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Invited review article

Proallergic cytokines and group 2 innate lymphoid cells in allergic nasal diseases

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Abbreviations:
AFRS, allergic fungal rhinosinusitis; AR, allergic rhinitis; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; DC, dendritic cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; HDM, house dust mite; IL, interleukin; ILC2, group 2 innate lymphoid cell; NAR, non-allergic rhinitis; TLR, toll-like receptor; TSLP, thymic stromal lymphopoietin; OVA, ovalbumin; PBMC, peripheral blood mononuclear cell

ABSTRACT

Recent advances in our understanding of proallergic cytokines and group 2 innate lymphoid cells (ILC2s) indicate their critical roles in type 2 immunity-mediated disorders. Proallergic cytokines, interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin, are released from epithelial cells in inflamed tissues and drive type 2 inflammation by acting on innate and acquired immune systems. ILC2s are an innate immune population that responds to proallergic cytokines by producing type 2 cytokines. In line with allergic disorders in the lung, skin, and intestine, emerging evidence suggests the involvement of proallergic cytokines and ILC2s in allergic nasal diseases such as chronic rhinosinusitis with polyps (CRSwNP), allergic fungal rhinosinusitis, and allergic rhinitis (AR). In CRSwNP patients, both proallergic cytokine levels and ILC2s frequency are increased in the nasal mucosa. Increased proallergic cytokine levels correlate with poorer disease outcomes in CRSwNP. Levels of nasal proallergic cytokines are also elevated in AR patients. In addition, animal studies demonstrate that cytokines are essential for the development of AR. It is becoming clear that the proallergic cytokine/ILC2s axis participates in allergic diseases by multiple mechanisms dependent upon the inflammatory context. Thus, a thorough understanding of these cytokines and ILC2s including their tissue- and disease-specific roles is essential for targeting the pathways to achieve therapeutic applications.

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Introduction

Recent major steps forward in our understanding of type 2 immune responses must include the discovery of three proallergic cytokines, interleukin (IL)-25 (also known as IL-17E), IL-33 (also known as IL-1F11), and thymic stromal lymphopoietin (TSLP), as well as a potent innate type 2 cytokine producer, group 2 innate lymphoid cells (ILC2s). IL-25, IL-33, and TSLP are produced by epithelial cells in barrier tissues as well as several immune cells in response to allergen exposure.[1] These cytokines both activate dendritic cells (DCs) to initiate Th2 responses and stimulate Th2 cells to enhance Th2 immunity.[1] In addition to inducing Th2 acquired immune responses, they also stimulate innate type 2 cells including basophils, mast cells, eosinophils, and ILC2s.[1] Thus, they play pivotal roles in both "acquired-type allergy" mediated by activated Th2 cells and antigen-specific IgE, and "innate-type allergy" induced without activation of the acquired immune system.[1,2]

ILC2s are a heterogeneous population comprising natural helper cells,[3] nuocytes,[4] and innate helper type 2 cells,[5] all characterized by a lack of surface lineage markers and the ability to produce large amounts of type 2 cytokines.[6] IL-25, IL-33, and TSLP strongly enhance ILC2 growth and induce the production of IL-5 and IL-13.[6]

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Some studies have shown that ILC2s also produce IL-4, IL-9, granulocyte-macrophage colony-stimulating factor (GM-CSF), and amphiregulin.[7–10] These cytokines promote eosinophilia, mucus production, M2 macrophage development, and tissue repair; thus, ILC2s are important effector cells in type 2 immune responses.[6] In addition to these effector functions, a growing body of evidence indicates that ILC2s mediate Th2 development by promoting DC activation[11,12] or by directly interacting with $CD4^+$ T cells.[8,13]

These observations highlight the critical and complex involvement of the IL-25-, IL-33-, and TSLP-ILC2s axes in the development and exacerbation of allergic inflammation. Thus, it is no surprise that these pathways also have important roles in allergic disorders of the upper airways. Although little information is available compared with other organs such as the lung, skin, or intestine, here we summarize the current understanding of the roles of epithelial-derived proallergic cytokines and ILC2s in nasal allergic diseases, namely chronic rhinosinusitis (CRS) and allergic rhinitis (AR).

Chronic rhinosinusitis

CRS is a nasal inflammatory disease with characteristic symptoms including nasal discharge, nasal congestion, facial pain, and hyposmia or anosmia for 12 weeks or more.[14] CRS can be further divided into two major subtypes, CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP), characterized by the presence or absence of polyps.[14] CRSwNP often accompanies tissue eosinophilia and is considered a Th2-dominated disease, while the immunological phenotype is likely to be skewed towards Th1 in CRSsNP patients.[14] Although CRS is a complex disease and the Th1 vs Th2 classification of the CRS subtypes might be an oversimplification,[15] emerging evidence supports the significant involvement of epithelial-derived proallergic cytokines and ILC2s in CRSwNP.

Human ILC2s were first isolated from lungs, gut, and inflamed nasal polyps,[16] and increased numbers of ILC2s were observed in the polyps from CRSwNP patients compared with nasal mucosa from CRSsNP patients or healthy controls.[7,16–20] Increased ILC2s frequencies in sinus mucosa were correlated with worsening nasal symptoms in CRS patients.[20] In addition, the ILC2 population is concentrated in polyps compared with sinus mucosa of CRSwNP patients.[21] These nasal polyp-derived ILC2s respond to IL-25, IL-33, and TSLP by producing IL-4, IL-5, IL-9, IL-13 and GM-CSF.[7,16,17] Thus, ILC2s may be an important source for type 2 cytokines in nasal polyps and contribute to tissue eosinophilia (Fig. 1). Furthermore, the preferential location of ILC2s in nasal polyps,[21] and gene expression analysis demonstrating that ILC2s express several factors involved in tissue remodeling,[22] suggest these cells contribute to polyp generation in CRSwNP (Fig. 1).

mRNA levels of IL-33 receptor, *ST2* (also known as *IL1RL1*), and numbers of $ST2^+$ cells are increased in polyps from CRSwNP or eosinophilic CRS patients.[17,23,24] Furthermore, an association between *ST2* polymorphisms and CRS was reported.[25] Among $CD45^+$ cells in the nasal mucosa from CRSwNP patients, ILC2s were the dominant source of IL-13 by *in vitro* stimulation of cells with IL-2 plus IL-33.[17] Although some studies have demonstrated that *IL33* expression levels were not altered among CRSwNP, CRSsNP, and healthy controls,[17,18,23] an interesting observation indicated that nasal epithelial cells from treatment-resistant CRSwNP patients expressed higher levels of *IL33* compared with treatment-responsive CRSwNP patients.[26] Therefore, altered IL-33 expression or an enhanced response of ILC2s to this cytokine in CRSwNP patients may aggravate disease severity and compromise the efficacy of treatments.

The expression levels of *TSLP* and *TSLPR* (also known as *CRLF2*) were higher in the nasal mucosa from CRSwNP[7,27,28] or eosinophilic CRS[29] patients compared with CRSsNP or healthy controls. In addition, nasal epithelial cells from CRSwNP patients had a greater up-regulation of *TSLP* expression in response to stimulation by poly I:C, a Toll-like receptor (TLR)3 ligand, compared with healthy controls.[7] Importantly, *TSLP* expression levels in nasal mucosa correlated to the polyp scores in CRS patients.[29] In addition to the observation of increased *TSLP* mRNA transcription, TSLP protein undergoes proteolytic cleavage by proteases in nasal polyps which enhances its bioactivity.[30] Increased TSLP activity in CRSwNP nasal mucosa may contribute to increased activation of DCs,[28] mast cells,[30] and ILC2s[7,16] (Fig. 1). ILC2s from nasal polyps also responded to IL-25,[16] and a study demonstrated elevated *IL25* levels in CRSwNP patients (Fig. 1).[31] Although the study did not observe an association between disease severity and *IL33* or *TSLP* levels, they showed that increased *IL25* levels correlated with poorer computed tomography (CT) scores in CRSwNP.[31]

These observations suggest the critical involvement of proallergic cytokines/ILC2s axis in the pathogenesis of CRSwNP. Although the relative contribution of ILC2s and Th2 cells in the type 2 milieu in CRSwNP is currently not clear, a study demonstrated that the number of ILC2s and Th2 cells was significantly correlated in nasal mucosa from CRSwNP patients.[18] Thus, ILC2s and Th2 cells may be simultaneously activated in the local allergic environment as both populations can respond to epithelial-derived proallergic cytokines.[1] Alternatively, they might cross-regulate each other as the dialogue between ILC2s and $CD4^+$ T cells was demonstrated in lungs[8] and intestines (Fig. 1).[13]

Allergic fungal rhinosinusitis (AFRS) is an endotype of CRS caused by bacterial or fungal infection,[14,32] and characterized by the presence of fungal hyphae in mucin in the sinus cavity, and serum fungi-specific IgE.[14,32] The local elevation of type 2 cytokines, IL-4, IL-5, and IL-13, is often observed in AFRS; thus the disease is considered a Th2-dominant type of CRS.[14,32] Currently, no study has directly investigated the role of proallergic cytokines in the pathogenesis of AFRS.[32] However, because both AFRS and CRSwNP are linked to type 2 immunity,[14,32] and fungi extracts or TLR ligands (fungal or bacterial accumulation present in AFRS patients) induce the expression of *IL25*,[33] *IL33*,[17] and *TSLP*[7] in nasal epithelial cells, epithelial-derived proallergic cytokines and ILC2s may also play important roles in AFRS analogous to that in CRSwNP. Further study is required to fully understand the subtype specific roles of proallergic cytokines and ILC2s in CRS.

Allergic rhinitis

AR is an IgE-mediated type 1 hypersensitivity reaction in nasal mucosa caused by nasal allergen exposure.[34,35] The characteristic symptoms of AR are sneezing, rhinorrhea, and nasal congestion caused by IgE-mast-cell-mediated early-phase responses of AR (5–30 min after allergen exposure).[34,35] In addition, type 2 cytokines and chemokines mediate the cellular influx into nasal mucosa, typically eosinophilia, which cause the late-phase responses of AR (approximately 6–24 h after allergen exposure) resulting in tissue damage and remodeling.[34,35] Because both AR and CRS are nasal inflammatory diseases, they are associated with each other with an estimated prevalence of AR of 60% in CRS patients.[14]

Several lines of evidence have indicated increased epithelial proallergic cytokine levels in AR patients. Three cytokines, IL-25,[36] IL-33,[37,38] and TSLP[36] were detected in the nasal lavage from patients with house dust mite (HDM)[36,37] or Japanese cedar pollen[38] AR. *IL33*,[39,40] *ST2*,[40] and *TSLP*[27,41–43] mRNA levels were high in nasal epithelia from several types of AR patients. $CD4^+$ cells in peripheral blood mononuclear cells (PBMCs) from AR patients with birch, grass,[44] or Japanese cedar[45] pollen sensitization expressed high levels of *IL25R* (also known as *IL17RB*) mRNA.[44,45]

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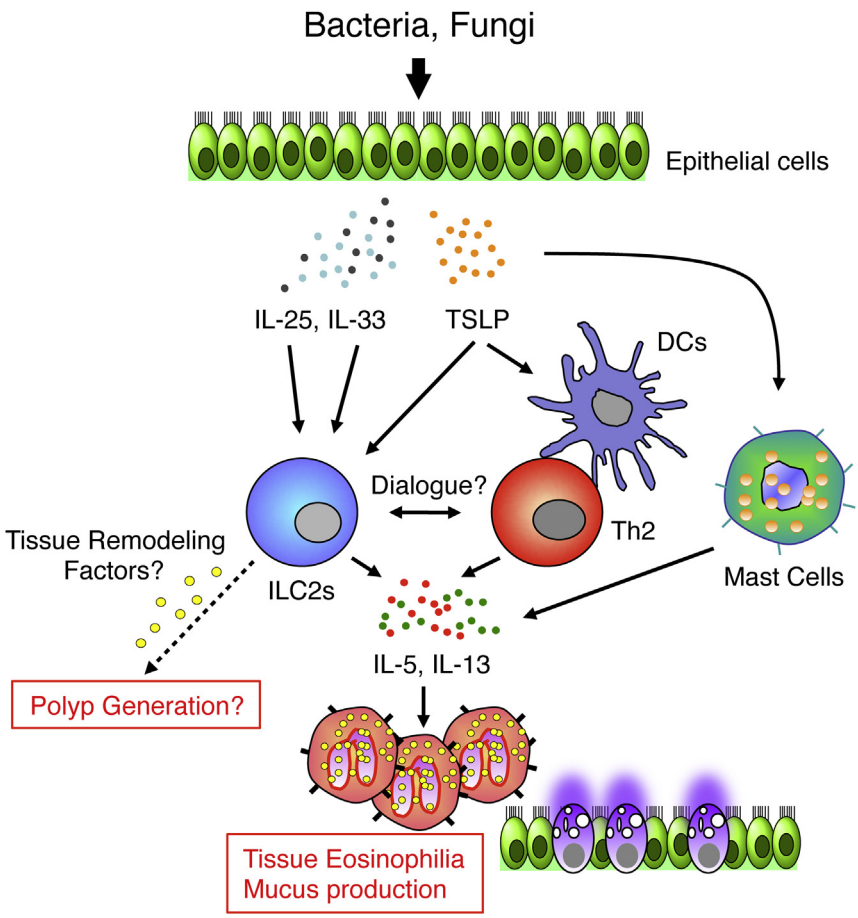

Fig. 1. Proallergic cytokines and group 2 innate lymphoid cells in chronic rhinosinusitis with nasal polyps. Although the cause of chronic rhinosinusitis with nasal polyps (CRSwNP) varies among patients, bacterial or fungal infection induces the production of proallergic cytokines from nasal epithelial cells. IL-25, IL-33, and TSLP stimulate group 2 innate lymphoid cells (ILC2s) to produce type 2 cytokines, IL-5 and IL-13. TSLP activates dendritic cells (DCs) to activate Th2 cells, and contributes to IL-5 production from mast cells. Because the numbers of ILC2s and Th2 cells are associated in the nasal sinus, these cells might cross-regulate each other. IL-5 and IL-13 induce eosinophilic infiltration into the nasal mucosa. ILC2s might also produce tissue remodeling factors that could be involved in polyp generation during disease.

A genome-wide association study predicted genetic polymorphisms in *IL33* locus linked to Japanese cedar pollenosis,[38] and serum IL-33 levels seemed to correlate with disease severity of grass and/or tree pollen AR.[46] In addition, an animal study using *Il33*$^{-/-}$ mice demonstrated a pivotal role for IL-33 in ragweed-specific AR.[39] After nasal ragweed pollen challenge of ragweed-sensitized mice, *Il33*$^{-/-}$ mice showed attenuated sneezing and eosinophilic and basophilic infiltration into the nose with lower serum ragweed-specific IgE titers and reduced ragweed-specific Th2 cell responses compared with wild-type controls.[39] IL-33 augments IgE-mediated histamine release from mast cells and IgE-independent cytokine and chemokine production from mast cells and basophils (Fig. 2).[39] In addition to gene-targeted mouse experiments, the treatment of ovalbumin (OVA)-sensitized mice with anti-IL-33 antibodies at the nasal OVA-challenge phase attenuated nose scratching behavior and nasal cellular infiltration[47] in mice, indicating the therapeutic potential of targeting IL-33 in post-sensitized AR patients.

As for IL-33, polymorphisms in *TSLP* locus are also associated with AR,[48–50] and nasal TSLP expression levels are linked to disease severity.[42,43] As TSLP is regarded as the master regulator for Th2 development by activating DCs,[1] TSLP-responsive CD1c^{+} DCs are recruited to nasal mucosa of grass pollen AR patients after allergen challenge.[51] TSLP-activated CD1c^{+} DCs strongly induce the proliferation of, and type 2 cytokine production from allergen-specific Th2 cells (Fig. 2).[51] An animal study using OVA-sensitized mice demonstrated that anti-TSLP antibody treatment at the nasal OVA-challenge phase ameliorated scratching behavior and nasal goblet cell hyperplasia.[52] Thus, analogous to the role of TSLP in asthma models, TSLP may have a critical role in developing Th2 responses in nasal mucosa (Fig. 2). Although the relative contribution of IL-33 and TSLP in AR is not clear, a study showed a positive correlation between IL-33 and TSLP levels in nasal mucosa,[18] suggesting that these cytokines cross-regulate each other either directly or indirectly.

IL-25 is also detected in nasal lavage from HDM AR patients,[36] and a mouse model of OVA-specific AR demonstrated up-regulated *Il25* mRNA levels in diseased nasal mucosa.[53] Allergen stimulation of basophils from birch or grass pollen AR patients, but not from healthy controls, up-regulated IL-25R expression on PBMCs.[44] The same study demonstrated that IL-25 stimulation of basophils inhibited cellular apoptosis and enhanced IgE-induced degranulation (Fig. 2).[44] In addition, IL-25 enhanced poly I:C-induced TSLP production from primary human nasal epithelial cells.[36]

Despite our understanding of the pivotal roles of epithelial-derived proallergic cytokines in AR pathogenesis, the role of ILC2s in AR is poorly understood. AR is an IgE- and Th2-dependent disorder[34,35] and the development of AR was completely abrogated in *Rag2*$^{-/-}$ mice, which lack both T and B cells but retain ILC2s, when

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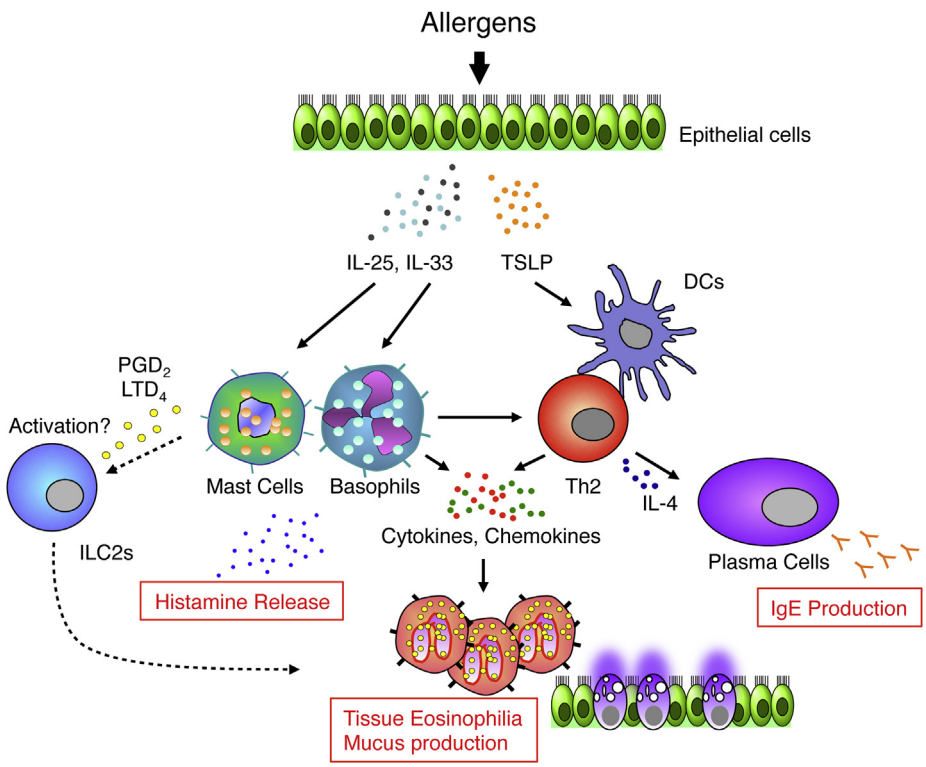

Fig. 2. Proallergic cytokines and group 2 innate lymphoid cells in allergic rhinitis. Nasal epithelial cells stimulated with allergens produce proallergic cytokines. TSLP activates dendritic cells (DCs) to drive allergen-specific Th2 cells. Following IgE crosslinking, IL-33 augments mast cell degranulation and IL-25 augments basophil degranulation, which enhances the early phase response of allergic rhinitis (AR). IL-33 also induces cytokines and chemokines production from mast cells and basophils, resulting in enhanced local type 2 immune responses. Allergen stimulation of mast cells and basophils induces the rapid release of lipid mediators, such as prostaglandin D_2 (PGD2) or leukotriene D_4 (LTD4), which may cause the temporal activation of group 2 innate lymphoid cells (ILC2s). Generation of nasal type 2 milieu results in eosinophilic infiltration and mucus production that mediates the late phase responses of AR.

mice were nasally sensitized with ragweed pollen.[54] This indicated that ILC2s alone cannot mediate the symptoms of AR including tissue eosinophilia,[54] which can be induced solely by activating ILC2s in lungs.[55] ILC2s are present in mouse nasal mucosa in the steady state,[54] although ILC2s do not expand in the allergic nasal mucosa (Y.K., S.A., and T.Y. unpublished observation). In a human study, the numbers and cytokine-producing activities of ILC2s in PBMCs from AR patients were comparable to those from healthy controls, whereas allergic asthma patients showed an increased number of ILC2s and increased cytokine production from ILC2s in PBMCs.[56] However, another human study of cat allergen-sensitized AR patients demonstrated an increased ILC2 frequency in PBMCs, 4 h after nasal cat allergen exposure.[57] Thus, even though AR conditions do not affect the state of ILC2s in the nose or periphery, these cells could be temporarily activated after allergen exposure and participate in the production of type 2 cytokines collaborating with other cells, such as Th2 cells, basophils, and mast cells. In addition to proallergic cytokines, ILC2s were activated by prostaglandin D_2[58] or leukotriene D_4[59] rapidly released from basophils and mast cells by allergen exposure in AR (Fig. 2).[34] Because recent studies have demonstrated the involvement of ILC2s in the development of Th2-acquired immunity in lungs,[8,11,12] whether this is also the case in nasal allergy should be investigated. The exact contribution of ILC2s in AR might be determined by using recently established mouse models in which the ILC2 population is specifically abrogated.[11,60]

AR is diagnosed by detecting systemic or local allergen-specific IgE in individuals who have rhinitis symptoms.[34,35] Rhinitis patients with negative allergen-specific IgE are classified as non-allergic rhinitis (NAR).[61] NAR is a heterogeneous population and some NAR patients show nasal eosinophilia and/or mastocytosis.[62,63] Importantly, NAR patients with eosinophils and/or mast cells have a lower quality of life and a higher risk for comorbidities compared with other NAR patients.[62,63] Because the presence of eosinophils or mast cells is reminiscent of type 2 inflammation, it is of interest to investigate the involvement of proallergic cytokines and ILC2s in NAR with eosinophils and/or mast cells. These pathways might activate type 2 inflammation without the presence of specific Th2-acquired immune responses.

Conclusions

Accumulating evidence indicates that proallergic cytokines and ILC2s pathways contribute to the pathogenesis of allergic nasal diseases. Importantly, some studies have shown that proallergic cytokine levels[29,31,42,43,46] or ILC2 numbers[20] correlated to the severity of nasal allergic diseases, implicating the control of these factors might be beneficial for the treatment of the diseases. In addition, the proallergic cytokine/ILC2s axis might mediate treatment resistivity in some allergy conditions.[26,64] Thus, targeting proallergic cytokines or ILC2s may improve treatment efficacy, especially in treatment-resistant patients. In addition to using cytokine-neutralizing antibodies, recent studies have demonstrated the potential therapeutic use of small molecule inhibitors against the proallergic cytokine/ILC2 pathway. For example, a STAT5 inhibitor, Pimozide, blocked the TSLP/STAT5 pathway and improved corticosteroid resistance of ILC2s in a lung inflammation model.[64] An anti-inflammatory lipid, lipoxin A_4, inhibited ILC2s activation.[65] Furthermore, ILC2-activating lipid mediators, prostaglandin D_2 or leukotriene D_4, pathways can be inhibited by

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currently available anti-allergy medicines.[66] However, despite the rapid advances in our understanding of the basic biology of proallergic cytokines and ILC2s, little is known about their specific roles in nasal tissues. Further studies investigating nasal diseases need to be conducted, and a deeper understanding of proallergic cytokines and ILC2s in the context of specific disease conditions may offer opportunities for the development of novel clinical interventions for nasal allergic diseases.

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Conflict of interest

The authors have no conflict of interest to declare.

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