follicular Th (Th2_{FH}) cells, which play a significant role in the IgE class-switching in B cells. IL, interleukin; TSLP, thymic stromal lymphopoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; MHC, major histocompatibility complex; TCR, T-cell receptor; HEV, high endothelial venules



such as T, B, and natural killer (NK) cells show similarities to Th1, Th2, and Th17/22 type of immune responses have been identified and named ILC.¹¹ In analogy to their T-cell counterparts, ILC are defined as type 1, 2 and 3 cells (ILC 1-3). ILC1 mainly produce IFN- γ , ILC2 produce IL-5 and IL-13,¹⁰⁸ and ILC3 produce IL-17 and IL-22.⁸⁵ ILC control the mucosal environment through close interaction with epithelial cells and other tissue cells, production of cytokines and chemokines promoting distinct types of tissue inflammation and immune response initiation.^{11,109} ILC can be detected in several body fluids and tissues such as sputum, peripheral blood, nasal polyps, and esophagus for their characterization in allergy and asthma patients.^{108,110}

Type 2 ILC are present in human lungs and mucosa and sense and respond to cytokines and stress signals. They require the transcription

factors retinoic acid receptor-related orphan receptor- α (ROR α), GATA3, and c-MYC for their development and expansion.¹¹¹⁻¹¹⁴ IL-33-activated ILC2 produce large quantities of IL-5, IL-9, and IL-13, and significantly contribute to virus-induced bronchial hyperreactivity and allergic asthma.^{115,116} The role of ILC2 in the pathophysiology of asthma and allergic inflammation has been shown in mouse models.^{116,117} IL-5- and IL-13-producing ILC2 accumulate in the sputum of patients with severe eosinophilic asthma and following allergen challenge.^{118,119} ILC2 engage in a complex bidirectional crosstalk with DC and Th2 cells in a localized tissue setting. They modulate the amplitude of the type 2 response to appropriately respond to the perceived environmental threat. They damage the lung and skin barrier mostly in an IL-13-dependent manner^{12,13} and play a role in the inflammation upon exposure to toxic environmental materials such as chlorine.¹²⁰

Recent evidence suggests the existence of a regulatory ILC (ILCreg) subset, which produces IL-10 and can derive from ILC2 via a unique immune regulatory and anti-inflammatory retinoic acid-induced pathway.¹²¹ Another ILC subset that contributes to immune regulation by enhancing regulatory B (Breg) cells, the human CD40L-expressing type 3 ILC, induce IL-10-producing immature transitional Breg cells that are localized in the marginal zone of human tonsils.¹²²

3.2 | MC

Innate granulocytes that include MC, eosinophils, and basophils serve as specified effectors in type 2 immune responses and are able to activate and modulate ILC2 functions.¹²³ Under the influence of type 2 cytokines, they promptly release large quantities of preformed mediators, such as cytokines, proteases, lipid mediators, and histamine.¹²⁴ Prostaglandins and leukotrienes are also potent ILC2 function modulators, and their levels are elevated as a consequence of myeloid cell recruitment and MC activation.¹²⁵ Recruitment of inflammatory cells, smooth muscle constriction, and increased vascular permeability directly depend on MC mediators' release.¹¹⁴

MC are long-lived players of immune activation at the early stages of infection. At later stages, they promote worm clearance and participate in protective immune responses during secondary infection.^{126,127} Helminthic infections trigger a type 2 immune response. Innate immune cells and intestinal epithelial cells secrete Th2 cytokines including IL-4, IL-5, IL-9, IL-13, IL-25, IL-33, and TSLP.⁸³ IL-33 causes the activation and proliferation of MC which results in their degranulation and release of preformed mediators known to modulate cells of the innate and adaptive immune system. Among these are IL-4 and IL-13 resulting in the alternative activation of macrophages¹²⁸; prostaglandin D₂, which cleaves IL-33 resulting, as mentioned above, in increased ILC2 induction through CRTH2 receptor interaction¹²⁷; and TNF- α , CXCL1, and CXCL2 secretion, leading to the recruitment and proliferation of neutrophils at the site of infection.^{129,130} In addition, MC degranulation induces effector mechanisms involved in worm expulsion such as goblet cell hyperplasia, increased mucin production, mitigation of tissue damage, intestinal smooth muscle contraction associated with heightened peristalsis, and the creation of an environment toxic to helminths.⁸² MC also play immune regulatory roles.¹⁰⁹

3.3 | Basophils

Basophils share some functional features with tissue-resident MC, including basophilic granules in the cytoplasm, cell surface expression of the high-affinity IgE receptor and the release of chemical mediators such as histamine and proteases in response to various stimuli. Basophils sustain the late phase of the allergic response by promoting inflammation and mucus production. In comparison with MC, ILC2 and eosinophils, these cells produce relatively high levels of IL-4, thus acting as major Th2 differentiation promoters.¹³¹

While mostly known to participate in IgE-mediated chronic allergic inflammation due to their expression of the high-affinity IgE receptor, Fc ϵ R1,¹¹⁴ basophils also respond to cytokines such as IL-3, IL-18, IL-33, and TSLP,¹³² as well as helminth-derived products.¹³³ Interestingly, basophils can function as APC and drive Th2 cell differentiation.¹³⁴ During a Th2 response, basophils are in close contact with DC in draining lymph nodes and can acquire peptide-MHC-II complexes from DC through trogocytosis. Because basophils endogenously express CD86, they can present antigen and provide IL-4 to naïve CD4 T cells, promoting Th2 cell differentiation.^{134,135} Basophil responsiveness undergoes significant circadian variability and that distinct patterns of rhythmicity can be recognized linked to delivered signals, activation parameters, and disease status.¹³⁶ Basophil activation test represents one of the most used in vitro assays that characterizes the allergic status of the patient and is open for further improvement.^{137,138} It is being widely used for diagnosis and patient monitoring in different allergic diseases.^{139,140}

Emerging evidence shows that through a bidirectional interaction with the central and peripheral nervous systems, MC, eosinophils, and basophils are central effector immune cells in causing pruritus in various skin diseases including AD or urticaria.¹⁴¹ In fact, they are considered to be the main source of pruritogens,¹⁴² including histamine, neuropeptides, cytokines, proteases, and lipid mediators. In the periphery, these cells are located in close proximity to the myelinated and unmyelinated nerves.¹⁴³ Thus, the interaction between the neuronal and immune systems at the local site is amplified inducing a potent immune reaction and many Th2 cytokines including IL-4, IL-13, and IL-31 have been recognized as some of the best target for the treatment of chronic pruritus in AD.¹⁴⁴ Targeting IL-31 was recently presented as one of the most efficient pruritus treatment approaches.^{145,146} Basophils infiltrate the skin along with eosinophils in several human pruritic skin diseases such as AD, prurigo, urticaria, bullous pemphigoid, eosinophilic pustular folliculitis, and scabies.^{145,147}

3.4 | Natural killer T cells and NK cells

Recent studies suggest a direct role of another innate cell subset, the natural killer T (NKT) cells, in the development and regulation of type 2 immune response although some controversies exist. NKT cells are an innate-like T-cell subset which expresses an invariant T-cell receptor alpha chain and recognizes lipids presented on CD1d. NKT cells are tissue-resident lymphocytes, but the prevalence of different NKT subsets differs markedly between tissues. They possess the ability to rapidly secrete large amounts of cytokines (mainly IFN- γ , IL-4, and IL-13). In the lung, NKT cells accumulate via CXCR6, and reside as an intravascular population.¹⁴⁸⁻¹⁵⁰ This strategic positioning may facilitate sensing of airborne antigens or infection as airway exposure to glycolipids or microbial cell wall components induced accumulation of NKT cells in the lung interstitium and bronchoalveolar space.¹⁴⁹ Multiple chemokines are induced in the lung after exposure to airborne NKT cell ligands,¹⁴⁹ including known NKT attractants

such as TARC/CCL17, MIG/CXCL9, and BCA-1/CXCL13.¹⁵⁰⁻¹⁵² It was suggested that CCR4 may be important in regulating NKT cell redistribution in the lung, since aerosolized delivery of exogenous CCL17 was sufficient to drive extravasation of NKT cells into the lung parenchyma.¹⁴⁹

Several studies have shown a protective role of NKT cells during the inflammatory responses to bacteria and parasites in diverse pulmonary bacterial infection models, including infections with *Streptococcus pneumoniae*, *Listeria monocytogenes*, and *Pseudomonas aeruginosa*.¹⁵³ Indeed, CD1d is expressed by several cell types in the lungs, including alveolar macrophages, CD11b⁺ DC, CD103⁺ DC, and mDC, all of which are potential antigen presenters for NKT cells. While it seems that NKT cells have a protective role during influenza and pulmonary bacterial infections (predominantly a type 1 response), their role in Th2 responses such as in asthma or chronic obstructive pulmonary disease (COPD) is still controversial.¹⁵⁴

Indeed, fungal and bacterial antigens from *Sphingomonas* species, *Aspergillus fumigatus*, and *Streptococcus pneumoniae* are recognized by NKT cells, and in mouse models induce asthma-like symptoms in an NKT cell-dependent manner.¹⁵⁵⁻¹⁵⁷ The involvement of NKT cells in allergic asthma is more controversial, with some studies finding that NKT cells are necessary for allergic pathology in mouse models^{158,159} and others reporting that NKT cells are not required.¹⁶⁰ In asthmatic patients, increased numbers of NKT cells in bronchoalveolar lavage samples¹⁶¹ and an increase in NKT cells after allergen challenge have been reported; however, some studies have failed to detect a difference in lung NKT cell numbers between asthmatic and nonasthmatic subjects.¹⁶² Reduced production of ovalbumin (OVA)-specific Th2-controlled immunoglobulin isotypes (IgE and IgG1) but not IgG2a was found in a mouse model for type I allergy against OVA when animals were administered specific bacterial cholesteryl glycosides. This suggests that NKT cells activated by the cholesteryl glycosides can potentially contribute to the homeostasis in the body following exposure to an excess of Th2 immunity.¹⁶³ NKT cells have been shown to induce AHR in the absence of adaptive immunity. In a murine model of asthma using glycolipid antigens to activate NKT cells, the latter stimulate the production of IL-33 from alveolar macrophages which in turn activate ILC2 to produce IL-13 and contribute to AHR.¹⁶⁴

Natural killer T cell populations resident in peripheral lymph nodes and skin exhibit an NK1.1⁺CD4⁺ phenotype, associated with expression of the transcription factor retinoic acid receptor-related orphan receptorROR gamma t, CCR6, CD103, and CD121a and generate IL-17 following activation.¹⁶⁵ While involved in type 2 immune response in other organs, skin resident NKT cells may play a major role during type I immune responses to infection and autoimmunity.¹⁶⁶

Natural killer cells are large granular lymphocyte and play an important role in innate immunity like NKT cells. Recent studies have demonstrated that NK cells and IFN- γ can suppress ILC2 responses in vitro and during allergic lung inflammation.¹⁶⁷⁻¹⁶⁹ NK cells deficiencies are distinguished in patients with AD and NK cells limit ILC2 inflammation in the skin in a murine model of AD induced by MC903. Moreover, NK cell-boosting IL-15 superagonist clearly shows the

beneficial effect in this murine model.¹⁷⁰ NKT cell, NK cell, and IFN- γ may play an essential role in the immunoregulation in the type 2 inflammation of lung and skin.

4 | EPITHELIUM AND EPITHELIAL CYTOKINES IN TYPE 2 IMMUNITY

4.1 | Type 2 immunity in response to noxious and innocuous stimuli

Type 2 immunity is induced not only by noxious stimuli, but also by innocuous stimuli (such as pollens, mites) and by inherited barrier disruption (such as by filaggrin deficiency).¹⁷¹ Stimulation of epithelium and/or epidermal barrier disruption promote inflammation through the release of epithelial cytokines as damage-associated molecular patterns and alarmins, such as IL-25, IL-33, and TSLP. This leads to the development of allergic, or type 2, diseases.¹⁷² The skin, lungs and gastrointestinal tract constitute the interface to the outside world and are continuously exposed to external pathogens. Various immune cells orchestrate immune responses at these sites by interacting with each other and with nonimmune cells, including epithelial cells.^{173,174} IL-25, IL-33, and TSLP represent essential cytokines from the injured epithelium that initiate type 2 immunity (Figure 7). However, all three cytokines do not act the same in all type 2 diseases and stimulants of these inflammations.¹⁷⁵ TSLP and IL-33 signaling reciprocally enhanced each other's protein release and expression in the lung following allergen challenge, and each other's receptor expression on lung ILC2 to enhance ILC2 activation.¹⁴ These cytokines can directly activate ILC2 and Th2 cells to produce type 2 cytokines.¹² Moreover, IL-33 and TSLP directly activate MC. TSLP stimulates Th0 cells and DC to induce a Th2-like process. TSLP also promotes B-cell proliferation.^{27,176}

Type 2 immune responses occur in response to parasitic helminths (eg, nematodes) and insects (eg, scabies), restricting sites permissive for parasite and insect reproduction and limiting barrier tissue damage. Such responses involve activation of ILC2 and Th2 cells, which secrete IL-4, IL-5, and IL-13 necessary for the accumulation of eosinophils and alternatively activated macrophages in involved tissues.^{171,177}

4.2 | IL-25 and type 2 immunity

IL-25 (IL-17E) is a member of the IL-17 cytokine family. Recent evidence indicates that IL-25 is expressed by epithelial and endothelial cells. IL-25-deficient mice fail to expel *Nippostrongylus brasiliensis* efficiently because of changes in the induction of Th2 type cytokine release and are very susceptible to experimental autoimmune encephalomyelitis.²⁷ Transgenic expression of IL-25 leads to blood eosinophilia and increased levels of IgE, IgG1, IL-5, and IL-13. IL-25 might be involved in pathogenesis of asthma. It is expressed at high levels in lungs of sensitized mice following allergen challenge, and transgenic mice that

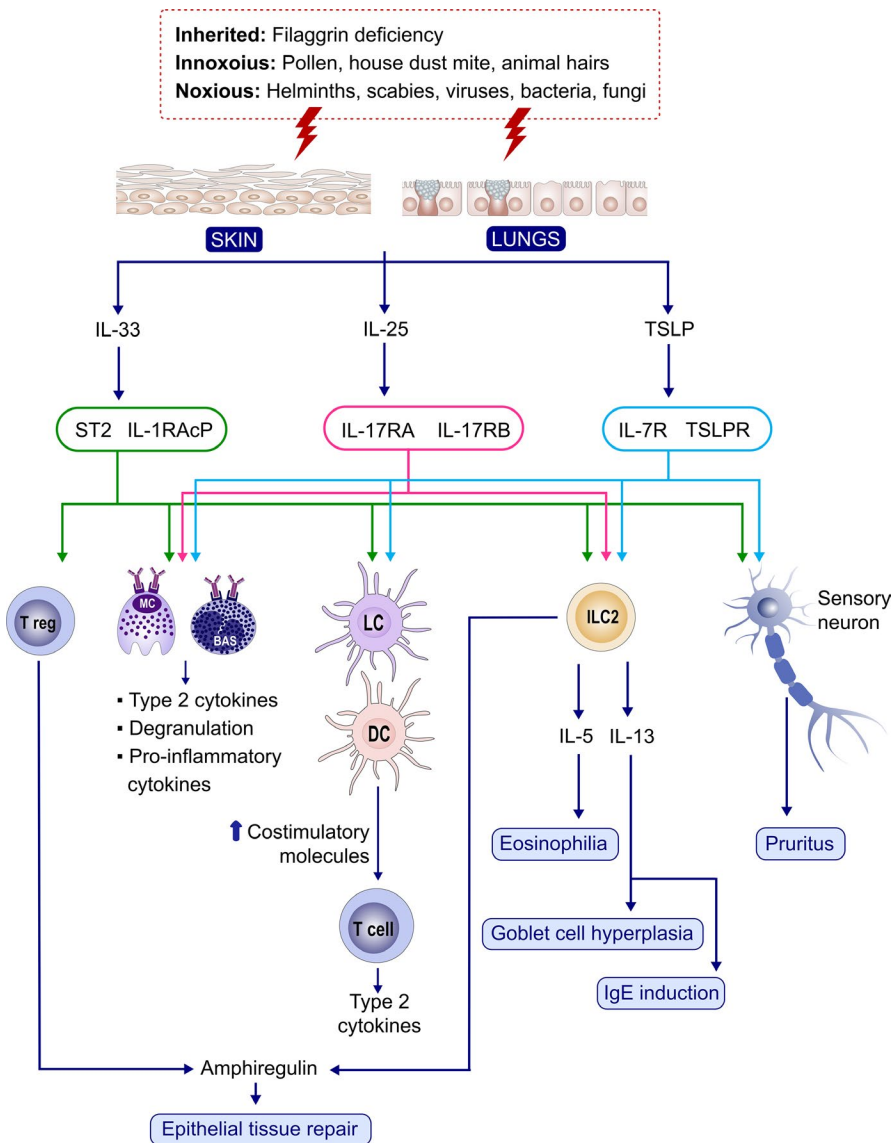


FIGURE 7 Immune and inflammatory response to allergens. Various noxious/innocuous triggers, including protease allergens, helminths, fungi, and viruses, induce the epithelial cells to secrete alarmins, such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). TSLP, IL-25, and IL-33 may initiate allergic inflammation by activating innate lymphoid cells 2 (ILC2), for production of large amounts of type 2 cytokines IL-5 and IL-13. ILC2 induce allergic inflammation, eosinophilia, goblet cell hyperplasia and immunoglobulin class-switch recombination in B cells, which leads to IgE production. TSLP activates dendritic cells (DC) and Langerhans cells (LC) to drive allergen-specific Th2 cells. Following IgE cross-linking, IL-33 and IL-25 augment mast cells (MC) and basophils (Baso) degranulation and produce type 2 cytokines. ILC2 also regulate fibrosis and tissue repair through IL-5, IL-13, or amphiregulin. TSLP and IL-33 can directly activate itch-sensory neurons and contribute to pruritus. IL, interleukin; IL-1RAcP, IL-1 receptor accessory protein

express IL-25 only in lungs have increased numbers of eosinophils and CD4⁺ T cells upon allergen-specific stimulation. IL-25 is constitutively expressed in tuft cells (also called brush cells) in the intestine and trachea¹⁷⁸ during inflammation.¹⁷⁹ IL-25 binds to a heterodimeric receptor consisting of IL-17RA and IL-17RB and activates MAPK (JNK and p38) and NF- κ B pathways. In contrast to T cells and B cells, ILC2 are directly stimulated by epithelial cytokines such as IL-25.

In mice, intranasal administration of IL-25 alone induces ILC2-mediated type 2 inflammation in the lung. Neutralization of IL-25 in the lungs with a soluble IL-25R fusion protein inhibited antigen-induced CD4⁺ T-cell recruitment into the airways, IL-5 and IL-13 production, and goblet cell hyperplasia.¹⁸⁰

4.3 | IL-33 and type 2 immunity

IL-33, a member of the IL-1 family of cytokines, is constitutively expressed at high levels in the nuclei of epithelial cells. After

epithelial cell injury or cellular activation through ATP signaling, these cells promptly release IL-33.¹⁸¹ Although already present at high levels in the steady state, the expression of IL-33 can be further increased during inflammation, such as COPDs, graft-versus-host diseases, helminth infection, and AD.¹⁸¹ IL-33 binds to a heterodimeric receptor formed by IL-1 receptor-like 1 (IL1RL1), also known as ST2 and the IL-1 receptor accessory protein, which leads to activation of NF- κ B and MAPK (ERK, p38, JNK) signaling pathways.¹⁸¹

The first evidence for a role of IL-33 in host defense was in helminth infection.¹⁸² IL-33 mediates together with IL-25 and TSLP worm expulsion by the activation of MC and ILC2 that increase IgA production via IL-6 and enhance goblet cell hyperplasia via IL-13. Consistently, human serum IL-33 levels correlate with clinical asthma and AD severity. Administration of IL-33 to mice led to airway inflammation through the activation of ILC2-producing type 2 cytokines that mobilize eosinophils and polarize alternatively activated macrophages. ST2-deficient mice have normal maturation of Th2 cells, but altered antigen-specific

Th2 type responses, increased rates of ventricular fibrosis, and cardiomyocyte hypertrophy in response to ventricular pressure overload. IL-33 deficiency mice showed attenuated eosinophilic pulmonary inflammation compared to wild-type mice in an OVA-induced asthma model. However, serum OVA-specific IgE levels were comparable in these two groups.¹⁸³⁻¹⁸⁶ IL-33 deficiency mice also showed attenuated eosinophilic pulmonary inflammation in protease-induced asthma model which is independent of T cells and B cells. IL33-IL1RL1 pathway polymorphisms are associated with asthma and specific wheezing phenotypes; most of the single nucleotide polymorphisms are associated with intermediate-onset wheeze, a phenotype closely associated with allergic sensitization.¹⁸⁷

On the other hand, IL-33 can induce the resolution of inflammation and repair of tissue damage. This is likely to be due to the effect of IL-33 on Treg and ILC2 to produce amphiregulin, which in turn supports epithelial tissue repair.¹⁸⁸ Thus, IL-33 plays an important role on both the induction of type 2 immunity and the resolution of inflammation.

4.4 | TSLP and type 2 immunity

Thymic stromal lymphopoietin is a member of the IL-2 cytokine family and is originally identified as a molecule that can stimulate murine thymocytes and promote B-cell proliferation and development.¹⁸⁹ TSLP is produced by epithelial cells at barrier surfaces upon mechanical injury (such as scratching), exposure to protein allergens with protease activity (such as pollens and mites) and cytokines (eg, TNF- α and IL-1 β).¹⁹⁰ It has been demonstrated that in AD and asthma, TSLP is highly expressed at the epithelium of the skin and lungs, respectively. TSLP binds to a heterodimeric receptor consisting of the IL-7 receptor (IL-7R) α -chain and the TSLPR chain. In mice, TSLP-signal transducer and activator of transcription (STAT) 5 axis in DC is a critical pathway to promote type 2 immune responses at barrier surfaces.¹⁹¹

Under inflammatory conditions, TSLP induces DC to upregulate costimulatory molecules such as OX40L, CD80, and CD86,¹⁹² which then drive IL-4, IL-5, and IL-13 production by CD4⁺ T cells in vitro. In vivo, TSLP-TSLPR signaling in epidermal Langerhans cells is critical to induce Th2 type immune responses in an OVA application-induced AD mouse model.¹⁹³ TSLP can also directly act on T cells: Circulating CD4⁺ T cells in AD patients show increased expression of the TSLPR compared to healthy subjects and the frequency of circulating TSLPR⁺ CD4⁺ T cells correlates with serum CCL17/TARC and IgE levels and eosinophil counts.¹⁹⁴ Additional pathways of TSLP to promote type 2 immunity are via acting on MC, ILC2, epithelial cells, macrophages, and basophils.¹⁹⁵

Moreover, keratinocyte-derived TSLP directly activates transient receptor potential cation channel subfamily A member 1 channels on sensory neurons,¹⁹⁶ which aggravates pruritus. Similarly, IL-31 released by type 2 immune cells in skin lesions mediates pruritus by stimulating neurons expressing IL-31 receptor subunit α (IL-31R α)¹⁹⁷ and increases neurite branching in the skin.¹⁹⁸ In a phase 2 trial, a humanized monoclonal anti-IL-31R α antibody significantly improved pruritus in AD patients.¹⁹⁹

Taken together, IL-25, IL-33, and TSLP are released by epithelial cells at mucocutaneous surfaces and share similar target cell populations to initiate and enhance type 2 immunity (Figures 1, 4 and 7). Therefore, it is important to understand how these epithelial cytokine pathways harmonize and the extent to which they are functionally distinct. Epithelial cytokines may be signals of local inflammation and tissue damage that serve as important checkpoints in the regulation of allergic inflammation at barrier surfaces. Targeting epithelial cytokines is a promising therapeutic option for type 2 allergic diseases.

5 | SKIN AND LUNG BARRIER AND TYPE 2 RESPONSE

5.1 | Bronchial epithelial barrier and type 2 responses

Bronchial epithelial cells are essential components of the innate immune response and lung tissue barrier. They produce antimicrobial peptides, cytokines, and chemokines, play a role in mucociliary clearance, activate eosinophils and Th2 cells, and recruit them to tissues.^{101,200-205} The epithelial barrier in the airways consists of mucus, surface liquids, microbiota, and junctional complexes between adjacent epithelial cells that comprise TJs. Homotypic and heterotypic interactions bind TJ molecules and establish cell-cell contact and regulate the paracellular passage of molecules.²⁰² During the last few years, a defective epithelial barrier has been demonstrated in affected organs in asthma, AD, allergic rhinitis, CRSwNP, EoE, and inflammatory bowel disease.^{12,28,202,206-215} It has been demonstrated that both type 1 and type 2 inflammatory processes occurring beneath the epithelium open the TJ barrier. Studies performed in bronchus and sinus have demonstrated a bidirectional effect of the opening and closing of the barrier.^{12,28,202,206-214} Closed epithelial TJs in the mucosal epithelium protect against exposome components, such as allergens, pollutants, microbes, and their enzymes and toxins.²¹⁶ Open epithelial TJs in the mucosa help to drain subepithelial inflammation, but at the same time allow the entrance of foreign substances to deeper tissues.¹² Type 1 inflammation below the mucosal surface is characterized by an opening of the barrier that via induction of epithelial cell apoptosis causes direct tissue injury. IFN- γ , Fas, Fas ligand, TNF- α , and tumor necrosis factor-like weak inducer of apoptosis have been reported as responsible molecules for skin keratinocyte death in eczema, mucosal epithelial cell death and shedding in asthma, CRS, and colitis.²¹⁷⁻²²¹ In type 2 inflammation, Th2 cells and ILC2 play major roles in the opening of the TJs, mainly via IL-4 and IL-13 as demonstrated by two recent studies.^{12,28,206} Bronchial epithelial cells from asthmatic patients show a significantly low TJ integrity in air-liquid interface (ALI) cultures compared with human bronchial epithelial cells (HBECs) from healthy subjects.²⁸ Th2 cells and their cytokines, IL-4 and IL-13, decreased barrier integrity in ALI cultures of HBECs from control subjects, but not in HBECs from asthmatic patients. They induced a physical separation

of the TJs of adjacent cells in immunofluorescence staining of the TJ molecules occludin and zonula occludens-1. The *in vivo* relevance of TJ/barrier disruption by ILC2 was examined in a murine model of IL-33-induced airway inflammation in wild-type, recombination-activating gene 2 (Rag2)-deficient, Rag2/Il2 γ -deficient, and ROR α -deficient staggerer mice. In this setting, ILC2 impaired the epithelial barrier by reducing transepithelial electrical resistance and increasing fluorescein isothiocyanate-dextran permeability in ALI cultures of HBECS. This was paralleled by decreased mRNA and disrupted protein expression of TJ components and was restored by neutralization of IL-13. Intranasal administration of recombinant IL-33 to wild-type and Rag2-deficient mice lacking T and B cells triggered TJ disruption, whereas in Rag2/Il2 γ -deficient and ROR α -deficient staggerer mice undergoing bone marrow transplantation that lack ILC2, the barrier was intact.¹² Direct nasal administration of IL-13 was sufficient to induce deficiency in the TJ barrier in the bronchial epithelium of mice *in vivo*. This highlights an essential mechanism in asthma pathogenesis, that is, that ILC2 are responsible for bronchial epithelial TJ barrier leakiness through IL-13.

5.2 | Epidermal barrier in the skin and type 2 response

The outer epidermis consists of two main functional components (Figure 8).²²² The superficial stratum corneum (SC) acts as a physical

barrier, preventing the ingress of irritants and allergens with the potential to induce a type 2 allergic response by the underlying keratinocytes in the deeper epidermis. The SC is typically composed of 12–16 layers of dead, flattened, corneocytes. Corneocytes contain keratin filaments aggregated by filaggrin.^{215,223} Filaggrin also provides the scaffold for a composed of a ceramide-rich lipid matrix into which the corneocytes are embedded. This lipid layer is important for waterproofing the skin. Filaggrin may also suppress protease activity.²²⁴

Corneodesmosomes are specialized cell-cell adhesion molecules specific to the SC that rivet corneocytes together to create a cohesive multicellular physical barrier. They consist of cell membrane anchored interlinking cadherins (desmoglein 1 and desmocollin 1), and corneodesmosin, a secreted serine-rich glycoprotein which consolidates the skin barrier and subsequent desquamation.²²⁵

Endogenously produced serine (kallikreins), cysteine, and aspartate (cathepsins) proteases regulate desquamation by degrading corneodesmosomes at the skin surface. Sodium dodecyl sulfate and other surfactants, the key ingredients of soap and skin cleansers,²²⁶ as well as many aeroallergens possessing protease activity (eg, house dust mite, pollens and pet allergens), can degrade corneodesmosomes, thus interfering with the integrity of the SC and inducing type 2 immune responses.

Cutaneous type 2 immune responses are typically induced by primary and secondary defects in SC which leave the underlying

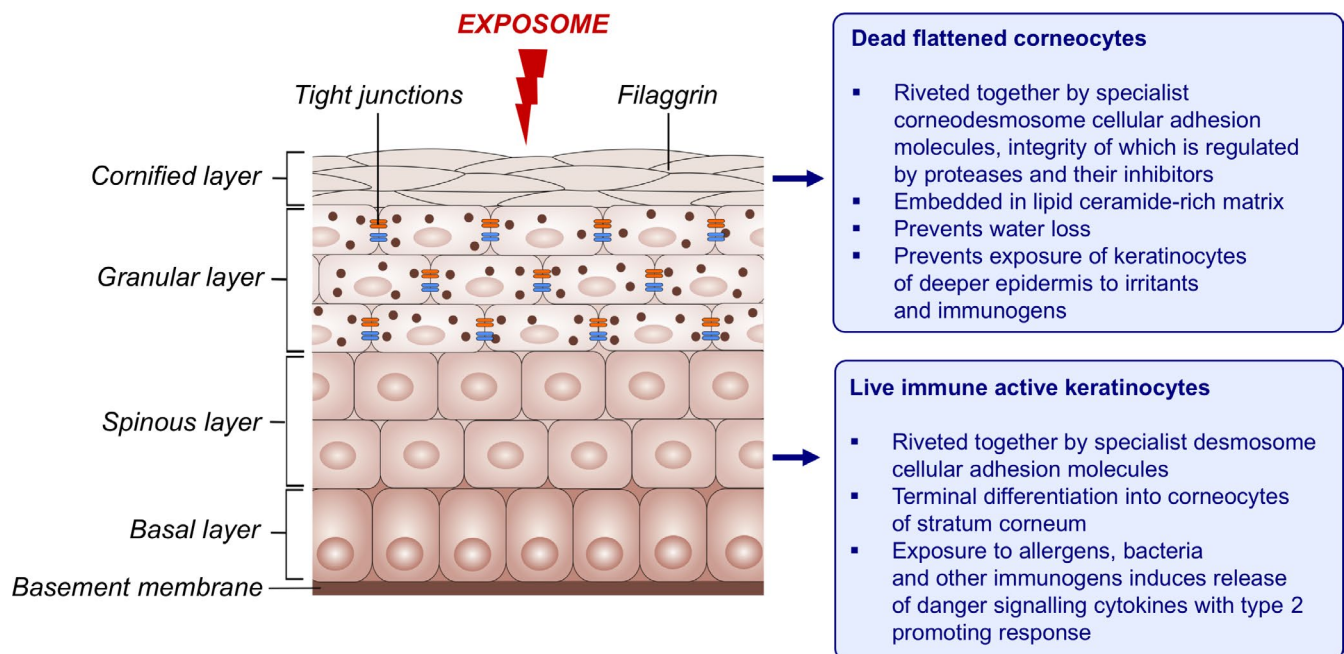


FIGURE 8 Epidermal differentiation of keratinocytes and skin barrier. The epidermis is separated from the underlying dermis by the basement membrane. Keratinocytes mainly compose the epidermis. As differentiation proceeds, keratinocytes progress upward through the different epidermal layers (basal layer, spinous layer, granular layer, and cornified layer). The smaller black dots in the cells of the granular layer represent keratohyalin granules. Tight junctions (TJs) are in stratum granulosum and contribute to epithelial barrier function by preventing leakage of extracellular fluid. In addition, the skin barrier consists of several layers of dead keratinocytes (corneocytes) glued together in a mixture of lipids. They consist of a mixture of ceramides, cholesterol, and fatty acids, and their composition is essential for the barrier function and to prevent water loss

TABLE 1 Contrasting effects of the superficial stratum corneum and deeper epidermis in inherited diseases related to type 2 immune responses

	Stratum corneum (SC) defects associated with type 2 immune responses and AD	Deeper epidermis defects not associated with type 2 immune responses and AD
Inherited diseases of the epidermis		
Cellular junctional proteins	Primary corneodesmosome defects Corneodesmosin (<i>CDSN</i>) deficiency: peeling skin syndrome, dermatitis Desmoglein 1 (<i>DSG1</i>) deficiency: severe dermatitis, multiple allergies, wasting Desmocollin 1 (<i>DSC1</i>) deficiency:	Primary desmosome defects Some forms of epidermolysis bullosa: Primary genetic blistering skin disease and fragility following minor trauma due to mutations in one of at least 20 genes coding for desmosomes and hemidesmosomes as well as components of the cytoskeletal keratin Claudin 1 (<i>CLDN1</i>) deficiency (murine model) leads to neonatal death due to fluid loss and sepsis
Defects in endogenous protease inhibitors	Serine protease inhibitor deficiency LEKTI (<i>SPINK5</i>) deficiency (Netherton syndrome) leading to increased kallikrein activity and corneodesmosome degradation: congenital ichthyosiform erythroderma, invaginated distal hair shafts, and multiple allergies	
Structural epidermal proteins	Defective filaggrin production Filaggrin (<i>FLG</i>) deficiency associated with AD, contact dermatitis, food allergies, allergen-associated asthma, and eczema herpeticum	Defective keratin production Some forms of Epidermolysis bullosa: Primary genetic blistering skin disease and fragility following minor trauma due to mutations in one of at least 20 genes coding for components of the cytoskeletal keratin, adhesion contacts, desmosomes and hemidesmosomes
Acquired diseases of the epidermis		

Abbreviation: AD, atopic dermatitis. LEKTI, Lympho-epithelial Kazal-type-related inhibitor; SPINK5, serine protease inhibitor Kazal-type 5

epidermal layers relatively intact to release danger signals/type 2 immune promoting cytokines such as IL-33 and TSLP.²²⁷⁻²³¹ Disorders of desmosome cell-cell junctions, which shear of not only the SC but also the deeper epidermis do not typically lead to AD but rather severe life-limiting skin diseases such as epidermolysis bullosa²³² and pemphigus vulgaris²³³ (Table 1).

The most common inherited disease associated with AD is filaggrin deficiency, affecting one in ten Northern Europeans, but only 1% of Africans.^{234,235} Mutations in this gene lead to ichthyosis vulgaris, AD, a 5-fold increased risk of food (peanut) allergy and allergen-associated asthma, and eczema herpeticum.²³⁶ The exact mechanism by which filaggrin deficiency leads to AD is still unclear, but probably involves a combination of disrupted SC formation and increased degradation due to less regulated endogenous protease activity.

In a filaggrin deficiency mouse model, IL-1 β and the NLRP3 inflammasome but not type 2 mediators or ILC2 mediated dermatitis.²³⁷ On the other hand, ILC2 damage keratinocytic TJ integrity via IL-13.¹³ IL-4 and IL-13 induce filaggrin downregulation in normal keratinocytes²³⁸ and secretion of periostin, a matricellular protein. The IL-13/periostin pathway plays a crucial role in the onset of allergic skin inflammation: IL-13 induces IL-24 secretion in keratinocytes. IL-24 downregulates filaggrin expression via STAT3 and thereby promotes barrier dysfunction.²³⁹

6 | LESSONS FROM PRIMARY IMMUNE DEFICIENCIES LINKED TO TYPE 2 IMMUNITY

Primary immunodeficiency diseases (PID) provide important clues as to the relative importance and redundancy of specific immune components and pathways in the development of type 2 immune diseases such as AD. There are now over 350 PID with specific underlying genetic causes.²⁴⁰ Although PID are classically thought of as predisposing to infection, it is increasingly recognized that they may also be associated with immune dysregulation leading to not only to autoinflammation and autoimmunity, but in some patients to allergy.²⁴¹ PID associated with excessive type 2 responses and atopic diseases can be divided into three main categories (Table 2, Figure 9).

6.1 | Defective effector T-cell maturation (eg, Omenn syndrome)

Infants born with serious, but incomplete, defects in T-cell development (leaky severe combined immune deficiency) classically show eosinophilia and erythroderma. These signs of a type 2 immune response might be confused with AD.^{242,243} Affected infants often

TABLE 2 Key categories and examples of primary immunodeficiency diseases associated with aberrant type 2 immune responses and allergic diseases

Disease category	Specific examples	Allergic phenotype	Predominant nonallergic clinical features
Defective effector T-cell maturation in early infancy	Leaky SCID (Omenn syndrome) <i>RAG1</i> , <i>RAG2</i> , <i>ADA</i> , <i>LIG4</i> , <i>RMRP</i> , <i>ILR27</i> , <i>CHD7</i> , <i>DCLRces</i> <i>C</i> , 22q11 microdeletion	Erythroderma, eosinophilia, high IgE	Opportunistic viral, bacterial fungal and parasitic infections, for example, bronchiolitis, gastroenteritis, atypical pneumonia, and thrush
Defective regulatory T-cell development	IPEX <i>FOXP3</i> , Wiskott-Aldrich syndrome below	Eczema, food allergies, raised IgE	Autoinflammatory enteropathy, autoimmune cytopenias, thyroid disease, insulin-dependent diabetes, alopecia
T-cell signaling defects	Wiskott-Aldrich syndrome <i>WASP</i> <i>DOCK8</i> deficiency <i>STAT3</i> deficiency (hyper-IgE syndrome, Job syndrome) <i>TYK2</i> deficiency <i>CARD11</i> deficiency IL-6 receptor (<i>IL6R</i>) deficiency	Eczema, food allergies, raised IgE Eczema, food allergies Eczema, food allergies, eosinophilia, high IgE Eczema Eczema, asthma, allergic rhinoconjunctivitis, food allergies, eosinophilic esophagitis Eczema, eosinophilia, high IgE	Opportunistic viral, bacterial, fungal, and parasitic infections, thrombocytopenia and bleeding, cytopenias, lymphoma Opportunistic viral infections, for example, molluscum Recurrent pyogenic lung infections, bronchiectasis, pneumatoceles, retained primary dentition Opportunistic viral, bacterial, and fungal infections of lung, gut, and skin Sinopulmonary infections, autoimmune cytopenias, inflammatory bowel disease, alopecia, lymphoma Sinopulmonary infections, bacterial skin infections

Abbreviations: IL, interleukin; IPEX, immunodysregulation, polyendocrinopathy, enteropathy, X-linked.

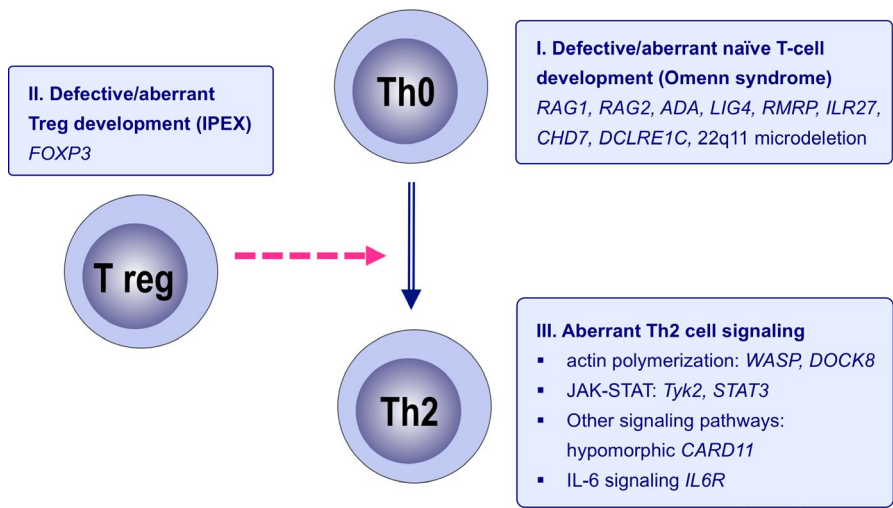


FIGURE 9 Primary immunodeficiency diseases associated with excessive type 2 responses and atopic diseases. I. Omenn syndrome is caused predominantly by mutations in the recombination-activating genes (*RAG*) 1 or *RAG2*. *RAG1* and *RAG2* are essential to the generation of mature B cells and T cells. II. Infants born with the immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome have eczema. Immunodysregulation is caused by a mutation in the *FOXP3* gene widely considered to be the master gene regulator of the Treg cell. III. This group includes defects in actin polymerization (eg, Wiskott-Aldrich syndrome and *DOCK8* deficiency), defects in JAK-STAT signaling (eg, *STAT3* deficiency and *Tyk2* deficiency), and defects in other immune signaling pathways (eg, hypomorphic/dominant negative *CARD11* deficiency) and cytokine pathways (eg, IL-6 receptor deficiency). IL, interleukin; STAT, signal transducer and activator of transcription; Treg, regulatory TRAG1

fail to thrive, suffer from thrush and other opportunistic infections, diarrhea, or bronchiolitis. Lymphocyte counts can show normal or even raised numbers of T lymphocytes, but B lymphocytes are usually absent. Urgent specialist referral is indicated as hematopoietic stem cell transplantation (HSCT) can be curative in over 90% of patients.

6.2 | Defective Treg-cell development

Infants born with the innate Treg defect immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome^{244,245} may have eczema and food allergies, although they are not usually the predominant or most troublesome clinical feature. In contrast,

refractory autoimmune enteropathy can be life-threatening, and autoimmune diseases of the thyroid (hypo- or hyperthyroidism), blood (hemolytic anemia and other cytopenias), insulin-dependent diabetes, and alopecia are also associated with significant morbidity. Urgent referral to a specialist center for patients with IPEX is important as HSCT is potentially curative. A number of other inherited Tregopathies are now recognized (*CTLA4*, *LRBA*, *BACH2*, *STAT3* gain of function, *IL10*, *IL10R* deficiencies), but again autoimmunity and autoinflammation rather than allergy are the main clinical features. Thus, despite their theoretical potential,²⁴⁶ innate and IL-10-producing Tregs appear to be largely redundant in the pathogenesis of allergy.²⁴⁷

6.3 | T-cell signaling defects

A complex ensemble of PID characterized by aberrant T-cell signaling is associated with allergy. This group includes defects in actin polymerization (eg, Wiskott-Aldrich syndrome^{248,249} and *DOCK8* deficiency),²⁵⁰ defects in JAK-STAT signaling (eg, *STAT3* deficiency previously called hyper-IgE syndrome or Job syndrome²⁵¹ and *Tyk2* deficiency), and defects in other immune signaling pathways (eg, hypomorphic/dominant negative *CARD11* deficiency)²⁵² and cytokine pathways (eg, IL-6 receptor deficiency).²⁵³ In most of these PID, atopic disease and food allergies are relatively mild and overshadowed by nonallergic complications. For example, in *STAT3* deficiency the main clinical features are not allergic, but rather recurrent pyogenic lung infections, bronchiectasis, pneumatoceles, and retained primary dentition. Of all the PID associated with allergy, hypomorphic/dominant negative *CARD11* deficiency is associated with the most severe allergic phenotype, with some patients suffering from life-threatening asthma, or allergic rhinoconjunctivitis requiring allergen immunotherapy. Low serum IgM may provide a clue to the correct diagnosis. *CARD11* has a number of roles in lymphocytes including linking antigen recognition with downstream NF- κ B activation. Further research into the type 2 promoting effect of *CARD11* mutations may provide a fruitful route to better understand the immune propensity to allergy.^{254,255}

7 | CONCLUSION

The field of type 2 immunity has experienced major progress over the past few years, unraveling new aspects of the cellular and molecular mechanisms in allergic diseases. A complex interplay of cellular players and effector molecules of both the innate and adaptive immune system orchestrates and mediates type 2 responses in the skin and lung. It has become clear that epithelial-derived cytokines such as IL-25, IL-33, and TSLP are particularly important in initiating type 2 responses, while IL-4, IL-5, and IL-13 act as core effector mediators and perpetuators in this setting. Beyond T cells, DC, MC,

and eosinophils, ILC2 have emerged as key players in type 2 immunity. Despite many analogies in the skin and lung, immune responses at these different sites are not identical, as evidenced, for example, by the diverse cellular infiltrates in AD and asthma. Recently, the effectiveness and safety of biologics for patients with asthma and AD have been established. Better understanding of type 2 immunity lead to efficient biological therapies to support the growing demand for asthma and AD.^{70,78-80}

This new knowledge in type 2 immunity research opens the door to relevant questions in this area. We need to further explore the importance of the different cellular players involved, how they interact with each other and with epithelial barrier components in the lung and skin. This will help us to better understand disease endotypes in asthma and AD and translate this knowledge to refined treatment recommendations and guidelines.

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CONFLICTS OF INTEREST

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