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Group 2 Innate Lymphoid Cells in Allergic Rhinitis

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Abstract: Allergic rhinitis (AR), which presents symptoms like sneezing and a runny nose, is categorized as an upper respiratory condition of type 2. Recent progress in comprehending AR has revealed the significant role played by type 2 cytokines, specifically interleukin (IL)-13, IL-4, and IL-5. These cytokines are released by helper T cells 2 (Th2) and innate lymphoid cells (ILC2s). ILC2s have the ability to interact with various immune cells and are essential in promoting both type 2 immune response and tissue repair, contributing to normal homeostatic functions within the body. This article presents a summary of the latest advancements in comprehending the activity of ILC2s, with particular emphasis on their potential role involvement in AR. It explores how they collaborate with Th2 cells to exacerbate nasal inflammation and interact with regulatory T cells (Tregs) to counteract the suppressive role mediated by Tregs during allergic inflammation. The significance of ILC2s in allergen-specific therapy is highlighted. A comprehensive understanding of ILC2s biology establishes a robust foundation for unraveling the pathogenesis of AR and devising innovative therapeutic approaches for its management.

Keywords: allergic rhinitis, group 2 innate lymphoid cells, cytokines, Treg cells, Th2 cells

Introduction

The characteristic indications of allergic rhinitis consist of sneezing, nasal blockage, itching in the nose and a runny nose. These symptoms are activated by breathing in allergens and managed by immunoglobulin E (IgE), which results in an increase of Th2 cells and type 2 cytokines within the nasal mucosa. AR is a prevalent global allergic disease.[1–3]

Group 2 innate lymphoid cells (ILC2s) play a crucial role in the establishment and preservation of immunity, alongside conventional Th2 cells. This diverse group of innate immune cells is indispensable for immune system functionality.[4,5] ILCs predominantly reside in mucosal tissues and exhibit rapid responsiveness towards environmental pathogens and damage. Upon being activated, ILCs release substantial quantities of cytokines, attract additional immune and inflammatory cells, trigger the activation of adaptive immune cells, and facilitate physiological as well as pathological responses.[6,7] There are three primary categories of ILCs that can be distinguished: ILC1s, ILC2s, and ILC3s.[5,7,8] The activity of ILC1s is regulated by a specific transcription factor known as T-box transcription factor. This regulation leads to the release of IFN-a and TNF-y when IL-1, IL-15, and IL-11 are activated.[6,7] GATA-binding protein 3 (GATA3) plays a crucial role in controlling the function of ILC2s,[9,10] resulting in the secretion of cytokines similar to Th2 cells such as IL-13 and IL-5. Activation of either IL-23 or IL-1β triggers the release of both IL-22 and IL-17 from ILC3s.[11–13] Numerous studies have indicated an increase in ILC2s among individuals with AR as well as mouse models.[14–16] These findings suggest that ILC2s may play a positive role in the development of AR.Hence, it is crucial to enhance our understanding of the involvement of ILC2s in the development of AR in order to devise more effective approaches for its management. Consequently, targeted activation of ILC2s may

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prove to be an important approach for treating AR. In this review, we provide a concise overview of the pathogenesis involved in ILC2s-induced AR, along with an examination of existing and prospective therapeutic strategies (Table 1).

How Do ILC2s Play a Role in AR

When allergens and other environmental factors are encountered, the activation of organizational cells and immune cells indirectly leads to the release of various immune and biological molecules.

These include cytokines derived from epithelial cells (such as TSLP, IL-25, and IL-33),[11–13,71–73] lipid mediators like prostaglandin D2 (PGD2) and cysteinyl leukotriene D4 (LTD4), as well as neuropeptides and hormones such as vasoactive intestinal peptide (VIP) and neuromedin U (NMU).[74–76] These molecules activate ILC2s to release type 2 cytokines such as IL-13, IL-5, IL-4 (Figure 1). Consequently, this leads to eosinophils recruitment, fibrosis development, glandular cells proliferation as well as epithelial mucus production.

Activation of ILC2s

Activation of ILC2s Through Cytokine Signaling

The epithelial cell-derived cytokines such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, can activate ILC2s, thereby exacerbating type 2 inflammation.

Some evidence suggests that levels of allergic cytokines derived from epithelial cells are elevated in patients with AR. Three types of cytokines, namely IL-25,[17] IL-33,[18,19] and TSLP were found in the nasal lavage fluid of AR patients who

Table 1 Clinical and Basic Studies on ILC2s in AR

Mechanism		Outcomes/Effects	Ref.
Cytokine Signaling	TSLP; IL-25; IL-33; IL-18	Active ILC2s; Promote the proliferation of ILC2s;	[17–28]
Lipid Mediators	PGs (such as PGD2); CysLTs (such as LTC4, LTD4, LTE4)	Cause ILC2 migration and encourage the synthesis of type 2 cytokines in human ILC2s	[29–36]
Neuropeptides (such as CGRP, VIP, NMU) and ICOS		Directly stimulate ILC2s	[25–28,31,37–43]
Small RNAs	MIR-155 miR-375	Actively participate in the activation of ILC2s; miR-375-mediated regulation contributes to modulate ILC2s cells via TSLP;	[44–47]
Leptin	Activated the PI3K/AKT pathway	Enhance transcription factors expression and type II cytokines production within ILC2s	[48,49]
Th2 Cells		ILC2s activate DCs to promote Th2 cell differentiation, the activation of CD4(+) T cells by ILC2s via MHCII; mDCs enhance the functionality of ILC2 by activating the IL-33/ST2 pathway, pDCs activation inhibits ILC2s function via IL-6.	[46,50]

(*Continued*)

Table 1 (Continued).

Mechanism		Outcomes/Effects	Ref.
Regulatory T Cells		Tregs is negatively affected by the release of IL-4 from ILC2s; ICOSL and OX40L expressed on ILC2s facilitate increased Tregs recruitment; AREG, derived from ILC2s, augments the inhibitory function of Tregs; Tregs possess the capacity to attenuate the activation of ILC2s by cell contact between Inducible T cell Costimulator (ICOS) and ICOs-Ligand, as well as the involvement of suppressive cytokines TGF-β and IL-10;	[51–61]
Mesenchymal Stem Cells (MSCs)	MSC-secreted extracellular vesicles (MSC-sEVs), especially those containing miR-146a-5p;	MSC-sEVs can inhibit mDCs activation on ILC2s through modulation of the PGE2-EP2/4 axis;	[47,62,63]
Lloprost		May have the potential to inhibit the proliferation and activation of ILC2s	[79]
Parasympathetic nervous system		Reduce ILC2s quantity and suppressing cytokines expression	[64]
MCC950		Suppress the proliferation of ILC2s	[65]
CC10 (Clara cell 10-kD protein)		Overexpression of CC10 inhibits the ILC2s' activation	[66]
MIR-150-5p		Inhibits the activity of ILC2s	[67]
Testosterone		Decrease the levels of type 2 cytokines in ILC2s and inhibit the proliferation of pure ILC2s stimulated	[68]
Allergen-specific immunotherapy (AIT)	Subcutaneous immunotherapy (SCIT)	Impact on the activation of ILC2s to treat AR; The skewing towards an ILC1/ILC2 response may be a determining factor;	[69,70]
	Sublingual immunotherapy (SLIT)		

were sensitized to HDM (house dust mite)[17,18] or cedar pollen.[19] Among them, the mRNA levels of IL-33,[20,21] ST2,[21] and TSLP[22–24,27] were significantly higher in the nasal epithelium of several types of AR patients.

AR patients sensitized to birch, grass,[25] and cedar pollen[26] exhibited elevated levels of IL25R (also known as IL17RB) mRNA expression in CD4+ cells that were isolated from peripheral blood mononuclear cells (PBMCs).[25,26] Increased expression levels of IL-13 and IL-5 in tissues were positively correlated with the transcription factors RORa and GATA3 mRNA being upregulated in ILC2s by epithelium-derived IL-25, this effect was inhibited by glucocorticoids.[37] Additionally, recent studies indicate that dose-dependent stimulation with IL-18 promotes the proliferation of ILC2s while inducing the expression of both IL-5 and IL 13.[28]

Stimulation of ILC2s Through Lipid Mediators

Lipid mediators, such as prostaglandins (PGs) and Leukotrienes (LTs), are essential for preserving homeostasis and controlling inflammation in the body. Notably, ILC2s express high levels of the PGD2 receptor, chemoattractant receptor

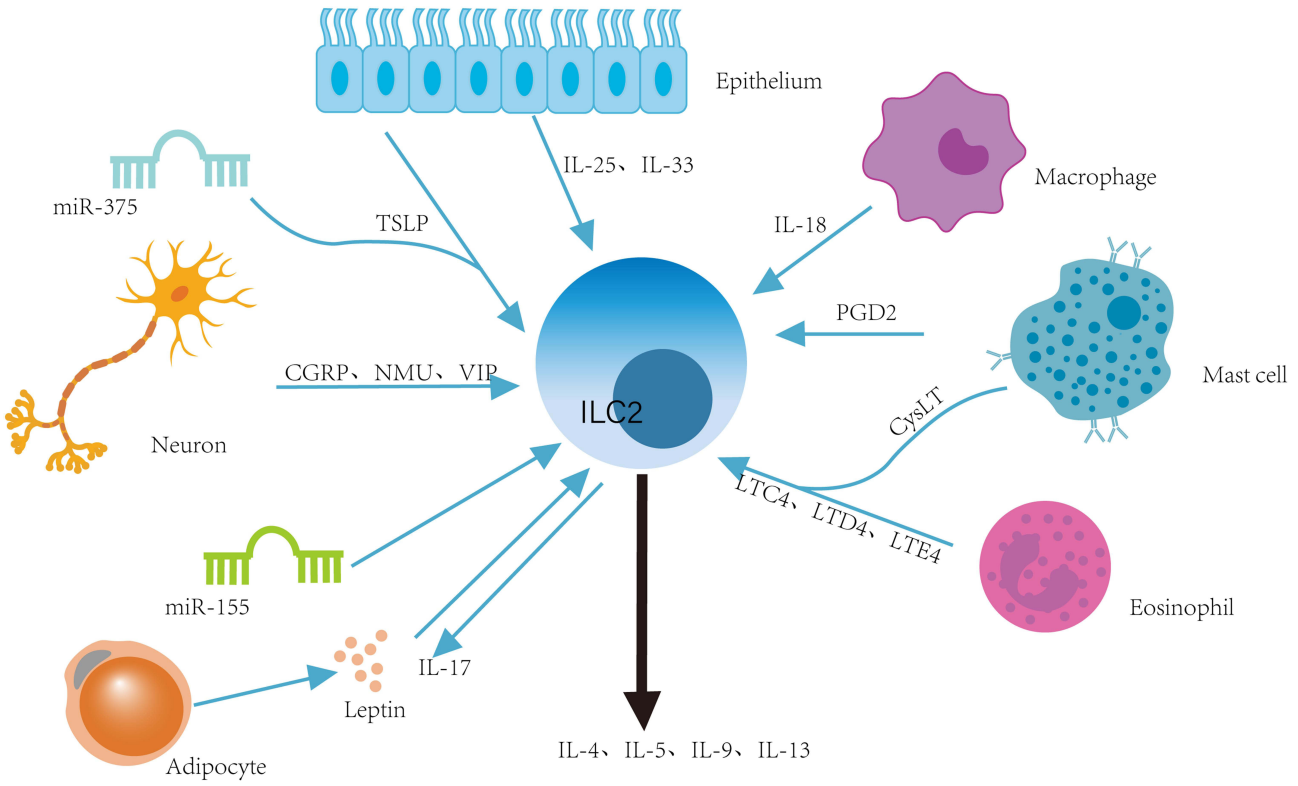

Figure 1 Activation of ILC2s.

Notes: When exposed to allergens and other environmental factors, the activation of tissue cells and immune cells indirectly leads to the release of various immune and biological molecules. These include cytokines derived from epithelium (such as TSLP, IL-25, and IL-33); mast cells and eosinophil stimulation by allergens induces the release of lipid mediators, such as prostaglandin D2 (PGD2) or Leukotrienes (such as LTC4, LTD4, LTE4); neuropeptides and hormones derived from Neuron (such as VIP, NMU, CGRP); macrophage-derived IL-18 can promote the proliferation of ILC2s, while inducing the expression of both IL-5 and IL 13; additionally, small RNAs (such as miR-375 and miR-155) can also modulate ILC2s function; these molecules activate ILC2s to release type 2 cytokines such as IL-13, IL-5, IL-4,IL-9; leptin can stimulate production of IL-17 within ILC2s.

Abbreviations: IL-33, interleukin 33; IL-25, interleukin 25; IL-18, interleukin 18; IL-17, interleukin 17; IL-4, interleukin 4; IL-5, interleukin 5; IL-9, interleukin 9; IL-13, interleukin 13; VIP, vasoactive intestinal peptide; NMU, neuromedin U; CGRP, calcitonin gene-related peptide; PGD2, prostaglandin D2; LTC4, cysteinyl leukotriene C4; LTD4, cysteinyl leukotriene D4; LTE4, cysteinyl leukotriene E4; CysLT, cysteinyl leukotrienes.

homologous molecule expressed on Th2 cells (CRTH2), and the LTC4 and LTD4 receptor cysteinyl leukotriene receptor 1 (CysLTIR). PGD2, LTC4, and LTD4, the ligands for these receptors, cause ILC2 migration and encourage the synthesis of type 2 cytokines in human ILC2s, such as IL-4, IL-5, and IL-13.[29–34]

Matsumoto et al discovered that in inferior nasal turbinate (INT) tissues of AR patients induced by house dust mite exposure, there was observed expression of CRTH2 and CysLT1R on ILC2s stimulation led to a significant increase in eosinophils count in nasal lavage fluid from AR patients along with elevated concentrations of PGD2 and CysLT. PGD2 and CysLT resulted in a dose-dependent increase in IL-5 production from ILC2s derived from PBMC. PGD2-CRTH2 and CysLT-CysLTIR axis might trigger ILC2s residing in tissue to generate Th2 cytokines, IL-13 and IL-5, therefore, by triggering the initiation of inflammation associated with allergies in individuals with AR.[35]

Qin et al found that CysLT1R was highly expressed on human circulating ILC2s from patients with AR. Moreover, LTE4, LTC4, and LTD4 significantly activated functionally active responses by stimulating AR and atopic dermatitis (AD) patients' derived ILC2s which might be a key factor contributing to allergic inflammation. However, in this study, they found that under the stimulation of LTE4, montelukast, a CysLT1R antagonist, could block the production of Th2 cell cytokines in PBMCs of AD patients, but had no effect on AR and healthy subjects. This means in AR, the activation of ILC2 to LTC4 and LTD4 instead of LTE4 is associated with increased expression of CysLT1R.[36]

Stimulation of ILC2s Through Alternative Mechanisms

Apart from cytokines and lipid mediators, ILC2s also contain neuropeptides such as calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), neuregulin U (NMU), and inducible T cell co-stimulator (ICOS).[25–28,31,37] Type 2 cytokines are directly stimulated in ILC2s by C3a, NMU, and VIP.[38–42,77]

In addition, small RNAs also have a significant impact on the pathogenesis of AR by modulating ILC2s function. miR-155 controls the generation of Th2 cytokines (IL-9, IL-13, IL-4, and IL-5), airway inflammation, and allergy-related symptoms. Elevation of miR-155 causes inflammation in the airway and symptoms of allergy by actively participating in the activation of ILC2s and suppressing the levels of transcription factor c-Maf.[49] Compared to the control group, patients or mice with AR showed elevated mRNA levels of miR-25, IL-33, and IL-25 in nasal mucosa tissue. The frequency of ILC2s in human peripheral blood was strongly connected with miR-155 levels and higher proportion of ILC2s. MiR-155 played a key role in regulating Th2 factor production and mediating allergic inflammation reaction in ILC2s during AR.[43] Further research indicated that this effect might be achieved through targeting TP53INP1.[44] The levels of TSLP, miR-375 expression, and the frequency of ILC2s were found to be notably elevated in individuals with AR when compared to the control group. miR-375-mediated regulation contributes to modulating ILC2s cells via TSLP.[45]

There have been investigations indicating a notable rise in the occurrence of ILC2s that produced leptin and IL-17 in the serum of AR patients compared to those in the control group.

Furthermore, when co-cultured with leptin, there was an increase observed in both the frequency of IL-17+ ILC2s and their production of IL-17, as opposed to the control group. Additionally, leptin stimulated the expression of RORyt and Ahr in ILC2s was noted. These findings implied that leptin had the ability to stimulate IL-17 production within ILC2s, which was reliant on RORyt and Ahr expression.[78] Moreover, studies conducted on AR mouse models and AR patient serum samples have demonstrated that leptin activated the PI3K/AKT pathway to enhance transcription factors expression and type II cytokines production within ILC2s.[48]

Interactions Between ILC2s and Key Immune Cells

Interactions Between ILC2s and Th2 Cells

ILC2s also have a role in mediating type 2 immune responses in AR. In established. AR mouse model using ovalbumin (OVA), the population and proportion of ILC2s were observed to increase. MHCII expression was detected on ILC2s, with enhanced levels of both the protein and mRNA under allergic conditions. Administration of CD4(+) T cells led to increased protein and mRNA levels of IL-5 and IL-13, which could be attenuated by the application of anti-MHCII antibodies or anti-CD4 antibodies. Relevantly, the symptoms of AR in mice model were significantly alleviated by transferring ILC2s along with anti-MHCII antibodies. These results indicated that in an AR mouse model, the activation of CD4(+) T cells led to the secretion of IL-13 and IL-5 by ILC2s via MHCII.[50] The investigation involved the levels of peripheral IL-33 (+) mDCs, pDC, and ILC2s when they co-cultured with human PBMCs, isolated from patients with AR. The results revealed the presence of ILC2s, mDC, and pDC within the nasal mucosa of AR patients. Furthermore, it was found that both allogeneic and autologous mDCs were capable of activating ILC2s in patients with AR to generate Th2 cytokines while increasing GATA-3 levels as well as signaling transducers' activation factors through interaction between IL −33-producing mDCs and ST2 on ILC2s being primarily responsible for this effect. Furthermore, high levels of IL-33 (+) mDC along with activated ILC2s were observed among antigen stimulated AR patients. Interestingly, activated pDCs inhibited cytokine production from ILC2s by secreting IL-6 within these individuals AR patients. While mDCs enhanced the functionality of ILC2 by activating the IL-33/ST2 pathway, pDCs activation inhibited ILC2s function via IL-6.[46] Collectively these studies indicate that there exists a synergistic relationship among Th2 cells and ILC2s which may exacerbate inflammatory response associated with AR.

Interactions Between ILC2s and Regulatory T Cells

Numerous investigations have demonstrated the regulatory role of ILC2s in Tregs function. The differentiation of Tregs is negatively affected by the release of IL-4 from ILC2s, leading to impair their inhibitory function and increased susceptibility to food allergy development.[51] Furthermore, the interaction between TL1A ligand and its receptor death

receptor 3 (DR3) leads to enhanced proliferation and type 2 cytokines synthesis by ILC2s.[52,53] Interestingly, TL1A also influences Tregs in allergic inflammatory skin diseases by increasing their proliferation and enhancing their inhibitory activity.[54] Conversely, ICOSL expressed on ILC2s fosters Tregs aggregation, while OX40L expressed on ILC2s facilitates increased Tregs recruitment in type 2 inflammation.[55,56] Additionally, in an antigen-induced arthritis model, Tregs' inhibitory action is enhanced by IL-9 generated by ILC2s.[57] Furthermore, AREG, a growth factor similar to epidermal growth factor primarily derived from ILC2s, augments the inhibitory function of Tregs when it binds to the epidermal growth factor receptor.[58,59]

Tregs, also known as regulatory T cells, possess the capacity to attenuate the activation of ILC2s. Research has discovered that the presence of inducible regulatory T cells (iTregs) in both humans and mice can effectively inhibit the production of pro-inflammatory cytokines IL-5 and IL-13, which are driven by ILC2, both in vivo and in vitro. This process necessitates cell contact between Inducible T cell Costimulator (ICOS) and ICOs-Ligand, as well as the involvement of suppressive cytokines TGF-β and IL-10,[60,61] potentially impeding the progression of type 2 inflammation in AR.

Inhibition of ILC2s Activation

Targeting the suppression of ILC2s mediators and activators may be a useful therapy approach for AR because of the markedly increased and activated levels of ILC2s in this condition.

In the past few years, a multitude of research has showcased the noteworthy contribution of mesenchymal stem cells (MSCs) and their exosomes released into the surrounding environment in addressing AR. Furthermore, numerous studies have revealed that these therapeutic effects on AR can be achieved by modulating the activity of ILC2s. In AR patients, it has been observed that induced pluripotent stem cell-derived MSCs (iPSC-MSCs) directly enhance both the levels and functionality of ILC2s levels. This effect is achieved through the interaction between ICOS-ICOSL in Lin (-) cells and pure populations of ILC2s. Additionally, iPSC-MSCs inhibit ILC2s activity by activating Tregs via the ICOS-ICOSL pathway.

Subsequently, MSC-induced Tregs suppress ILC2s by secreting IL-10 within co-culture system.[47] Furthermore, studies using an AR mouse model have demonstrated that MSC-secreted extracellular vesicles (MSC-sEVs), especially those containing miR-146a-5p, can prevent ILC2s-mediated allergic airway inflammation.[62] Notably, research has also indicated that that MSC-sEVs can inhibit mDCs activation on ILC2s in AR patients through modulation of the PGE2-EP2/4 axis.[63]

The inhibitory pathways that activate ILC2s may represent alternative treatment options.

In a mouse model of acute allergic rhinitis induced by IL-33 stimulation, the administration of Lloprost, an analog of PGI2, has demonstrated its ability to decrease the mRNA expression levels of IL-13, IL-5 GATA3, and ST2. This suggests that Llopros may have the potential to inhibit the proliferation and activation of ILC2s during episodes of acute allergic inflammation in mice.[79]

The study revealed a notable rise in the number of ILC2s within the nasal mucosa of individuals in the AR group, in addition to the higher levels of gene expression for GATA3, CD25, and CD90(Thy1) components associated with ILC2s when compared to both the AR treatment group and the control group. These findings suggest that the parasympathetic nervous system may exert its inhibitory effect on AR by reducing ILC2s quantity and suppressing cytokines expression within these cells.[64]

By enhancing lung inflammation caused by ILC2s, neuromedin U (NMU), a highly conserved multifunctional neuropeptide released by cholinergic neurons, contributes to the pathophysiology of asthma. It is unknown, nevertheless, just how NMU affects ILC2s in AR and associated illnesses. A study involving AR patients observed a significantly higher proportion of circulating ILC2s in these individuals compared to healthy subjects. Furthermore, compared to healthy people, the PBMC of AR patients activated by NMU or IL-33 released considerably more IL-5 and IL-13. In AR patients, stimulation of PBMC or ILC2s with NMU resulted in greater production of the inflammatory cytokines IL-5 and IL-13 compared to IL 33. Furthermore, inhibition of the ERK pathway limited the activation and proliferation of NMU-induced ILC2s. Overall, this study demonstrates that in AR patients, NMU efficiently stimulates ILC2s to generate Th2

cytokines, while inhibition of the ERK pathway can prevent this activation. These findings offer novel insights into the neuroimmune mechanisms underlying AR.[80]

The crucial role of miR-155 in activating ILC2s during AR has been discussed. Recent research indicates that by controlling the immune system's homeostasis in AR, blocking the Notch pathway may reduce the inflammation caused by miR-155. Stimulation of human nasal epithelial cells (HNEpCs) with ovalbumin (OVA) intranasally significantly enhances Th2 immune response and leads to an increase in the expression of IgE, IL-4, GATA3, miR-155, and NF-KB. The Notch signaling system, however, deteriorates in AR, as demonstrated by lower Notch1, Notch2, RBPj, and Hesl levels. Treatment with y-secretase inhibitor IX (DAPT) effectively counteracts these effects while also dose-dependently inhibiting wound healing and proliferation of HNEpCs.[81] In addition, an animal experiment revealed elevated levels of circ_0067835 in nasal mucosa tissue from AR mice. Inhibition of circ_0067835 led to a decrease in the levels of type 2 cytokines and ILC2s in the AR mouse model. The expression of miR-155 is targeted and upregulated by circ_0067835, while GATA3 is regulated as a downstream target through the circ_0067835/miR-155 axis. Suppression of circ_0067835 results in reduced activity of miR-155, leading to decreased levels of cytokines and ILC2s. These findings indicate that circ_0067835 effectively inhibits ILC2s during the AR response through the involvement in the miR-155/GATA3 axis.[82]

The involvement of ILC2 and NLRP3 inflammasome has been observed in allergic reactions and inflammatory responses. The effects of MCC950, an inhibitor targeting the NLRP3 inflammasome, were examined on ILC2s, IL-13 +ILC2s, NLRP3 inflammasome, IL-5+ILC2s, as well as Th2-related factors in a group of 30 patients diagnosed with AR. The investigation demonstrated a direct association between NLRP3 inflammasome levels and IL-5+ILC2s, ILC2s, IL-13 +ILC2s in patients with allergic rhinitis. Administration of MCC950 or inhibition of IL-1β/IL-18 effectively suppressed the proliferation of ILC2s as well as Th2-related factors such as GATA3, IL-5, IL-13 and RORa. In addition, the administration of MCC950 resulted in a reduction in the levels of ILC2s, as well as IL-5+ILC2 and IL-13+ILC2s, in both mouse models and patients with AR. Overall, the response of ILC2s was effectively suppressed by MCC950 treatment.[83] The potential role of ILC2s and CC10 (Clara cell 10-kD protein) in AR is currently being investigated in a separate study. In an experimental mouse model of AR induced by ovalbumin, it was observed that the overexpression of CC10 led to an improvement in nasal mucosal damage among the mice with AR. The study revealed activation of ILC2s in AR patients and mice with elevated IgE, IL-25, IL-4, IL-5, IL-13, IgG1, and IL-33 levels. In addition, it was shown that CD127+ activates ILC2s.Overexpression of CC10 inhibited the ILC2s' activation. This study highlights the effect of CC10 on ILC2s activation, leading to reduced nasal mucosal damage. Furthermore, the expression of CD127+ could potentially be utilized as a marker to indicate the activation of ILC2s in both mice with AR and patients diagnosed with AR.[65] However, the underlying mechanism through which CC10 inhibits the activation of ILC2 remains elusive. Further investigation is warranted to elucidate this potential mechanism. In both human subjects with AR and mice models of AR, there is a reduction in the expression of miR-150-5p while an increase in the expression of ICAM-1, p-GATA-3, and p-p38 can be observed. Additionally, elevated levels of ILC2s are also detected. Lentivirus therapy targeting miR-150-5p can alleviate AR symptoms such as sneezing, scratching, mucosal inflammation, serum type 2 cytokines as well as OVA-specific IgE production in AR mice while reducing ILC2s levels. It has been discovered that miR-150-5p directly binds to the 3'-UTR of ICAM-l, resulting in downregulation of ICAM-1 expression. This subsequently reduces p-GATA-3, p-p38 levels, and inhibits the activity of ILC2s thereby relieving the symptoms of AR. These results indicate that the increased expression of miR-150-5p suppresses the ICAM-1/p38 pathway, which is essential for the development and activity of ILC2s. As a result, allergy symptoms in AR are effectively diminished.[66]

Some research has indicated that there may be disparities between genders in terms of the occurrence and severity of AR. A study involving mice lacking T/B cells found that female mice displayed higher levels of inflammatory infiltration and produced larger quantities of IL-5 and IL-13, particularly when compared to male mice induced with IL-33, which resulted in increased levels of ILC2s. However, no significant differences were observed in the levels of circulating ILC2s between male and female patients. The administration of testosterone therapy notably decreased the levels of type 2 cytokines in ILC2s and inhibited the proliferation of pure ILC2s stimulated by epithelial cell cytokines. These findings suggest that androgens have an inhibitory effect on ILC2s.[67]

ILC2s in the Treatment of AR

Subcutaneous Immunotherapy (SCIT) and Sublingual Immunotherapy (SLIT)

Allergen-specific immunotherapy (AIT) is widely recognized as the primary and most efficient treatment approach for patients suffering from AR.[68] AIT can be delivered via subcutaneous injection (SCIT) or sublingual administration (SLIT), both of which are proven to be secure and efficacious methods of delivery. Both these routes have the potential to induce enduring tolerance even after discontinuation of treatment for numerous years. Numerous research studies have provided evidence of the therapeutic benefits of SCIT and SLIT for individuals with AR who exhibit sensitivity to HDM,[84,85] pollen,[86–88] or other allergens.[89] In recent years, numerous research studies have focused on uncovering the potential molecular mechanisms and clinical efficacy of allergen immunotherapy. SLIT using Artemisia annua extract has also demonstrated a significant reduction in Th2 cells, while simultaneously increasing levels of natural regulatory T cells (nTreg) and type 1 regulatory T (Trl) cells. These findings were observed in blood samples obtained from patients with seasonal AR (SAR) or Japanese cedar pollen allergy.[90,91] Numerous studies have indicated that alanine aminotransferase (ALT) plays a crucial role in the treatment of AR by influencing the activity of ILC2s. In patients with house dust mites-sensitized AR who underwent subcutaneous immunotherapy containing Der P extracts, the immunotherapy group had significantly lower amounts of ILC2s than the untreated group, according to peripheral blood tests. This finding demonstrates that Der p-SCIT effectively inhibits ILC2s in patients with HDM-AR.[92] Another study conducted by a different research team demonstrated a significant reduction in circulating ILC2s frequency among both responding AIT patients and healthy individuals, as opposed to non-responsive AIT patients and those diagnosed with AR. On the contrary, unlike non-responsive patients undergoing AIT and individuals with AR, both healthy participants and responsive AIT patients exhibited a higher occurrence of ILC1. Additionally, responsive AIT patients demonstrated significantly reduced frequencies of natural cytotoxic receptor (NCR) and NCR-ILC3s compared to both healthy participants and AR patients. Notably, the ratio between ILC1 and ILC2s closely resembled that observed in healthy subjects among responding AIT patients. The expression level of CD69, an activation marker for ILC2s, was significantly reduced upon allergen restimulation in peripheral blood mononuclear cells (PBMC) from responsive AIT patients in contrast to those from AR patients. However, there was no noticeable disparity in the expression of CD69 between AIT patients who responded well to treatment and healthy subjects. This study also provides evidence supporting the impact of allergen immunotherapy on regulating immune responses mediated by innate lymphoid cells such as attenuated activation of ILC2s among AIT-treated AR patients. The skewing towards an ILC1/ILC2 response may be a determining factor in the successful outcome of AIT.[15] Not only in Der p-SCIT but also in birch pollen (BP) SCIT, ILC2s plays an important role. Weekly administration of SCIT in mice with BP-induced allergic airway inflammation caused an increase in the levels of innate cytokines IL-33, GM-CSF, IL-25, and IL-5(+) ILC2s within the lungs. Additionally, treatment with BP SCIT resulted in a decrease in the number of IL-5(+) ILC2s, inhibition of mast cell tryptase-like release, suppression of Th2 cytokine production, reduction in eosinophil recruitment, and attenuation of peribronchial inflammatory infiltrate. Despite these effects, the production of innate cytokines and collagen deposition within the airways remained unaffected. This suggests that while BP SCIT can suppress adaptive and some innate immune responses effectively, it is insufficient to stop IL-33 expression and collagen deposition in mice's airways.[69] Impact on allergen-specific Th2 responses and induction of IL-10(+) and/or TGF-B (+) CD4(+) CD25(+) Tregs are two key components of immunotherapy targeting grass pollen allergies. CD4(+) CD25(+) IL-35(+) A unique subset of induced Tregs with regulatory characteristics has been discovered: forkhead box protein 3-negative T (IL-35 inducible regulatory T [iTR35]) cells. Compared to non-allergic controls, the seasonal AR (SAR) group showed higher proportions of ILC2s and IL-5(+) cells, IL-13(+) cells, and IL-5(+) IL-13(+) ILC2s in patients with grass pollen allergy, SLIT-treated patients (SLIT group), and non-atopic control participants. In the presence of IL-25 or IL-33, the generation of IL-5 and IL-13 by ILC2 was suppressed by the presence of IL-35. Furthermore, it suppressed effector T cell-induced allergen-driven Th2 response by inhibiting B-cell-mediated CD40 ligand expression, IgE production mediated by both IL-4- and IL-21, allergen-driven T-cell proliferation, as well as dendritic cell-mediated Th2 cytokine production. The activity of Th2 cells, including their proliferation and production of cytokines, was suppressed by iTR35 cells. Moreover, compared to SAR patients, patients receiving SLIT and NACs showed higher numbers of iTR35 cells and higher levels of allergen-driven IL-35. These findings suggest that

SLIT induces the generation of iTR35 and IL-35 cells, which serve as possible new immune-modulators, highlighting the clinical significance of SLIT in restoring protective iTR35 cells Populations.[70] In conclusion, ILC2s play a vital role in AIT, and further investigation into its mechanism of action is likely to unveil new therapeutic possibilities for AR treatment.

Conclusion and Perspective

There has been a lot of excitement and interest in the research of ILC2s since their complete description was published in 2010. A growing body of evidence suggests that ILC2s are significantly involved in the progression, sustenance, and spread of type 2 airway inflammatory disorders like allergic rhinitis AR, chronic rhinosinusitis with nasal polyps (CRSwNP), and asthma. When ILC2s are stimulated by allergens, a series of activation events is triggered via cytokines (such as IL-33, IL-25, and TSLP) derived from epithelial cells, lipid mediators (including leukotriene D4 and prostaglandin D2 [PGD2]), neuropeptides, and hormones (like neuromodulin U [NMU] and vasoactive intestinal peptide). This leads to the release of cytokines such as IL-13, IL-4, and IL-5. This sequence of events results in the recruitment of eosinophils, formation of fibrosis, proliferation of glandular cells, and production of mucus by epithelial cells, thereby contributing to the progression of AR. Recent studies have shed light on the regulatory function exerted by specific microRNAs in activating ILC2s. Moreover, certain substances such as MSC-sEVs, lloprost, MCC950, CC10, miR-150-5p, and testosterone have been identified as inhibitors of ILC2 activation. These substances could potentially serve as targets for AR therapy. ILC2s also collaborate with Th2 cells to exacerbate inflammatory processes and interact with Tregs to counteract Tregs-mediated suppression on allergic inflammation. Furthermore, the involvement of ILC2s in allergen-specific therapies is significant, and further investigations are expected to augment our comprehension of the mechanism of action of ILC2s in AR, offering novel perspectives for therapeutic interventions (Table 1). Nonetheless, there are several aspects regarding the functioning of ILC2s in AR that remain poorly understood, including the potential suppressive impact of ILC2s on Tregs activities in AR. Although thorough exploration of the role of ILC2s in AR demands substantial research efforts, in the future, these initiatives should result in the creation of novel treatments for the management of inflammatory airway illnesses, including AR.

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Disclosure

The authors report no conflicts of interest in this work.

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