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Innate lymphoid cells: The missing part of a puzzle in food allergy

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Abstract: Food allergy is an increasingly prevalent disease driven by uncontrolled type 2 immune response. Currently, knowledge about the underlying mechanisms that initiate and promote the immune response to dietary allergens is limited. Patients with food allergy are commonly sensitized through the skin in their early life, later on developing allergy symptoms within the gastrointestinal tract. Food allergy results from a dysregulated type 2 response to food allergens, characterized by enhanced levels of IgE, IL-4, IL-5, and IL-13 with infiltration of mast cells, eosinophils, and basophils. Recent studies raised a possible role for the involvement of innate lymphoid cells (ILCs) in driving food allergy. Unlike lymphocytes, ILCs lack They represent a group of lymphocytes that lack specific antigen receptors. ILCs contribute to immune responses not only by releasing cytokines and other mediators but also by responding to cytokines produced by activated cells in their local microenvironment. Due to their localization at barrier surfaces of the airways, gut, and skin, ILCs form a link between the innate and adaptive immunity. This review summarizes recent evidence on how skin and gastrointestinal mucosal immune system contribute to both homeostasis and the development of food allergy, as well as the involvement of ILCs toward inflammatory processes and regulatory mechanisms.

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Innate lymphoid cells: The missing part of a puzzle in food allergy

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Abstract

Food allergy is an increasingly prevalent disease driven by uncontrolled type 2 immune response. Currently, knowledge about the underlying mechanisms that initiate and promote the immune response to dietary allergens is limited. Patients with food allergy are commonly sensitized through the skin in their early life, later on developing allergy symptoms within the gastrointestinal tract. Food allergy results from a dysregulated type 2 response to food allergens, characterized by enhanced levels of IgE, IL-4, IL-5, and IL-13 with infiltration of mast cells, eosinophils, and basophils. Recent studies raised a possible role for the involvement of innate lymphoid cells (ILCs) in driving food allergy. Unlike lymphocytes, ILCs lack They represent a group of lymphocytes that lack specific antigen receptors. ILCs contribute to immune responses not

Abbreviations: AD, Atopic dermatitis; AREG, amphiregulin; COPD, Chronic pulmonary obstructive disease; DCs, Dendritic cells; EoE, Eosinophilic esophagitis; FLG, Filaggrin; FPIES, Food protein induced enterocolitis syndrome; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GUT, Gastrointestinal system; ILCs, Innate lymphoid cells; iTregs, Inducible Tregulatory cells; KLRG1, Killer cell lectin-like receptor subfamily G member 1; LT α cell, Lymphoid tissue inducer cells; NK cell, Natural killer cell; OIT, Oral immunotherapy; PGD2, Prostaglandin D2; ROR γ t, Retinoic acid-related orphan receptor gamma t; TGF- β , Transforming growth factor- β ; TNF- α , Tumor necrosis factor- α ; TSLP, Thymic stromal lymphopoietin; ZO-3, Zonula occludens-3.

Umit M. Sahiner, Janice A. Layhadi equally contributed to this study.

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only by releasing cytokines and other mediators but also by responding to cytokines produced by activated cells in their local microenvironment. Due to their localization at barrier surfaces of the airways, gut, and skin, ILCs form a link between the innate and adaptive immunity. This review summarizes recent evidence on how skin and gastrointestinal mucosal immune system contribute to both homeostasis and the development of food allergy, as well as the involvement of ILCs toward inflammatory processes and regulatory mechanisms.

KEYWORDS

immune tolerance, innate immunity, skin

1 | INTRODUCTION

Food allergy is defined as an adverse reaction which occurs reproducibly on exposure to a certain food and arises from a specific immune response.¹ Food allergies affect up to 7%–8% of the population and have been increasing in prevalence in the last two decades. They are more commonly observed in children compared with adults, with the majority of allergies involving peanut, tree nuts, egg, milk, wheat, soy, fish, and shellfish.^{1,2} The common underlying mechanism of various food allergies is the breakdown of immunological and clinical tolerance to an ingested food, which results in IgE-mediated reactions like anaphylaxis or non-IgE-mediated disorders, such as eosinophilic esophagitis (EoE) and food protein-induced enterocolitis syndrome (FPIES).^{2,3} Sensitization to food allergens usually occur through the skin and/or gastrointestinal tract and less commonly through the respiratory tract, due to impaired barrier functions.^{4,5} Following sensitization, some of these individuals go on to develop clinical allergy. The interaction between the microbiota, immune system, epithelial barriers, and genetic factors results in a dysregulated type 2 response to food allergens. Recent studies demonstrated the involvement of a novel cell type, known as innate lymphoid cells (ILCs), in driving food allergy.^{6,7} The involvement of ILCs in food allergy is not well defined; however, elevated levels of Interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP) observed in allergic patients raise a possible role for these cells because these cytokines are strong stimuli of a subset of these cells, the ILC2s.^{8–10} For instance, it was shown that IL-33 promotes food allergy through the expansion and activation of ILC2s, resulting in the large production of IL-4 that suppresses regulatory T-cell function in the skin, lung, and small intestine.¹¹

ILC2s have also been shown to be potent producers of IL-9, which was highly expressed in a study of children with peanut allergy.¹² In addition, the expression of IL-33 was increased in esophageal biopsies of pediatric EoE patients¹³ and ILC2s were increased in esophageal biopsies from patients with active EoE.¹⁴

2 | CLASSIFICATION AND PLASTICITY OF ILCs

ILCs are novel subsets of lymphoid cells that lack antigen-specific receptors, making them distinct from T and B cells. They respond to a number of inflammatory cytokines and lipid mediators such as IL-1, IL-18, IL-33, IL-23, and IL-25 (IL-1 and IL-12 family cytokines).¹⁵ Helper ILCs can be classified into ILC1, ILC2, ILC3, and lymphoid tissue inducer (LTi) cells based on their cytokine production and transcriptional profiles with ILC1s, ILC2s, and ILC3s resembling CD4⁺ T helper (Th)1, Th2 and Th17/22 cells, respectively (Figure 1).^{16,17} LTi cells are indispensable for the initiation of secondary lymphoid organ development during embryonic life.¹⁸ Adult LTi cells are Neuropilin-1⁺ (NRP1⁺) ILC3-like cells that are key inducers of ectopic lymphoid aggregate (ELA) formation.¹⁹ In addition to this, natural killer (NK) cells represent the “cytotoxic” ILCs corresponding to CD8⁺ cytotoxic T cells.^{16,20}

ILC1s are defined by the expression of T-bet (T-box expressed in T cells) transcription factor and can be activated by macrophage- and dendritic cell (DC)-derived IL-12 and IL-18. The activation of ILC1s lead to the production of interferon (IFN)- γ . Upon exposure to intracellular pathogens, an increase in ILC1 number is observed in order to protect against viruses and bacteria.²¹ They have been implicated in conditions such as Crohn's disease,²² Celiac disease,²³ and chronic pulmonary obstructive disease (COPD).²⁴

ILC2s are under the control of transcription factor GATA-3 and once activated by epithelium-derived IL-25, IL-33, and TSLP, they produce type 2 cytokines IL-5 and IL-13.^{16,24} The role of ILC2s is defined in several diseases such as allergic asthma,^{25,26} allergic rhinitis,²⁷ atopic dermatitis (AD),²⁸ and eosinophilic esophagitis.¹⁴

ILC3s are divided into 2 different subgroups of cells which can be distinguished by the expression of the natural cytotoxicity receptor Nkp44.²⁹ Retinoic acid-related orphan receptor (ROR γ t) is the transcription factor for all ILC3 subtypes. They secrete IL-17, IL-22, granulocyte-macrophage colony-stimulating factor (GM-CSF), and/or tumor necrosis factor (TNF)- α in response to myeloid-derived IL-1 β and IL-23.³⁰ ILC3s can both promote or suppress the immune

FIGURE 1 Classification and plasticity of ILCs. Depending on their cytokine production and transcriptional profiles, ILCs can be categorized into ILC1, ILC2, ILC3, and lymphoid tissue inducer (LTi) cells. ILC1s can be activated by macrophage- and dendritic cell (DC)-derived cytokines (IL-12 and IL-18), to produce Interferon (IFN)- γ . ILC2s express transcription factor GATA-3 and can be activated by epithelium-derived IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Upon activation, ILC2s produce type 2 cytokines IL-5 and IL-13. ILC3s can be further classified depending on their expression of NKp44 receptor. In response to IL-1 β and IL-23, ILC3s secrete IL-17, IL-22, granulocyte-macrophage colony-stimulating factor (GM-CSF) and/or tumor necrosis factor (TNF)- α . ILC subsets are highly plastic and can trans-differentiate in response to changing cytokine milieu. The transdifferentiation of ILC2s into ILC1s or ILC3s can be reversed by IL-4. On the other hand, IL-12 drives differentiation of ILC2 toward ILC1 and IL-1 β , IL-23, and TGF- β drive differentiation of ILC2 toward ILC3.

relationship with each other: ILC3s induce IL-15 production in B cells via BAFF receptor, while IL-15, a potent growth factor for ILC3s, up-regulates CD40L expression on ILC3s. IL-15-activated CD40L⁺ ILC3s help the differentiation of IL-10-secreting, functional immature transitional regulatory B cells in a CD40L and BAFF receptor-dependent manner. This mechanism contributes to the maintenance of immune tolerance to innocuous antigens and becomes insufficient in allergic diseases.³³ Tonsils are important mucosal sites of immune tolerance, where a generation of functional allergen-specific Treg cells occurs. It was shown that ILC3s and Breg cells colocalize in the interfollicular regions of palatine tonsils, together with Treg cells. These data suggest that there are regulatory niches in tonsils.³⁴

More extensive information on ILC surface markers and cytokine production can be found in recent reviews,^{20,29,31} with ILC3s being associated with the pathology of inflammatory bowel diseases,³⁵ COPD,³⁶ and psoriasis.³⁷

Beyond this classification, ILCs display plasticity and heterogeneity across tissues.³⁸⁻⁴⁰ ILCs display plasticity, which is defined as being able to change their phenotype and function in response to microenvironmental changes. This feature further complicates current studies and classification of ILCs. In the presence of IL-12, ILC3s and ILC2s lose their ROR γ t and GATA-3 expression, respectively, and can transdifferentiate into ILC1s- expressing T-bet and -producing IFN- γ .^{23,41,42} ILC1s can be reconverted into ILC3s by stimulation with IL-1 β , IL-23, and retinoic acid.⁴³ Similarly, IL-4 can reconvert ILC1s into ILC2s,²⁴ while IL-1 β , IL-23, and TGF- β drive ILC2 transdifferentiation toward IL-17-producing ILC3.⁴⁴ ILCs plasticity and heterogeneity across tissue may highlight their involvement in food allergy.

3 | IMMUNE SYSTEM OF THE SKIN AND ILCs

The skin acts as an interface between the host and the environment and serves as a mechanical and biological barrier against chemical and physical effects and pathogenic microorganisms. Skin-associated immune cells are important for this protection and their dysregulation can contribute to the pathogenesis of food allergy. Among these cells, macrophages, DCs, mast cells, T cells, B cells, neutrophils, and ILCs orchestrate the defense while taking part in homeostatic functions.^{45,46}

Studies in humans revealed that during homeostatic skin conditions, ILCs are mainly localized in the dermis, with the exception of ILC3s which are found within the epidermis.^{47,48} A recent study also revealed that ILCs are compartmentalized within sebaceous glands and a subset of ROR γ t⁺ ILCs found within hair follicles can modulate these sebaceous glands.⁴⁹ ILC2s are the most abundant subset of ILCs found in the healthy skin, constituting nearly one-third of the skin-resident lymphocytes in mice.⁴⁷ ILC3s in healthy human skin are also present in high numbers.⁵⁰ Skin ILCs migrate to the tissue from the circulation. This idea is supported by the expression of CCR10 and cutaneous leukocyte antigens in some of the circulating ILCs.^{37,51}

In the steady state, ILC2s are involved in homeostasis and wound healing.⁴⁶ Multiphoton microscopy study reveals the perivascular distribution of ILC2s and their close proximity to skin-resident mast cells, suggesting that these cells affect each other during homeostasis and inflammation.⁴⁷ ILC2s are the main source of IL-13 in the skin resulting in the inhibition of the mast cell functions.⁴⁷ ILC2s express amphiregulin (AREG) which is an epidermal growth factor-related molecule and plays an important role in tissue repair in the skin and airways after acute epithelial damage.^{52,53} It was previously demonstrated that acute cutaneous injury promoted ILC2 response which prevented epithelialization and effective wound closure.⁵⁴ ILC3s have also been shown to take part in skin repair. Both mouse and human studies showing accumulation of IL-17F-producing ILC3s in the wound site. In an ILC3-deficient mouse model, a delay in epidermal proliferation, macrophage accumulation, and wound healing was observed, demonstrating ILC3 contribution in the repair of skin tissue.⁵⁵

In addition to homeostasis and wound repair, ILCs have an important role in disease processes of the skin such as that of allergy. Exposure of the skin to allergens and exogenous molecules frequently trigger a type 2 cytokine production associated with elevated TSLP, IL-33, and IL-25.^{47,53,56-58} This process is characterized by the secretion of IL-4, IL-5, and IL-13 by ILC2s, increased eosinophil numbers and mast cell activation.^{47,53,58} ILC2s can also disrupt keratinocyte tight junction barrier integrity by their IL-13 production.⁵⁹ In the context of atopic dermatitis (AD), ILC2 receptors for IL-25, IL-33, and TSLP have been demonstrated as upregulated within the skin lesions.^{37,53,60,61} Furthermore, an increase in the proportion of ILC2s is also observed within AD skin lesions, suggesting an important role of ILC2s in skin inflammation.⁴⁷

Additionally, a novel mechanism for ILC2 activation in AD is through tumor-associated surface molecule B7-H7. This protein is in AD skin and subsequently activates NKp30 expression on ILC2s in human.⁶² Experimental models have demonstrated that ILC2s and their stimulator epithelial cytokines TSLP, IL-13, and IL-25 play an important role in the pathogenesis of food allergy.^{9,63} A study involving murine model revealed that ILC2 plays a role in skin to gut cross-talk following mechanical skin injury. ILC2 expansion in this model is driven by IL-25 and IL-33, which leads to the production of IL-4. This production of IL-4 can then result in the expansion of intestinal mast cells thereby promoting IgE-mediated food anaphylaxis.⁶⁴ Though this requires further validation, these emerging evidence may support the notion that ILC2 is an important and potent driver of the skin immune system in type 2 inflammation like AD and toward the pathogenesis of food allergy.

4 | MUCOSAL IMMUNE SYSTEM OF THE GUT AND ILCs

The gastrointestinal system (gut) is the largest lymphoid tissue in the body which interfaces with the external environment. Interaction of three distinct cellular compartment shapes the

biological behavior of this system. The first cell compartment is the epithelial mesenchymal cell monolayer composed of diverse cell types and presents a physical and biological barrier against nonself components of the lumen, including pathogens and allergic molecules. The second cell compartment comprises the innate and adaptive immune system cells including mast cells, dendritic cells, ILCs, T- and B-cell types, and humoral components like sIgA, sIgE, and sIgG. The third compartment of this ecosystem is the commensal microbiota. Through the communication of these three different cell compartments, either an immune tolerance to antigens and commensal bacteria occurs or an inflammatory mucosal immune response develops. Moreover, immune reactions against harmful microorganisms are also shaped by the interaction of these three cell compartments.^{65,66}

Luminal antigens are taken up and processed by DCs for presentation to T cells. This leads to the development of mucosal antigen-specific immune responses such as Th1, Th2, T regulatory (Tregs), Th17 cell type, or IgA-producing B cells. During homeostasis, the predominating ILC type is the ILC3s which is found mostly in the intestinal lamina propria but also in the lymphoid structures.^{23,67} ILC3s are also involved in limitation of pathologic adaptive immune responses against commensal bacteria in the gut,⁶⁸ with a recent study demonstrating them as important producers of IL-2 in the gut, which plays a role in driving Treg cells.⁶⁹ In addition to ILC3, other ILC subsets, notably the LT α , have been described in the gut. LT α cells are necessary for the development of lymphoid tissues in the fetal GUT and they can also produce cytokine IL-17.^{70,71} IL-22, a cytokine produced by ILC3, can induce epithelial tight junction proteins thereby promoting epithelial barrier function.⁷² ILC3-derived IL-22 also induces the production of antimicrobial peptides in the gut.⁷³

ILC2s are enriched within the mucosal barrier of the gut and experiments in mice have shown that ILC2s can regulate intestinal eosinophil homeostasis⁷⁴ and are involved in restoring the epithelial barrier function by the production of AREG (Figure 2).⁷⁵ Whether human ILC2s are enriched and exert similar functions within the gut is still unclear.

5 | THE LINK BETWEEN SKIN BARRIER DISRUPTION AND RESPONSE TO FOOD ALLERGENS IN THE GUT

Food allergy frequently develops during infancy.⁷⁶ For this reason, exposure to food allergens early in life may be protective toward the development of allergy, establishing oral tolerance before sensitization to the allergen. The LEAP study showed that early introduction of peanut decreased school-age peanut allergy by 81% in children at high risk of developing peanut allergy due to egg allergy or severe eczema.⁷⁷ Although the GUT mucosa is continuously exposed to allergens and commensal microorganisms, the immune system usually mounts a tolerant response to these antigens. Induced regulatory T cells (iTregs) and Tr1 lymphocytes play an important role in this immune tolerance. Tolerogenic CD103⁺ dendritic cells present the

luminal antigens and induce Foxp3⁺ Tregs in a Transforming growth factor- β (TGF- β) and retinoic acid-dependent pathway.^{78,79} In children who become tolerant toward cow's milk allergens ("outgrow" the disease), the level of Tregs have been found to be higher than those with persistent cow's milk protein allergy.⁸⁰ Genetic and environmental factors shape the immune responses in the skin when exposure to food allergens occurs. In two epidemiologic studies, AD and the filaggrin (FLG) gene mutation have been identified as potential risk factors for the development of food allergy.^{81,82} In experimental food allergy models, epicutaneous exposure to food allergens resulted in intestinal food allergy development in a Th2-dependent manner.^{56,83} Despite the advancement in studies, the mechanism by which allergic sensitization in the skin is able to disrupt oral tolerance and how this leads to the development of food allergy in the gut remains unclear.

It is proposed that the triggering effect of epicutaneous food allergens stimulates TSLP, IL-33, and IL-25 production in the skin keratinocytes; these alarmins induce the activation of ILC2s and DCs.^{47,53,56-58,78,79} The migration of DCs to the lymph nodes triggers the proliferation of Th2 effector and memory cells.⁸⁴ Following ingestion of the food to which the individual is sensitized, it is postulated that these Th2 cells migrate into the intestine and communicate with ILC2s, which, in turn produce IL-13. Intestinal epithelial cells also produce IL-33 and IL-25, further stimulating ILC2s. As a result of this, an allergic immune response develops toward this food allergen.^{85,86}

6 | ILCs IN FOOD ALLERGY AND ORAL TOLERANCE DEVELOPMENT

6.1 | IgE-mediated food allergy

IgE-mediated food allergy is the most common type of food allergy and affects up to 10% of infants in western populations.^{87,88} It is characterized by specific IgE (sIgE) production and interaction of sIgE with different immune cells (Th2 cells, mast cells, and basophils).^{88,89} The intestinal mucosa is capable of secreting alarmins which can activate ILC2s.⁹⁰ In an experimental food allergy model, it was found that deficiency of IL-33 receptor (ST2) prevented the development of food allergy.¹¹ In another study, TSLP and basophils were both found to be important in allergic cutaneous sensitization while IL-33 was found to be necessary for the induction of IgE-dependent anaphylaxis.⁹¹ IL-33 release following skin injury has been shown to induce IgE-mediated mast cell degranulation and anaphylaxis. Furthermore, blocking of ST2 prior to oral challenge has reduced the severity of anaphylactic reactions without affecting the Th2 response to the allergen.⁵ Another important alarmin, IL-25, has also been shown to increase following food challenges.⁹ The study also showed that mice defective of IL-25 were more resistant to symptoms of food allergy. After allergic sensitization, IL-25 and IL-2 derived from CD4⁺ Th2 cells stimulate ILC2s resulting in the production of large amounts of IL-13, amplifying the IgE-mediated

FIGURE 2 Development of IgE-mediated food allergy in mucosal immune system of the gut. Epicutaneous food allergen can be captured by dendritic cells (DCs) and can trigger the production of thymic stromal lymphopoietin (TSLP), interleukin-33 (IL-33), and IL-25 in the skin keratinocytes, resulting in the activation of ILC2s. DCs can migrate to the lymph nodes to activate T cells through MHC II-dependent interaction. Once food to which the individual is sensitized to is ingested, Th2 cells migrate to the intestine where they can interact with ILC2 to induce the production of type 2 cytokines. Intestinal epithelial cells also produce IL-33 and IL-25, further activating ILC2s. Cytokines produced by ILC2 (IL-5, IL-9, and IL-13) can subsequently lead to the activation of eosinophil, mast cells, and induction of IgE isotype switching of B cells, all of which contribute to an allergic immune response toward the food allergen.

experimental food allergy. In addition to this, ILC2s with defective IL-13 production showed reduced ability to develop allergic inflammation resulting in resistance to food allergy.⁹ It has been demonstrated in a mouse model of food allergy that IgE-activated mast cells activate ILC2s for IL-13 production in an IL-4R α -dependent manner, and ILC2s amplify systemic anaphylaxis by increasing target tissue sensitivity to mast cell mediators.⁷ These findings support the key role of ILC2s in food allergy in an IL-13-dependent manner.

Tregs regulate the functions of ILC2s and suppress their type 2 cytokine production. Reciprocally, ILC2s secrete IL-4 which down-regulates Treg functions and increases mast cell activation.¹¹ In the steady state, these networks function to facilitate tolerance; however, genetic and environmental factors, such as microbiota

dysregulation, may stimulate alarmin production from the intestinal epithelial cells resulting in ILC2 activation.⁹⁰ Of note, the medium-chain triglycerides in peanut have been shown to increase alarmin production, thus promoting allergic sensitization and anaphylaxis.⁹² iTregs are inhibited by the effect of IL-4,¹¹ and after re-exposure to food allergens, activated mast cells can stimulate IL-33 production and ILC2 activation. This forms a positive feedback loop on mast cell activation and a negative feedback loop on iTregs, promoting the persistence of food allergy.^{93,94}

Commensal bacteria also have indirect effects on host immune responses toward food antigens. Some *Clostridia* strains induce the accumulation of Tregs in the colon.^{95,96} *Clostridia* also trigger ILC3s to produce IL-22, strengthening the epithelial barrier. In mice, *Clostridia*

containing microbiota suppressed food allergic responses.⁹⁷ In response to the microbial signals, macrophages secrete IL-1 β which mediates GM-CSF release from ILC3s. GM-CSF induces IL-10 and retinoic acid production by DCs and macrophages and subsequently promotes the induction of Tregs. Any interference with this cross-talk results in the loss of oral tolerance to food allergens.⁹⁸

6.1.1 | Eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is a chronic disease characterized by gastroesophageal reflux disease, and dysphagia leading to food impactions and strictures. Pathologically, esophageal remodeling consists of epithelial hyperplasia with barrier dysfunction, subepithelial fibrosis, and smooth muscle dysmotility.⁹⁹ EoE is associated with elevated levels of total IgE and IgE sensitization to foods and aeroallergens.¹⁰⁰ In children with EoE, sensitization to both food and environmental allergens may be observed in 75% of patients.¹⁰¹ Elimination of food allergens or elemental diets can reduce disease symptoms in 70%–99% of patients; however, relapse is very common after a re-introduction of food allergens.¹⁰² Response to food elimination and re-introduction suggests that chronic food antigen hypersensitivity is an essential feature of EoE. In addition, some patients with EoE have a history of food anaphylaxis,^{101,103} and there may be a progression from IgE-mediated food allergy to the later development of EoE toward the same food.¹⁰⁴

Oral immunotherapy (OIT) for food allergy may induce the development of EoE in 2%–10% of patients and usually resolves after discontinuation of treatment.^{105,106} Furthermore, OIT is known to stimulate the production of IgG₄, which may be important in the pathogenesis of EoE.^{107,108} Whilst EoE was initially suspected to be an IgE-mediated allergy to food and plant allergens, investigations involving targeted food elimination diets and IgE blocking failed to support this notion. Moreover, measuring sIgE levels and/or skin prick testing was not sufficient to clearly identify the responsible food allergen.^{109–112} Following these observations, while EoE is often associated with IgE sensitization, it is not considered to be an IgE-mediated food allergy.

There is increasing evidence for epithelial barrier dysfunction in EoE followed by eosinophilic inflammation like AD. The expression of FLG, zonula occludens (ZO)-3, and claudin-1 is decreased in EoE patients, correlating with spongiosis,¹¹³ and mutations in FLG are higher in patients with EoE.¹¹⁴

Investigations to the role of ILC2s in EoE pathogenesis and food allergy revealed that ILC2s were significantly increased in tissues from patients with active EoE versus inactive EoE and were also higher than ILC2s in controls. Importantly, the proportions of ILC2s in biopsy specimens correlated with the numbers of eosinophils in esophagus tissue.¹⁴ Both IL-33 and TSLP activate ILC2s from esophageal lymphoid tissue which provides a proof of concept for ILC2s induction in EoE (Figure 3).¹⁴ Indeed, TSLP is highly expressed in EoE tissue.^{99,115} TSLP produced by epithelial cells and type 2 cytokines

(IL-5 and IL-13) produced by inflammatory cells, including ILC2s, are key factors in determining EoE pathogenesis. IL-5 production leads to esophageal eosinophilia and IL-13 induces EoE-specific epithelial gene expression and remodeling like angiogenesis.¹¹⁶ Moreover, eosinophil granulocyte-derived extracellular traps stimulate IL-33 and TSLP production in airway epithelial cells which enhance ILC2 activation and cytokine production.¹¹⁷ IL-33 expression is increased in pediatric EoE development consistent with the role of this cytokine in the pathology.¹³ The inhibition of the esophageal Treg function by IL-33 may induce loss of antigen-specific tolerance and provide a mechanistic rationale for EoE development.¹³

Given that ILC2s are located close to mast cells in human lung, a crosstalk between these two cell types are highly plausible.^{118,119} In EoE, a crosstalk between ILC2 and mast cells is likely mediated through IL-9, though this needs to be further validated.^{14,118–120} These findings therefore support a potential role for ILC2s in active EoE pathogenesis.

6.1.2 | Atopic dermatitis

AD is lapsing chronic inflammatory skin disease characterized by epithelial barrier dysfunction and type 2 inflammation.¹²¹ During the development of AD, environmental allergens and genetic factors affect the skin barrier function and trigger type 2 inflammation. This may lead to the failure of the mechanisms of oral tolerance, resulting in the development of food allergy. An increased risk for hen's egg allergy as early as 4 months of age has also been shown in infants with AD.⁸¹ An important genetic risk factor for AD is the FLG gene mutation. FLG mutations cause skin barrier disruption and decrease the level of E-cadherin which is an important inhibitor of ILC2s through its receptor (Killer cell lectin-like receptor subfamily G member 1 (KLRG1)).⁵³ In an experimental model of AD with FLG mutation, it was shown that skin inflammation is associated with the expansion of IL-5-producing ILC2s. Additionally, mice with FLG mutation showed increased frequency of ILC2s in the skin in comparison with control subjects.²⁸

Interaction of ILC2s with other cell types may also be important in the development of AD. Although basophils in healthy human skin are rare, they are enriched in the dermis of AD lesions and located in close proximity to ILC2. ILC2s express IL-4 receptor α (IL-4R α) and proliferate in an IL-4-dependent manner. IL-4 is supplied by basophils during AD inflammation, which suggests a relationship between these two cell types in AD pathogenesis.¹²²

Dermal ILC2s locate perivascularly and are in close proximity to the skin-resident mast cells. ILC2s produce IL-9 and IL-13, and these cytokines may activate mast cells. On the other hand, mast cells produce IL-25, Prostaglandin D2 (PGD2), and Leukotriene C4 (LTC4) which can activate the ILC2s.¹²³ Both mast cells and ILC2s can be activated by TSLP which may potentiate the function of both of these cell types. Additionally, ILC2s are capable of producing IL-5 which can activate eosinophils (Figure 4).

FIGURE 3 Role of ILC2 in eosinophilic esophagitis (EoE). Exposure of esophageal epithelium to food allergens result hyperplasia, impaired barrier and the release of thymic stromal lymphopoietin (TSLP) and interleukin-33 (IL-33). TSLP and IL-33 can activate ILC2 resulting in the release of cytokines IL-4, IL-5, IL-9, and IL-13. IL-13 production by ILC2 can induce EoE-specific epithelial gene expression and remodeling such as angiogenesis. Production of IL-4 can result in IgE-class switching in B cells while IL-5 production can lead to esophageal eosinophilia. On the other hand, a crosstalk between ILC2 and mast cells (MC) has been suggested through IL-9 which results in the degranulation of MC and secretion of mediators such as histamine.

FIGURE 4 Pathophysiology of atopic dermatitis (AD) and the role of ILC2s in AD. A mutation of the filaggrin (FLG) gene results in skin barrier disruption allowing increased penetration of allergens. Damaged keratinocytes result in the release of alarmins such as interleukin-25 (IL-25), IL-33 and thymic stromal lymphopoietin (TSLP) which can all act to activate dermal ILC2. As FLG mutation also results in a reduction in the level of E-cadherin, an important inhibitor of ILC2s through its receptor KLRG1, activation of ILC2 is further enhanced in AD. Activated ILC2 can secrete high amounts of IL-9 and IL-13 which can activate skin-resident mast cells (MC). In parallel, MC produce IL-25, Prostaglandin D2 (PGD2) and Leukotriene C4 (LTC4) which can activate ILC2. The interaction of ILC2s with other immune cells are also important for the development of AD. IL-4-dependent proliferation of ILC2 can be achieved through its interaction with basophils that are enriched in the dermis of AD lesions. Additionally, ILC2s can secrete IL-5 which can activate eosinophils. The function of ILC2s can be regulated by regulatory T cells (Treg).

FIGURE 5 The development and functional role of IL-10⁺ ILC2. Immature ILC2s (iILC2s) are derived from ILC precursor (ILCP). Exposure of iILC2s to TSLP and IL-33 can result in the activation of ILC2 which triggers the production of type 2 cytokines such as IL-5, IL-13 and IL-9. Activated ILC2 can also produce IL-4 which can in turn promote the differentiation of naïve T cells into Th2 cells. On the other hand, iILC2 exposed to IL-7, IL-33, and retinoic acid (RA) can result in the generation of IL-10⁺ ILC2s which have the capacity to produce IL-10, IL-5, and IL-13. IL-10⁺ ILC2s are functional and can suppress ILC2s and Th2 responses.

7 | THERAPEUTIC APPLICATIONS AND FUTURE PERSPECTIVES

Pathological processes in food allergy are related to type 2 inflammation, both in IgE-mediated and non-IgE-mediated diseases. Of the various key players involved in type 2 inflammation, ILC2s have been shown to be key drivers of the pathophysiology. In many allergic diseases, glucocorticosteroids are among the main therapeutics and their effect on suppressing ILC2s has been shown previously.^{124,125} TSLP is related to steroid resistance and blockage with anti-TSLP antibody (AMG157) decreases eosinophilic inflammation in target tissues.^{126,127} IL-25 and IL-33 are also attractive targets for treating allergic diseases. PGI2 analog cicaprost inhibits IL-33-induced ILC2 proliferation in experimental mouse models and decreases IL-5 and IL-13 secretion in humans.¹²⁸ Blocking of IL-25, IL-33, or TSLP by antibodies like tezepelumab have been reported to be beneficial for treating allergic patients.¹²⁹ Cytokines released by ILC2s may be targeted to suppress type 2 inflammation. Humanized monoclonal Ab against IL-5 (mepolizumab) and a human Ab against IL-4R α (dupilumab) were found to be effective against several allergic diseases in humans.^{130,131} Dupilumab targets the IL-4R, thereby inhibiting both IL-4 and IL-13 and improves uncontrolled moderate-to-severe atopic dermatitis as well as persistent asthma.^{132,133}

Many other molecules and pathways relevant to ILC2 activation are also being explored. CRTH2 (CD294), a receptor for PGD₂ expressed by ILC2s, promotes ILC2 migration and IL-13 production.¹³⁴ Currently, selective CRTH2 antagonists like fevipiprant and timapiprant are being tested for the treatment of allergic diseases.^{135,136} Furthermore, leukotriene receptor antagonists, such as montelukast and zafirlukast can prevent ILC2 activation by inhibiting the cysteinyl leukotriene receptor 1 (CysLT1R).¹³⁷ Lipoxin A4 (LXA4) functions as an inhibitor of ILC2s¹²⁰ and severe asthma patients have a LXA4 deficiency,¹³⁸ making LXA4 a treatment option in these patients. Considering that upregulation of c-Myc expression is essential for activation and in vivo pathogenic effects of ILC2s, the inhibition of it can be a promising novel strategy to combat allergic diseases.¹³⁹

Regulatory immune cells have also emerged as potential targets. One such example includes Treg cells which can suppress ILC2-driven inflammatory pathways. Moreover, several recent studies have revealed the existence of ILC2s that can produce IL-10. In vitro studies revealed that these IL-10-producing ILC2s are induced following stimulation of ILC2s with IL-2, IL-7, IL-33, and retinoic acid. These regulatory ILC2s are not equivalent to Treg cells as they lack the Treg master transcription factor FoxP3.^{140,141} Moreover, these IL-10-producing ILCs are functional and can suppress Th2 cell responses (Figure 5).¹⁴²

These regulatory ILC2s are induced following subcutaneous (SCIT) and sublingual grass pollen immunotherapy (SLIT),¹⁴¹ as well as house dust mite SCIT treatment.¹⁴³ These observations suggest a potential utility of regulatory ILCs as a target for the treatment of food allergy.

8 | CONCLUSION

Food allergy is an increasing problem throughout the world. Despite numerous available studies and decades of ongoing research, questions about the mechanism of food allergy, oral tolerance, and the role of ILCs and other immune cells have in these processes remain unanswered. ILCs provide a bridge between native and adaptive immunity thereby having a crucial role in the immune system. There is a growing awareness about the role of plasticity of ILCs in different inflammatory conditions and future studies may provide more insights to understanding how the skin and the gastrointestinal mucosal immune systems work both in homeostasis and in progression to food allergy. In particular, it is of great interest to identify physiologically relevant stimuli that directly or indirectly activate ILC2 in the skin which may lead to epicutaneous sensitization. Moreover, an association of AD and food allergy is found stronger in infancy than childhood, despite epicutaneous sensitization being more developed at a later life.¹⁴⁴ Mechanisms of epicutaneous sensitization during infancy and the involvement of ILCs in this context has yet to be identified. Finally, possible interaction of ILC with a novel subset of T cells known as T follicular helper 13 (T_{FH}13) cells which have been implicated in food allergy remains to be identified.¹⁴⁵ Understanding the contribution of ILCs to inflammatory processes and regulatory mechanisms in food allergy may help to develop novel therapeutics that target ILCs to treat food allergy and to induce immune tolerance.

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CONFLICT OF INTEREST

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