Innate Lymphoid Cells: The Missing Part Of A Puzzle In Food Allergy

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Abstract

Food allergy is an increasingly common disease worldwide, and is thought to be driven by an uncontrolled type 2 immune response. Current knowledge about the underlying mechanisms that initiate and promote an inappropriate immune response to dietary allergens is limited. Sensitization through the skin in early life is considered to be a key event. 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 during acute reactions. Recent data implies a possible role of innate lymphoid cells (ILCs) in driving food allergy. ILCs represent a group of lymphocytes that lack specific, recombined antigen receptors. They contribute to immune responses not only through the release of 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 evidences 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 towards inflammatory processes and regulatory mechanisms.

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 T regulatory cells
KLRG1: Killer cell lectin-like receptor subfamily G member 1
LTi cell: Lymphoid tissue inducer cells
NK cell: Natural killer cell
OIT: Oral immunotherapy
PGD2: Prostaglandin D2
RORγt: Retinoic acid related orphan receptor gamma t
TGF-β: Transforming growth factor-β
TSLP: Thymic stromal lymphopoietin
TNF-α: Tumor necrosis factor-α
ZO-3: Zonula occludens-3

Introduction

Food allergy is defined as an adverse reaction to food which is reproducible and arises from a specific immune response.\(^1\) Food allergies affect up to 7-8% of the population and have been increasing in prevalence, although the incidence has probably stabilised in Western countries. Prevalence is higher in children compared to adults, with the most common food triggers being peanut, tree nuts and seeds, egg, milk, wheat, soy, fish and shellfish.\(^1-3\) The common underlying mechanism is the breakdown of immunological and clinical tolerance to an ingested food, causing either IgE-mediated reactions (including anaphylaxis) or non-IgE-mediated disorders such as eosinophilic oesophagitis (EoE) and food protein induced enterocolitis syndrome (FPIES).\(^4\) Sensitization to food allergens usually occurs through the skin and/or gastrointestinal tract (and less commonly through the respiratory tract), due to impaired barrier function.\(^5, 6\) Following sensitization, many – but not all – individuals go on to develop clinical reactivity. The interaction between microbiota, the immune system, epithelial barrier function and genetic factors results in a dysregulated type 2 response to food allergens. Recent studies have demonstrated the possible involvement of a novel cell type, known as innate lymphoid cells (ILCs), in driving food allergy.\(^7\) While their role is not currently well-defined, the elevated levels of Interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP) observed in allergic patients imply a possible role because these cytokines are strong stimuli of a subset of these cells, the ILC2s.\(^7-9\) For instance, recently, 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 cells function in the skin, lung and small intestine.\(^10\) ILC2s have been shown to be potent producers of IL-9, which was highly expressed in a study of children with peanut allergy.\(^11\) In addition, the expression of IL-33 was increased in esophageal biopsies of pediatric EoE patients\(^12\) and ILC2s density was increased in esophageal biopsies from patients with active EoE.\(^13\)

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 such as IL-1, IL-18, IL-33, IL-23, and IL-25 (IL-1 and IL-12 family cytokines) and lipid mediators.\(^14\) Helper ILCs can be classified into ILC1, ILC2, ILC3...
and lymphoid tissue inducer (LTi) subtypes based on their cytokine production and transcriptional profiles (Figure 1): in this regard, ILC1s, ILC2s and ILC3s resemble CD4^+ T helper (Th)1, Th2 and Th17/22 cells, respectively. LTi cells are indispensable for the initiation of secondary lymphoid organ development during embryonic life. Adult LTi cells are Neuropilin-1+ (NRP1+) ILC3-like cells that are key inducers of ectopic lymphoid aggregate (ELA) formation. In addition to this, natural killer (NK) cells represent the “cytotoxic” ILCs corresponding to CD8^+ cytotoxic T cells.

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. They have been implicated in conditions like Crohn’s disease, Celiac disease and chronic pulmonary obstructive disease (COPD).

ILC2s are under the control of transcription factor GATA-3, and once activated by epithelium-derived IL-25, IL-33 and TSLP, they produce the type 2 cytokines IL-5 and IL-13. The putative role of ILC2s have been defined in several diseases including allergic asthma, allergic rhinitis, atopic dermatitis (AD) and eosinophilic esophagitis.

ILC3s are divided into 2 different subtypes, which can be distinguished by the expression of the natural cytotoxicity receptor NKp44. Retinoic acid-related orphan receptor (RORγt) is the transcription factor for all ILC3 subtypes. ILC3s 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-1β and IL-23. They can both promote or supress the immune response depending on the microenvironment and presence of cytokines within the tissues. Retinoic acid and active form of vitamin D (1,25-dihydroxyvitamin D3) have antagonistic effects on the expression of effector cytokines and gut-homing integrin by human ILCs. The balance between these vitamins may be an important factor in the functioning of ILCs in allergic disease, including food allergy.

Activated CD40L^+ ILC3s reside on the border of T cell–B cell areas in tonsils and are in close contact with B cells in vivo. CD40L^+ ILC3s and B cells are a symbiotic relationship: ILC3s induce IL-15 production in B cells via BAFF-receptor, while IL-15, a potent growth factor for ILC3s, upregulate 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 contributes to the maintenance of immune tolerance to innocuous antigens and is thought to become insufficient in allergic diseases. Tonsils are a crucial site for the generation of functional allergen-specific Treg cells and are therefore important mucosal sites for the development of immune tolerance. ILC3s and Breg cells co-localize in the interfollicular regions of palatine tonsils, together with Treg cells. These data suggest that there are regulatory niches in tonsils.

More extensive information on ILC surface markers and cytokine production can be found in recent reviews. ILC3s have been associated with the pathology of inflammatory bowel diseases, COPD and psoriasis. Beyond this classification, ILCs display plasticity and heterogeneity across tissues. ILCs are able to change their phenotype and function in response to changes in the local microenvironment, a characteristic which confounds attends to delineate and classify their role. In the presence of IL-12, ILC3s and ILC2s lose their RORγt and GATA-3 expression respectively, and can trans-differentiate into ILC1s expressing T-bet and producing IFN-γ. ILC1s can be reconverted into ILC3s by stimulation with IL-1β, IL-23 and retinoic acid. Similarly, IL-1β and IL-4 can reconvert ILC1s into ILC2s.

**Immune system of the skin and ILCs**

The skin acts as an interface between host and 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: macrophages, DCs, mast cells, T cells, B cells, neutrophils and recently
described ILCs orchestrate the defense while taking part in homeostatic functions. 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. A recent study reported that ILCs are compartmentalized within sebaceous glands, and a subset of RORγt+ ILCs found within hair follicles can modulate these sebaceous glands. ILC2s are the most abundant subset of ILCs found in the healthy skin, constituting nearly one third of the skin-resident lymphocytes in mice. ILC3s in healthy human skin are also present in high numbers. 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.

In the steady state, ILC2s are involved in homeostasis and wound healing. 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. ILC2s are the main source of IL-13 in the skin resulting in the inhibition of the mast cell functions. 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. Recently, it was shown that acute cutaneous injury promoted ILC2 response which prevented epithelialization and effective wound closure. 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.

In addition to homeostasis and wound repair, ILCs have an important role in disease processes of the skin. Exposure of the skin to allergens and exogenous molecules frequently trigger type 2 cytokine production associated with elevated TSLP, IL-33 and IL-25. This is characterized by the secretion of IL-4, IL-5 and IL-13 by ILC2s, increased eosinophil numbers and mast cell activation. ILC2s can also disrupt keratinocyte tight junction barrier integrity by their IL-13 production. ILC2 receptors for IL-25, IL-33 and TSLP is upregulated in AD skin lesions and an increase in the proportion of ILC2s is also observed, suggesting an important role of ILC2s in skin inflammation. Additionally, a novel mechanism for the ILC2 activation in AD is the tumor-associated surface molecule B7-H7 which increases in AD skin and activates NKp30 expression on ILC2s in human. 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. A recent study involving murine model reported that ILC2 is an essential mediator of skin to gut crosstalk following mechanical skin injury. ILC2 was driven by IL-25 and IL-33 and resulted in the expansion of intestinal mast cells, thereby promoting IgE-mediated food anaphylaxis. Therefore, ILC2s may be an important and potent driver of the skin immune system in type 2 inflammation like food allergy and AD (Figure 2).

Mucosal immune system of the GUT and ILCs

The gastrointestinal system (GIT) is the largest lymphoid tissue in the body which interfaces with the external environment. Interaction of three distinct cellular compartment shapes the biological behaviour 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 allergenic 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. Communication between these three different cell compartments results in either immune tolerance to antigens and commensal bacteria, or a milieu in which an inflammatory mucosal immune response can develop. Moreover, immune reactions against harmful microorganisms are also shaped by the interaction of these three cell compartments.

Luminal antigens are taken up and processed by DCs and presented to T cells leading 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. ILC3s are also involved in limitation
of pathologic adaptive immune responses against commensal bacteria in the gut, with a recent study demonstrating them as important producers of IL-2 in the gut, which plays a role in driving Treg cells.

ILT1 cells are necessary for the development of lymphoid tissues in the fetal GIT and they can also produce cytokine IL-17. IL-22, a cytokine produced by ILC3, can induce epithelial tight junction proteins thereby promoting epithelial barrier function. ILC3-derived IL-22 also induces the production of antimicrobial peptides in the gut. Moreover, experimental data have shown that in mice, ILC2s regulate intestinal eosinophil homeostasis and are involved in restoring the epithelial barrier function by the production of AREG (Figure 3). Whether human ILC2s exert similar functions is still unclear.

**The link between skin barrier disruption and response to food allergens in the GIT**

Food allergy frequently develops in infancy, so establishing oral tolerance though exposure to food allergens early in life may be protective against food allergy. The LEAP study showed that the introduction of peanut into the infant diet before 12 months of age decreased the risk of peanut allergy by 81% at age 5 years in children at high risk of developing peanut allergy due to egg allergy or severe eczema. Although the GIT 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. In children who “outgrow” and become tolerant to cows milk protein, the level of Tregs are higher than in those with persisting allergy to cow’s milk. Genetic and environmental factors shape the immune responses in the skin when an 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. In animal models, epicutaneous exposure to food allergens resulted in intestinal food allergy development in a Th2 dependent manner. However, the mechanism by which allergic sensitization in the skin is able to disrupt oral tolerance and lead to the development of food allergy remains unclear. It has been proposed that the triggering effect of epicutaneous food allergen exposure stimulates TSLP, IL-33 and IL-25 production in skin keratinocytes; these alarmins induce the activation of ILC2s and dendritic DCs. The migration of DCs to the lymph nodes triggers the proliferation of Th2 effector and memory cells. Ingestion of the food in the context of pre-existing sensitization may cause migration of these Th2 cells into the GIT where they communicate with ILC2s, which, in turn produce IL-13. Intestinal epithelial cells also produce IL-33 and IL-25, further stimulating ILC2s. These processes then induce the development of food allergy.

**ILCs in food allergy and oral tolerance development**

**IgE-mediated food allergy** is the most common type of food allergy, and affecting up to 10% of infants in western populations. It is characterized by specific IgE (sIgE) production and IgE interaction with different immune cells (Th2 cells, mast cells and basophils). The intestinal mucosa is capable of secreting alarmins which can activate ILC2s. In an experimental food allergy model, it was found that deficiency of IL33 receptor (ST2) prevented the development of food allergy. 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. The release of IL-33 following skin injury has been shown to induce IgE-mediated mast cell degranulation and anaphylaxis; blocking ST2 prior to oral challenge reduced the severity of reaction without affecting the Th2 response to the allergen. Another important alarmin, IL-25, has also been shown to increase following food challenges. The authors also demonstrated that mice deficient in IL-25 were more resistant to the symptoms of food allergy. Following allergic sensitization, IL-25 and IL-2 derived from CD4+ Th2 cells stimulate ILC2s resulting in the production of large amounts of IL-13 and amplifying the IgE-mediated response in this experimental model. In addition, ILC2s with defective IL-13 production had a reduced ability to develop allergic inflammation, resulting in resistance to food allergy. In a murine model of food allergy, IgE-stimulated mast cells induced IL-13 production from ILC2s in an IL-4Rα-dependent manner; in addition, ILC2s amplified systemic anaphylaxis by increasing target tissue sensitivity to mast cell mediators. These findings support a key role of ILC2s in food allergy.
Cytokine production.

...stimulate alarmin (IL-33, TSLP) production in airway epithelial cells that enhances ILC2 activation and...
specimens correlated with numbers of eosinophils in esophagus tissue. This supports a role for ILC2s in EoE pathogenesis. Mast cells and IL-9 have also been implicated. ILC2s produce IL-9 and are located close to mast cells in human lung, suggesting a crosstalk between these two cell types. Both IL-33 and TSLP activate ILC2s from esophageal lymphoid tissue which provides a proof of concept for ILC2s induction in EoE (Figure 4). Indeed, TSLP is highly expressed in EoE tissue.

Atopic dermatitis (AD) is a relapsing chronic inflammatory skin disease characterized by epithelial barrier dysfunction and type 2 inflammation. 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. Infants with AD at 4 months of age are at increased risk for allergy to hen’s egg. An important 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)). In an experimental model of AD with FLG mutations, skin inflammation was associated with the expansion of IL-5-producing ILC2s. Additionally, mice with FLG mutations showed increased frequency of ILC2s in the skin in comparison to control subjects.

Interaction of ILC2s with other cell types may also be important. 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-4Rα) 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. 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. Both mast cells and ILC2s can be activated by TSLP which may potentiate the function of both of these cell types.

Therapeutic applications and future perspectives

Pathological processes in food allergy are related to type 2 inflammation, in both IgE mediated and non-IgE mediated diseases. ILC2s have been shown to be key drivers of the pathophysiology. Glucocorticosteroids are often used as therapy and their effect on suppressing ILC2s has been previously demonstrated. TSLP is related to steroid resistance and blockage with anti-TSLP antibody (AMG157) decreases eosinophilic inflammation in target tissues. 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. Blocking of IL-25, IL-33, or TSLP by antibodies like tezepelumab have been reported to be beneficial for treating allergic patients. 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-4Rα (dupilumab) were found to be effective against several allergic diseases in humans. 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.

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. Currently, selective CRTH2 antagonists like fevipiprant and timapiprant are being tested for the treatment of allergic diseases. Furthermore, leukotriene receptor antagonists, such as montelukast and zafirlukast can prevent ILC2 activation by inhibiting the cysteinyl leukotriene receptor 1 (CysLT1R). Lipoxin A4 (LXA4) functions as an inhibitor of ILC2s and severe asthma patients have a LXA4 deficiency, 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, its inhibition might prove to be a promising novel strategy to combat allergic diseases.

Regulatory immune cells have also emerged as potential targets, for example Treg cells which can suppress ILC2-driven inflammation. Several recent studies have shown the existence of a novel regulatory ILC counterpart, with the capacity to produce IL-10. These IL-10-producing ILCs are distinct from Treg cells in
in vitro studies and can be induced following stimulation with retinoic acid in the periphery. Moreover, these IL-10-producing ILCs are functional and can suppress Th2 cell responses. These ILCs with regulatory capacity have also been demonstrated to be induced following subcutaneous (SCIT) and sublingual grass pollen immunotherapy (SLIT). These preliminary, yet promising, observations highlight the potential utility of regulatory ILCs as a target for the treatment of food allergy. Finally, possible interaction of ILCs with a novel subset of T cells known as T follicular helper 13 (T<sub>FH13</sub>) cells which have been implicated in food allergy remains to be identified.

Conclusion

Food allergy is an increasing problem throughout the world. There remain significant unanswered questions about its pathogenesis. ILCs provide a bridge between native and adaptive immunity thereby having a crucial role in immunity. There is a growing awareness about the plasticity of ILCs in different inflammatory conditions. It is likely that future studies will provide more insights to understanding how the skin and gastrointestinal mucosal immune systems interact, both in homeostasis and in the progression to food allergy. In particular, it will be important to identify physiologically relevant stimuli that directly or indirectly activate ILCs in skin, which may lead to epicutaneous sensitization. A strong association of AD and food allergy is found stronger in infancy than childhood, despite epicutaneous sensitization being more evident in later life. Mechanisms of epicutaneous sensitization during infancy and the role of ILCs have yet to be identified. 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.

FIGURE LEGENDS

Figure 1. Classification and plasticity of ILCs.
Figure 2. Pathophysiology of the atopic dermatitis (AD) and the role of ILC2s in AD.
Figure 3. Development of IgE-mediated food allergy in mucosal immune system of the gut.
Figure 4. Role of ILC2 in eosinophilic esophagitis (EoE).

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