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Contributions of innate lymphocytes to allergic responses

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Abstract

Purpose of Review.—Allergic diseases represent a growing global health concern, especially among pediatric populations. Current strategies for the treatment of allergies and asthma focus on limiting the severity of the symptoms; however, additional research investigating the mechanisms promoting inflammation in the context of allergic reactions may lead to the development of more effective therapeutic strategies.

Recent findings.—Novel studies have highlighted the contributions of innate lymphocytes to the induction of inflammatory responses to allergens. Remarkably, neuron-derived signals, hormones, and even vitamins have been suggested to modulate the activity of innate lymphocytes, opening new windows of opportunity for the treatment of allergic inflammation

Summary.—These studies highlight the complex interactions of the nervous, endocrine and immune system that promote pathology in the context of allergic inflammation. Further studies are required to understand these interactions in order to aid in the development of novel and much-needed therapies to treat allergic conditions.

Keywords

Type 2 cytokine responses; type 17 cytokine responses; innate lymphocytes; allergic diseases

Introduction

Allergic diseases are an increasing public health concern worldwide, especially among children(1). These diseases are defined as hypersensitive inflammatory responses to a molecule or allergen, which is generally considered benign. Common allergens include house dust mite-derived antigens, skin dander from animals, plant pollens, fungi-derived antigens, and certain food antigens, all of which affect different barrier surfaces including the skin, respiratory, and digestive tracts. Included among the most prominent allergic diseases are atopic dermatitis (AD), allergic contact dermatitis, allergic rhinitis, anaphylaxis,

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food allergy, and several forms of asthma. As of 2010, it was estimated that 20–25% of the United States' total population suffered from one or more allergic diseases(1). It has also been reported that there is an increasing linear trend in skin, respiratory, and food allergies reported among children in the United States(2, 3). The increased prevalence of allergies and asthma has resulted in a heavy economic burden in the United States. For example, in 2007, there were a reported 1.75 million asthma-associated emergency room visits and 456,000 hospitalizations resulting in \$19.7 billion in health care costs in the United States (1, 3). Unfortunately, these striking costs are also present globally, with the World Health Organization estimating the number of patients with asthma at 235 million as of 2013(1, 3).

Currently, the clinical guidelines for treatment of allergies focus on education, avoidance, pharmacotherapy, and immunotherapy(4). Further, immunotherapy regimes focused on inducing immune tolerance to prevent symptoms and disease progression, are still considered secondary to pharmacotherapy and are not available to treat many allergic diseases(5, 6). Thus, it is critical to better understand the mechanisms that mediate allergic responses in order to design more effective treatments to combat this diverse set of diseases. Since it is difficult to investigate these pathways in humans, animal models that can be experimentally manipulated have provided an invaluable resource and have greatly informed our understanding of allergic inflammation. Some of the most commonly used animal systems employ sensitization strategies with model antigens such as ovalbumin (OVA), treatment with proteases that damage the epithelium such as papain, administration of cytokines including recombinant interleukin (IL) –33, as well as exposure to common allergens such as those found in house dust mite (HDM), *Alternaria alternata*, and *Aspergillus fumigatus* extracts (Table 1) (7–9). Collectively, these models have provided insight into the cellular and molecular mechanisms promoting allergy-associated pathology and have revealed major roles for type 2 and type 17 cytokines in driving allergic inflammation. Type 2 and type 17 cytokine responses are promoted by both innate and adaptive immune cells which will be briefly introduced in the below paragraphs.

Type 2 cytokine responses are initiated following the damage caused by some allergens, which results in the secretion of damage-associated signals, such as IL-25, IL-33 and thymic stromal lymphoietin (TSLP) by the epithelium and some hematopoietic cells(10). In response to these factors, type 2 innate lymphoid cells (ILC2s) along with other innate cells like basophils, mast cells, and dendritic cells, mount a robust inflammatory response characterized by the secretion of cytokines such as IL-4, IL-5, IL-9, and IL-13, as well as lipid inflammatory mediators including prostaglandins and leukotrienes. Collectively, these molecular events drive a number of effector mechanisms that have long been associated with allergic diseases, including the induction of type 2 T helper (T_H2) cells, M2 macrophage polarization, mucus production, eosinophil recruitment, smooth muscle cell contraction, tissue remodeling, as well as the generation of IgE-producing B cells(11).

In addition to the well-established contributions of type 2 cytokine responses to allergic inflammation, studies have also revealed increased IL-17A levels in the tissues and sera of patients suffering from AD and severe asthma(12, 13). Further, it has been reported that exposure to fungal spores is associated with increased risk of asthma in both children and adults(13–16), suggesting that an IL-17-mediated response might participate in the induction

of allergic diseases. Type 17 cytokine responses are initiated by stimulation of antigen presenting cells (APCs), such as dendritic cells or macrophages, by fungal or bacterial antigens resulting in the production of IL-1, IL-6, IL-23, and transforming growth factor β (TGF- β). These mediators induce the early secretion of IL-17A, IL-17F, and IL-22 by multiple innate lymphocytes such as $\gamma\delta$ T-cells, invariant natural killer T-cells (iNKT cells), and ILC3s(17, 18). Collectively, the activation of these cells results in the generation of pro-inflammatory mediators from macrophages and local non-immune cells, propagation of IgG-producing B-cells, polarization of T_H17 cells, and promotes the formation of tertiary lymphoid follicle-like structures(17–20). Altogether, these events promote inflammation characterized by increased neovascularization, eosinophil influx, and neutrophil recruitment into inflamed tissues (21–25).

This article will focus on highlighting recent studies that have demonstrated a role for type 2 and type 17 cytokines in promoting allergic inflammation. Since the contributions of T_H2 cells, IgE-producing B cells and T_H17 cells to allergic inflammation are well established and have been extensively reviewed previously(26, 27), they will not be heavily covered in this article. Instead, we focus on the recent studies highlighting the essential contributions of innate lymphocytes to the initiation of allergic diseases and highlight the role they are reported to play in promoting adaptive type 2 and type 17 responses. Further, since type 2- and type 17-mediated inflammation are required to provide protection against pathogens such as helminth parasites and fungi, studies investigating the mechanisms that regulate anti-helminth or anti-fungal immunity will be mentioned when similar aspects of these cytokine responses are thought to be operational in the context of allergies and asthma.

Type 2 innate lymphoid cells (ILC2s) promote allergic inflammation

Considering their potent ability to secrete cytokines, it is not surprising that ILC2s have been shown to contribute to the development of allergic inflammation in well-established animal models of airway inflammation, including those initiated by HDM extracts, papain, *Alternaria alternata* antigens, sensitization and challenge with OVA, as well as treatment with recombinant IL-33. Further, ILC2s are reported to contribute to murine models of food allergy and AD-like disease(28–31). Consistent with these murine studies, ILC2s have been found to accumulate in tissue explants of patients suffering allergic conditions, such as asthma, allergic rhinitis, and AD(29, 32, 33). These critical findings have motivated several recent studies analyzing distinct aspects of ILC2 biology, including their developmental pathways, the mechanisms regulating their activation and inhibition, as well as their distinct effector contributions to different modules of allergic inflammation. The following sections will highlight these studies and describe how they inform our understanding of the cellular events required to promote allergic inflammation.

Tissue-specific microenvironments regulate ILC2 development and activation

Although the specific cellular and molecular pathways that govern ILC2 development are not completely understood as reviewed previously(34), the events that regulate their presence in specific tissues might alter susceptibility to allergic inflammation. For example, it was recently reported that ILC2s accumulate in the lungs during the alveolarisation phase

occurring during the post-natal period, which correlated with increased expression of IL-33 by the pulmonary epithelium(35). Remarkably, the same study demonstrated that mice exposed to allergens during the early post-natal period resulted in more robust ILC2-mediated inflammatory responses as compared to sensitization during the adult phase. Further, the increased susceptibility to allergens observed during the post-natal period was inhibited by blockade of IL-33 with the soluble decoy receptor sST2(35), suggesting that the remodeling of lung tissue during development may alter the responsiveness of ILC2s to allergens and thus the susceptibility to allergen-induced airway inflammation. Complimentary to this observation, another novel study demonstrated the profound differences that tissue-microenvironments might have on the responsiveness of ILC2s to allergens(36). For instance, single-cell transcriptional analysis of murine ILC2 populations isolated from the skin, lungs, gut, fat and bone marrow revealed that while these cell populations share some characteristics, such as the expression of the transcription factor GATA-3 and the receptor for IL-7, tissue-resident ILC2s exhibit heterogeneous expression of cytokine receptors that might allow them to respond to distinct mediators secreted in a compartmentalized manner(36). Specifically, skin-derived ILC2s exhibited an elevated expression of IL-18 receptor compared to other ILC2 subsets. Further, IL-18-deficient mice exhibited diminished ILC2 responses in a model of AD-like disease(36), suggesting that tissue-specific microenvironments might have a profound effect on ILC2-mediated responses in the context of allergic inflammation.

Regulatory mechanisms of ILC2 responses in the context of allergic inflammation

Murine and human studies have reported that ILC2s activate in response to cytokines (IL-25, IL-33, TL1A, TSLP, IL-2, IL-4, and IL-9), lipid inflammatory mediators (prostaglandin D2 (PGD₂) and cysteinyl leukotrienes), as well as free fatty acids (linoleic and oleic acid) (29, 37–48). Contrary to mediators of activation, several molecules have now been demonstrated to inhibit ILC2 responses including type I and type II interferons, IL-12, IL-27, PGE₂, PGI₂, glucocorticoids, and the resolvins lipoxin A4 and maresin 1(49–54), illustrating the complex mechanisms that regulate ILC2 functions. In addition to these well-described mediators, recent studies have also demonstrated that ILC2s respond to stimulation with hormones, vitamins, complement proteins, and neuron-derived signals (Figure 1). The following sections will discuss these exciting observations and comment on the possible role these newly described pathways may play in regulating the development of allergic inflammation.

The complement system represents an intricate pathway of soluble mediators that trigger innate inflammatory responses to bacteria, viruses, and parasites. Complement activation results in the secretion of anaphylatoxins, including C3a and C5a, which have been shown to contribute to allergic inflammation(55). Recently, C3a circulating levels were found to be increased in a murine model of HDM-induced allergic airway inflammation and C3a was sufficient to induce cytokine secretion by ILC2s(55). Further, C3a receptor 1 (C3ar1)-deficient mice exhibited reduced ILC2-mediated responses following exposure to HDM, as well as IL-33 and absence of C3ar1 impaired ILC2 activation of OVA-specific T cells(55). Collectively, these studies suggest that C3a may promote allergic inflammation via its ability to regulate ILC2 activation.

It is well established that allergic diseases have a distinct prevalence between male and females(56–59). Although the prevalence for asthma was found to be higher in males over females during childhood(56), this trend was reversed after puberty, resulting in a higher prevalence of asthma and other allergic diseases in adult females compared to adult males(57–60), suggesting that changes during puberty might affect susceptibility to allergic conditions. However, the molecular mechanisms that drive these differences remain to be defined. Consistent with the above epidemiological studies, male mice were found to have reduced ILC2-mediated inflammation, in response to HDM, compared to female mice(61). Remarkably, male castration increased ILC2 responses to levels comparable to those observed in female mice, suggesting that male hormones might operate as negative regulators of ILC2s. Further, ILC2 progenitors were found to express androgen receptor and androgen-receptor inhibition resulted in an increased expansion of ILC2s that correlated with elevated allergic inflammation(61). These studies suggest that hormone-mediated signaling might regulate ILC2 activity, however, further studies are required to determine the impact of sex hormones on ILC2 responses. Another hormone that has been suggested to regulate ILC2 functions is the hormone of energy expenditure, leptin. Leptin-deficient mice exhibited attenuated allergic responses following exposure to papain, which correlated with diminished ILC2 numbers(62). Further, ILC2s isolated from leptin-deficient mice exhibited reduced proliferation rates following allergen exposure(62). Interestingly, increased levels of leptin has been shown to be a characteristic of obese individuals, that are reported to be at a higher risk of developing asthma(63). Consistent with these studies, mice maintained on a high fat diet developed an exacerbated allergic response that correlates with increased ILC2 accumulation in the lymph nodes(64). These studies suggest that factors like alterations in sex hormones or diet can affect ILC2 responses in the context of allergies; however, more studies are required to elucidate the precise regulatory mechanisms by which hormones and metabolites regulate ILC2 biology.

The ability of vitamins to regulate ILC2 responses has also been recently highlighted. For example, retinoic acid (Vitamin A) was found to synergistically potentiate the cytokine-mediated activation of human ILC2s *in vitro*, an effect that was inhibited by treatment with vitamin D(65). Conversely and perhaps paradoxically, pharmacological inhibition of retinoic acid signaling resulted in the population expansion of intestinal ILC2s that enhanced protection against the nematode *T. muris*(66). Further, inhibition of retinoic acid signaling resulted in the enhanced acquisition of fatty acids by ILC2s, which were found to utilize fatty acid oxidation over glycolysis to fulfill their metabolic demands(67). Collectively, these studies suggest that vitamins may have complex regulatory effects on ILC2s; however, more comprehensive studies are required to determine the effects of vitamins on ILC2 responses in the context of allergic diseases.

Neuron-derived signals have also recently been found to modulate ILC2 responses in the context of models of allergic disease and helminth infection. For example, ILC2s were found to express the receptor for the neural peptide neuromedin U (NMU) under homeostatic conditions(68–70). Further, HDM exposure enhanced the expression of the NMU receptor by ILC2s and stimulation with NMU was found to enhance ILC2 responses and allergic inflammation following treatment with IL-25. Moreover, exogenous treatment with NMU was sufficient to induce ILC2-mediated pulmonary inflammation and promoted helminth-

induced ILC2 responses(68–70), suggesting that NMU might regulate ILC2 activation in response to multiple stimuli. In addition to the NMU receptor, ILC2s have been found to express the β_2 -adrenergic receptor (β_2 AR), which interacts with the neurotransmitter epinephrine(71). However, in contrast to NMU-mediated signals, treatment with β_2 AR agonists resulted in diminished ILC2 proliferation and ILC2-mediated allergic inflammation (71). Another neurotransmitter that has been suggested to regulate ILC2s is acetylcholine, which signals through the α_7 nicotinic acetylcholine receptor (α_7 nAChR). ILC2s were found to express α_7 nAChR, which was increased following *in vitro* treatment with IL-33(72). Similar to β_2 AR agonists, α_7 nAChR agonists were sufficient to inhibit ILC2 activation *in vitro* and attenuated ILC2-mediated inflammation following intranasal exposure to rIL-33 or *Alternaria alternata* extracts(72). Interestingly, these studies also found that ILC2s are localized in close proximity to neurons. Consistent with these findings, activation of nociceptive neurons (neurons that respond to damaging stimuli) resulted in elevated inflammatory responses in a model of OVA-induced allergy(73). Further, silencing of airway sensory neurons resulted in reduced eosinophil and macrophage infiltration as well as airway hyperresponsiveness in HDM-mediated or OVA-induced allergy models(73), suggesting that neuronal activation has a profound contribution to allergic inflammation.

In addition to the interactions between neurons and ILC2s, a recent study highlighted the potential role of pulmonary neuroendocrine cells (PNECs) in the context of allergic inflammation. PNECs are highly specialized epithelial cells that are innervated by neurons and secrete hormones and neurotransmitters such as serotonin, calcitonin gene-related peptide (CGRP), and gamma-aminobutyric acid (GABA); in response to hypoxia(74). Remarkably, mice deficient in PNECs exhibited reduced immune cell infiltration and mucus production in response to OVA or HDM extracts(75). Additionally, exposure to allergic stimuli resulted in increased expression of PNECs-secreted mediators including CGRP and GABA. Further, exogenous treatment with CGRP and GABA were sufficient to restore distinct parameters of allergic inflammation in PNEC-deficient mice and PNECs were found to be increased in lung sections of asthmatic patients(75), suggesting that PNECs and their secreted soluble mediators might have a critical role in regulating allergic inflammation. Similar to neurons, IL-5 expressing ILC2s were found to localize in close proximity to PNECs(75), suggesting that PNECs and ILC2s might establish complex interactions that promote allergic inflammation. Collectively, these studies highlight the complex regulatory pathways and cell types that regulate ILC2 activation in the context of allergic inflammation.

Effector mechanisms of ILC2s to allergic responses

Following their activation, ILC2s are reported to secrete IL-4, IL-5, IL-9, and IL-13 that initiate molecular and cellular events that promote allergic inflammation including eosinophil recruitment, mucus production, smooth muscle cell contraction, as well as M2 macrophage and T_H2 cell polarization(37). Further, ILC2s are reported to directly contribute to the remodeling of the epithelium observed in the context of allergic inflammation by releasing soluble factors that induce epithelial cell proliferation such as amphiregulin and arginase 1(76, 77). In addition to their own effector mechanisms, ILC2s have been shown to communicate with other innate immune cells and can be activated in response to basophil-derived IL-4 in a murine model of AD-like disease(29, 45). Moreover, recent studies have

suggested that ILC2s might also contribute to the initiation of adaptive responses to allergens by promoting the activation and polarization of T_H2 cells. Specifically, ILC2s express MHCII and co-stimulatory molecules such as ICOS and OX40L(78–80), which participate in antigen presentation to T lymphocytes. Further, ILC2s were sufficient to induce antigen-mediated T cell activation *in vitro* and contributed to the induction of T_H2 responses in a murine model of protease-driven allergy(78–80). In addition to their own ability to present antigens, ILC2s have also been shown to skew dendritic cell activation in a manner that allows them to promote robust T_H2 responses following allergen exposure. For example, ILC2-derived IL-13 was reported to induce the recruitment of dendritic cells to the lymph nodes and stimulated their secretion of the T_H2-associated chemokine, CCL17 following exposure to papain(81, 82). Collectively, these studies demonstrate that ILC2s contribute to allergic inflammation via multiple distinct mechanisms.

Innate sources of IL-17 contribute to allergic inflammation

The role of T_H17 responses in the context of allergic diseases is not well understood. While it is well established that neutrophils and IL-17 levels increase in the tissues and sera of patients suffering from certain phenotypes of asthma and AD(12, 13), the precise contributions of IL-17 to the pathogenesis of allergies and asthma remain to be fully defined as described previously(83). Further, the innate cellular sources of IL-17 in the context of allergic inflammation remain poorly defined. The following sections will focus on highlighting the innate cell populations reported to produce IL-17 in the context of allergic inflammation. Skin-resident $\gamma\delta$ T-cells are a heterogeneous population of cells comprised by IFN γ -producing dendritic epidermal T cells (DETCs) and dermal $\gamma\delta$ T-cells that are known to secrete vast amounts of IL-17 and IL-22 upon activation(84). Interestingly, dermal $\gamma\delta$ T-cells were found to be necessary for the maximum development of hypersensitivity responses in a murine model of allergic contact dermatitis(84). This observation is consistent with previous studies reporting the increased presence of $\gamma\delta$ T-cells in children with severe allergic AD(85). In addition, $\gamma\delta$ T-cells have been reported to contribute to allergic inflammation in murine models of asthma and allergic conjunctivitis(86–88); however, whether these studies translate to relevant human diseases remains unknown.

Eosinophils are frequently associated with allergies and asthma and are known to be highly prevalent in affected tissues. Importantly, murine studies employing an OVA-induced model of allergic asthma suggest that eosinophils might contribute to allergic responses via their ability to produce IL-17 and IL-23 (25). Additionally, natural killer (NK) cells are a known source of IL-17 that are reported to increase in peripheral blood of patients with asthma(89). However, recent murine studies employing acute and chronic models of HDM-induced airway inflammation demonstrated that NK cells are not necessary for the development of allergen-induced inflammation(90). In summary, additional studies are required to further determine the contributions of eosinophils and NK cells to the development of allergic inflammation. (91–93).

In addition to eosinophils and NK cells, studies also suggest that lung-resident ILC2s represent an innate source of IL-17 production. For example, an ST2⁺ subset of lung ILC2s were found to produce IL-17 in the presence of papain or IL-33, resulting in a highly

pathogenic inflammatory response that was reduced upon IL-17 neutralization. ILC2 production of IL-17 was dependent on expression of the aryl hydrocarbon receptor (Ahr) as this effect was abrogated in Ahr knockout mice. Interestingly, this response was specific to a ST2⁺ subset of ILC2s and was not promoted by ST2⁻ ILC2s(94). Altogether, these studies suggest that there are multiple innate sources of IL-17 (Figure 2) and highlight the need to further define the role of type-17 cytokine responses in the context of allergic inflammation. Better defining the dynamic relationship between type 2 cytokines and IL-17-mediated inflammation may inform therapeutic strategies to treat various manifestations of allergic inflammation.

Conclusions

Allergic diseases represent a significant and worldwide public health concern and their prevalence has been consistently increasing for decades. Despite the availability of therapies to treat the symptoms of allergic inflammation, there is an urgent need for novel therapeutics that target the underlying cause(s) of these diseases. Clinical and experimental studies have indicated that type 2 and type 17 cytokine responses contribute to allergic inflammation and recent studies suggest that innate immune cells are important sources of these cytokines.

Innate lymphocytes such as ILC2s and $\gamma\delta$ T-cells have been shown to substantially contribute to type 2 and type 17 cytokine responses in the context of allergic inflammation, suggesting that therapeutic strategies designed to target these cells may be successful in alleviating pathologic inflammation. Additionally, novel studies involving neuron-derived signals, hormones, fatty acids, and vitamins; which contribute to ILC2-mediated allergic inflammation, demonstrate the complex interactions between the nervous, endocrine, epithelial, and immune system. All of which participate in promoting allergic inflammation. These studies highlight the complexity of allergic diseases and may inform the design of new therapeutic opportunities to combat these disease states.

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Key points

- Clinical and experimental studies have indicated that type 2 and type 17 cytokine responses promote the detrimental inflammation observed in the context of allergies and asthma.
- Type 2 innate lymphocytes (ILC2s) have been identified as important contributors in the context of several allergic diseases.
- Neuron-derived signals, hormones, and vitamins are reported to regulate ILC2 responses, suggesting that these pathways may possess therapeutic potential.
- $\gamma\delta$ T-cells, NK cells, eosinophils and a subset of ILC2s have been proposed to contribute to IL-17-mediated allergic inflammation.

Figure 1. Regulators of ILC2-mediated allergic inflammation.

ILC2s are critical mediators of allergic inflammation that are activated in response to cytokines (IL-4, IL-25, IL-33) and inflammatory mediators such as prostaglandins and cysteinyl leukotrienes (Cys-Lkt), free fatty acids (OA and LA), complement proteins (C3a), and neuron-derived signals (NMU, CGRP, GABA). Further, it has also been demonstrated that ILC2s can be negatively regulated by β_2 AR agonists, β_7 nAChR agonists, Vitamin A, and testosterone. Gaining a better understanding of positive and negative regulators of ILC2 responses may inform new strategies to treat allergic inflammation. OA: oleic acid, LA: linoleic acid. NMU: neuromedin U. CGRP: Calcitonin gene-related peptide. GABA: gamma-aminobutyric acid

Fig 2. Innate sources of IL-17 in allergic responses.

Recent research has demonstrated that exposure to allergens, in conjunction with exposure to fungal-derived signals results in robust type 17-mediated cytokine responses characterized by the accumulation of neutrophils and T_H17 cells. Different innate immune cells have been reported to contribute to the early secretion of IL-17 in response to allergic exposure including dermal γδ T cells, epithelial cells, eosinophils, NK cells, and a subset of ILC2s. Further studies are required to define the contributions of these cells to the pathology associated with allergies and asthma.

Table 1.

Common experimental animal models of human allergic conditions.

Molecule	Sensitization route	Challenge route	Acute or chronic	Disease model	Reported mechanisms of inflammation	Refs.
Papain	Intranasal	N/A	Acute	Asthma	Cytokine alarmin release due to proteolytic activity targeting the epithelium.	(81)
House dust mite (HDM) extracts	Intranasal and/or intraperitoneal	Intranasal	Acute or chronic	Asthma	Protease activity of major HDM antigen Der p 1.	(55)
<i>Alternaria alternata</i> extracts	Intranasal	N/A	Acute	Fungal-induced asthma	Serine proteases secreted by the fungus induce type 2 cytokine responses, Fungal activation of dendritic cells.	(72)
<i>Aspergillus fumigatus</i> extract	Intraperitoneal or subcutaneous with adjuvants	Intranasal	Chronic	Fungal-induced asthma	Serine proteases secreted by the fungus induce type 2 cytokine responses, Fungal activation of dendritic cells.	(103)
Recombinant IL- 33	Intranasal	N/A	Acute	Asthma	Cellular responses elicited by IL-33 administration.	(27)
Ovalbumin (OVA)	Oral or intraperitoneal with adjuvants	Intranasal	Chronic	Asthma	Innate and adaptive lymphocyte activation following sensitization and exposure to a model antigen.	(73)
		Epicutaneous	Chronic	Atopic dermatitis		(7-9)
		Oral	Chronic	Food allergy/ anaphylaxis		(7-9)
Calcipotriol (MC903)	Topical	Topical	Acute	Atopic dermatitis	TSLP release by keratinocytes resulting in basophil and ILC2 activation.	(28,45)