ABSTRACT

Chronic rhinosinusitis with nasal polyps (CRSwNP), a type 2-based upper airway disease, is mainly characterized by high asthma comorbidity and recurrence after surgery. It has been shown that type 2 cytokines, including interleukin (IL)-4, IL-5, and IL-13 released from T helper 2 (Th2) cells as well as group 2 innate lymphoid cells (ILC2s), contribute to chronic inflammation of CRSwNP. This review summarizes recent progresses made in our understanding of ILC2 activity, particularly ILC2 accumulation at airway inflammation sites, cooperation with Th2 cells in aggravating the CRSwNP inflammatory process and interactions with regulatory T cells (Tregs) in resisting Tregs-mediated suppressive function in allergic inflammation. A better understanding of the biology of ILC2s should lay a good foundation in elucidating the pathogenesis of CRSwNP, and subsequently may lead to the development of new therapeutic strategies for the management of CRSwNP.

Keywords: Sinusitis; nasal polyps; innate immunity; lymphocytes; Treg cells; eosinophils; respiratory tract diseases; asthmas; cytokines

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is chronic inflammation of the sinus mucosa, with a prevalence of approximately 1.1% to 4.3% worldwide.\(^1\),\(^2\) The principal manifestation of CRSwNP is T helper 2 (Th2) cell inflammation with marked eosinophilic infiltration, which is often accompanied by asthma comorbidity and recurrence after surgery.\(^3\)\(^-\)\(^5\) Except classic Th2 cells, group 2 innate lymphoid cells (ILC2s) compose a heterogeneous population of innate immune cells, which play a key role in the generation and maintenance of immunity especially on the mucosal surface; they have also been shown to produce large amounts of type 2 cytokines in response to interleukin (IL)-33.\(^6\),\(^7\) Similar to CD4\(^+\) Th cells, ILCs are divided into 3 different groups (ILC1/2/3) based on their function, cytokine profiles and expressed transcription factors. In particular, ILC1s express T-bet for their development and function, and secrete interferon (IFN)-\(\gamma\); ILC2s require GATA3 and ROR\(\alpha\) for their development and predominantly release type 2 cytokines such as IL-4, IL-5, IL-9 and IL-13; and ILC3s depend on ROR\(\gamma\)t for their differentiation and produce IL-17 and/or IL-22 cytokines. Critically, an increase in ILC2s has been demonstrated in the local mucosa.
of CRSwNP patients, with even higher numbers being present in CRSwNP patients with comorbid asthma.\textsuperscript{6,8,9} Thus, a further understanding of the role of ILC2s in the pathogenesis of CRSwNP would certainly help in better management of chronic inflammation in CRSwNP. To this end, this review summarizes recent progress made in evaluating activation, migration, and function of ILC2s in CRSwNP.

**ACTIVATION AND FUNCTION OF ILC2s**

Epithelial cell-derived cytokines IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) have been shown to activate ILC2s, which further aggravate type 2 inflammation.\textsuperscript{10-13} The induction of IL-25, IL-33 and TSLP in CRSwNP is mainly dependent on various allergenic stimuli (e.g., house dust mite [HDM], *Alternaria alternata* and papain) and microbial infections (*Staphylococcus aureus* and virus). Not surprisingly, the expression of epithelial cell-derived cytokines has a close link with disease severity or eosinophil infiltration in CRSwNP.\textsuperscript{14-17} Additionally, locally elevated cysteinyl leukotrienes (cysLTs) and prostaglandin D2 (PGD2) in CRSwNP tissue have also been shown to act as potent stimulators for the activation of ILC2s (Fig. 1).\textsuperscript{18-21}

Activated ILC2s secrete type 2 cytokines, IL-5 and IL-13, and consecutively trigger persistent airway inflammation. Amphiregulin (AREG) released from ILC2s is crucial for tissue repair and restores epithelial integrity and lung function during periods post infection.\textsuperscript{22} ILC2s have also been shown to produce IL-8 and granulocyte macrophage colony-stimulating factor (GM-CSF), which can also induce activation and survival of neutrophils and macrophages. ILC2-derived IL-9 acts in an autocrine manner to prolong survival of ILC2s in the lungs and stimulates mast cell accumulation in local tissues. Interactions of ILC2 with Th2 cells promote and/or enhance type 2 immune responses.

**Fig. 1.** ILC2s in CRSwNP. ILC2s are activated by epithelial-derived cytokines as well as by other biological mediators such as lipid mediators. Upon activation, ILC2s are able to initiate allergic inflammation through both the innate and adaptive immune responses. Activated ILC2s release IL-5, which mainly contributes to eosinophilia; and IL-13, which promote airway hyperresponsiveness, goblet cell hyperplasia, mucus production and activation of DC. ILC2s induce B-cell proliferation as well as IgA, IgM, IgE and IgG1 production. Activated ILC2s are able to release IL-8 and GM-CSF, which can also induce activation and survival of neutrophils and macrophages. ILC2-derived IL-9 acts in an autocrine manner to prolong survival of ILC2s in the lungs and stimulates mast cell accumulation in local tissues. Interactions of ILC2 with Th2 cells promote and/or enhance type 2 immune responses.

ILC2, group 2 innate lymphoid cell; CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin; DC, dendritic cell; Ig, immunoglobulin; GM-CSF, granulocyte macrophage colony-stimulating factor; Th2, T helper 2.
factor (GM-CSF) following stimulation with PGD2, IL-2, or IL-33 plus TSLP.\textsuperscript{13,18} Moreover, stimulation by a combination of IL-33 and IL-25 can markedly enhance PGD2-induced production of IL-8 and GM-CSF by ILC2s.\textsuperscript{18} Indeed, as some populations of difficult-to-treat chronic rhinosinusitis patients have an elevated expression of IL-8 in local tissue, and elevated levels of IL-8 in eosinophilic CRSwNP patients are associated with increased attraction and activation of neutrophils and high rate of recurrence in these patients,\textsuperscript{23-25} we have speculated that ILC2s may also contribute to the infiltration of neutrophils via secretion of IL-8 in this patient group.

**MIGRATION OF ILC2s IN ALLERGIC AIRWAY DISEASE**

Although ILC2s are known to accumulate in allergic airways, little is known about the contribution of local proliferation of ILC2s versus the migration of ILC2s from circulation. Generally, ILC2s exist in relatively low numbers in the lungs under normal conditions. Studies of mice administered IL-33 and \textit{A. alternate} have demonstrated that ILC2 precursors (ILC2P) migrate from bone marrow to the lung and locate around the large airways and blood vessels rather than alveolar capillaries,\textsuperscript{26-28} suggesting that these cells are recent emigrants. In this case, it is important to define the signals that control ILC2 migration to and within tissues.

The migration of ILC2s in different tissues is partially mediated by distinct chemokines. Our group has demonstrated that C-X-C motif chemokine ligand 16 (CXCL16) is able to induce chemotaxis of murine ILC2s, and that a specific anti-CXCL16 neutralizing antibody significantly reduces ILC2s accumulation and inhibits airway hyperresponsiveness in IL-33 and HDM-induced airway inflammations.\textsuperscript{29} Other studies have demonstrated that the frequency of lung ILC2s is significantly decreased in CXCR6\textsuperscript{GFP/GFP} mice compared to their CXCR6-sufficient counterparts in a papain-challenged allergic mouse model.\textsuperscript{30} Similarly, C-C motif chemokine ligand (CCL) 22, a high-affinity ligand at the CC chemokine receptor 4 (CCR4), recruits murine ILC2s in the lung tissues compared to wild-type (WT) mice in the context of systemic IL-25 abundance, and CCR4-deficient mice display impaired migration of ILC2s to the lung.\textsuperscript{31} Although CCL8 may also be chemotactic for human ILC2s like CCL22,\textsuperscript{32} a recent study has demonstrated that use of natural CCR8 agonists to block the binding site of CCL8 in ILC2s of mice did not significantly alter the migration of ILC2s compared to CCL8-treated or control ILC2s.\textsuperscript{33} The authors thus suggested that CCL8 was not important for the migration of ILC2 in mice. CCL25 reportedly induces the migration of mouse nasal-associated lymphoid tissue-derived ILC2s via activation of CCR9 on ILC2s \textit{in vitro}.\textsuperscript{34} However, our study has shown that CCL25 could not induce the migration of ILC2s via CCR9 in the lung of mice, owing to different levels in chemokine receptors in different tissues regulating ILC2 migration.\textsuperscript{29}

Adhesion molecules are reportedly also involved in the migration of ILC2s. Evidence suggests that β2 integrins (CD18) on ILC2s may be required for \textit{A. alternata}-induced ILC2 trafficking from the circulation into the lung, because blocking β2 integrins significantly decrease the number of ILC2s in the lung without affecting their proliferation, apoptosis and function.\textsuperscript{34} Additionally, ILC2s have been shown to express S1PR1 and migrate into the lymphatics in a sphingosine 1-phosphate (SIP)-dependent manner, via a mechanism similar to that previously described for T cells egressing from secondary lymphoid organs and the thymus.\textsuperscript{35}

On the other hand, ILC2s that migrate to inflammation sites further proliferate after stimulation with IL-2, IL-4, IL-9, TL1A, leukotriene D4, neuromedin U or inducible T cell

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co-stimulator (ICOS), and its ligand ICOSL interaction. Interestingly, ILC2s can produce CCL1 protein, which markedly increases after activation, and CCL1 in turn induces ILC2 proliferation and type 2 cytokines production. Treatment of cultures of WT ILC2s with neutralizing anti-CCL1 antibodies significantly inhibits the cell expansion in vitro. These findings suggest that in order to decrease the aggregation of ILC2s at inflammation sites, it is important to consider not only to reduce the migration of ILC2s, but also to inhibit the proliferation of ILC2s.

INTERACTIONS BETWEEN ILC2 AND Th2 CELLS

ILC2s are generally regarded as another important resource of type 2 cytokines, which are also involved in Th2-cell differentiation, proliferation and cytokine production (Fig. 2). Investigations using a papain-induced murine model of allergic lung inflammation have shown that IL-13 produced by ILC2s facilitates migration of activated dendritic cells (DCs) to lymph nodes (LNs) and subsequently promotes Th2-cell differentiation. Similarly, in vitro studies have demonstrated that IL-4-derived from ILC2s potently drives Th2 differentiation, which is much impaired by specific deletion of IL-4 from ILC2s in vivo in a natural Th2-dependent model of human helminthiasis. Additionally, ILC2s have also been shown to be involved in the recruitment of memory Th2 cell in response to allergens. For example, a study involving a papain-induced murine model has shown that IL-13 released from ILC2s is essential for...
rapid release of CCL17 by CD11b+CD103 DCs, which in turn promotes the migration of CCR4+ memory Th2 cells to the lungs of the animal following repeated papain challenge.\(^{45}\)

The cognate interactions between ILC2s and CD4+ T cells via major histocompatibility complex class II (MHC II)-antigen (Ag) presentation and co-stimulatory signals modulate Th2-cell proliferation and differentiation in a cell contact-dependent manner. MHC II molecules expressed on ILC2s interact with antigen-specific Th2 cells to instigate cross-talk between the cells, resulting in cyclic release of cytokines IL-2, IL-4 and IL-13 by Th2 cells to promote ILC2 proliferation as well as the release of cytokines from ILC2s to induce proliferation of Th2 cells.\(^{46-48}\) Furthermore, addition of anti-MHC II antibody to the co-culture or depletion of MHC II in ILC2s diminishes the proliferation of T cells.\(^{46-48}\) Similarly, CD80 and CD86 expressed on ILC2s are also involved in IL-2 secretion and T-cell proliferation through interaction with CD28 on T cells.\(^{46}\) Animal studies have demonstrated that OX40L, a tumor necrosis factor (TNF) receptor superfamily ligand expressed by activated ILC2s, is also important in allergic airway inflammation as it modulates proliferation and survival of Th2 cells by binding to OX40 on the T cells.\(^{49-51}\) Similarly, ILC2s expressing ICOSL are known to enhance survival, proliferation and cytokine secretion of Th2 cells.\(^{52,53}\) Another study has shown that programmed death-ligand 1 (PD-L1) expressed on ILC2s can lead to increased expression of GATA3 and production of IL-13 by Th2 cells both \textit{in vitro} and \textit{in vivo} through interaction with PD-1 on the T cells, which paves the way for a robust adaptive anti-helminth Th2 cell-mediated response.\(^{55}\) Furthermore, the finding that CRSwNP patients exhibit greater infiltration of ILC2s and Th2 cells in the local mucosa compared to healthy controls\(^{51,56-59}\) suggests that the synergism between ILC2s and Th2 cells may lead to a vicious circle, which further aggravates type 2 inflammation characteristics in CRSwNP.

**INTERACTIONS BETWEEN ILC2 AND REGULATORY T CELLS (Tregs)**

Several studies have indicated that ILC2s can also regulate the function of Tregs (Fig. 3). IL-4 secretion by ILC2s inhibits Treg cell differentiation and impair the suppressive function of
Tregs, thereby promoting the development of food allergy. Additionally, when the ligand TL1A, a member of the TNF superfamily, binds to its receptor, death receptor3 (DR3), expressed on human and murine ILC2s, the proliferation of ILC2s, and the synthesis of type 2 cytokines from ILC2s are increased. Interestingly, TL1A has been shown to also act on Tregs to increase proliferation and enhance the suppressive activity of Tregs in allergic inflammatory skin disease. These data suggest that there may be competitive binding of TL1A between Treg and ILC2s. In contrast, ICOSL expressed by ILC2s can promote Treg accumulation, and OX40L expressed on ILC2s can cause an increase in the recruitment of Tregs during type 2 inflammation. Moreover, IL-9 produced by ILC2s has been shown to enhance the suppressive function of Tregs in an antigen-induced arthritis model. ILC2s are also the major source of AREG, an epidermal growth factor like growth factor, which enhances suppressive function of Tregs on binding to epidermal growth factor receptor.

On the other hand, Tregs are also able to inhibit the activation of ILC2s. Previous studies have demonstrated that human and murine induced Tregs (iTregs) can both generate suppressive effects by secretion of IL-10 and transforming growth factor (TGF)-β, which inhibit the production of IL-5 and IL-13 by ILC2s in a ICOS-ICOSL-dependent cell-to-cell contact manner in vivo and in vitro. Moreover, administration of the lipid mediator maresin-1 has been shown to inhibit activation of ILC2s and to promote the generation of Tregs, which in turn dampens type 2 immune reaction in a murine model of OVA-challenged airway inflammation. Indeed, taken together with the finding that Tregs are reduced in the peripheral blood and the sinus mucosa of CRSwNP patients, these data suggest that decreased activity of ILC2s may enhance the inhibitory function of Tregs and thus moderate development of type 2 inflammation in CRSwNP.

ILC2 PLASTICITY

Recently, plasticity and heterogeneity of ILC2s has been noted in airway disease. Pro-inflammatory cytokines of the IL-1 family, IL-1β and IL-18, potently induce proliferation and type 2 cytokine production from ILC2s. In the presence of IL-12, IL-1β and IL-18 can reduce the expression of GATA3 on ILC2s and induce the transition of ILC2s into IFN-γ-producing ILC1s. Furthermore, it has been shown that notch signalling and cysLTs as well as a combination of cytokines IL-1β, IL-23 and TGF-β can promote the differentiation of ILC2s into an IL-17-producing ILC3-like phenotype. During influenza virus and S. aureus infections, ILC2s in murine lungs exhibit phenotypic plasticity, which is characterized by down-regulated GATA3 expression and low ability to produce type 2 cytokines. In chronic rhinosinusitis (CRS) patients, CD117+IL-1R+ ILC2s are exclusively present in CRSwNP associated with production of type 2 cytokines, whereas CD117+IL-1R+ ILC2s are mainly found in the nasal mucosa of CRSsNP patients, with lower eosinophilia in the local tissues. Although the function of CD117+IL-1R+ ILC2s is presently not clear, the presence of these different subsets of ILC2s in CRS suggests that the local environment may possibly influence the stability of ILC2s in chronic airway disease.

CORTICOSTEROID SENSITIVITY OF ILC2s

The finding that the protein level of TSLP is elevated in CRSwNP may be of significance, as TSLP may play a key role in the induction of corticosteroid resistance of ILC2s. Treatment
with corticosteroids has been shown to suppress airway inflammation, and attenuate proliferation and type 2 cytokine production by ILC2s isolated from the blood of asthmatic subjects.\(^7\) However, in the presence of airway inflammation, TSLP plays a pivotal role in inducing corticosteroid resistance of LC2 in a MEK and STAT5-dependent manner, and reverses the corticosteroid-induced inhibition of ILC2 activity.\(^7\) Indeed, BAL ILC2s from asthmatic patients with elevated TSLP have also been found to be steroid resistant, and this steroid resistance could be reversed by clinically available inhibitors of MEK and STAT5.\(^7\)

Similarly, studies of OVA-induced asthma models have demonstrated that the ILC2s of mice challenged with a combination of OVA and IL-33 develop corticosteroid resistance and fail to exhibit corticosteroid-induced suppression in accumulation of ILC2s, expression of type 2 cytokines, and mucus production.\(^8\) On the other hand, corticosteroid treatment has also been shown to reduce the frequency of ILC2s in CRSwNP tissues.\(^8,9\) Moreover, in the presence of dexamethasone, both ILC2s and Th2 cells from mild asthmatics show attenuated generation of type 2 cytokines stimulated by IL-33, supporting the concept of susceptibility of these cells to steroids.\(^8,9\) Thus, the potential role of ILC2s as the source of type 2 cytokines and their involvement in CRSwNP makes ILC2s an attractive cell type for therapeutic intervention, beyond their susceptibility to steroids.

**SUMMARY AND OUTLOOK**

Since the detailed description of ILC2s in 2010, this cell type has been studied with great interest and excitement. There is accumulating evidence that ILC2s are essential for the initiation, maintenance and propagation of diseases involving type 2 airway inflammation, including allergic rhinitis, CRSwNP and asthma. In particular, ILC2s can produce large amounts of type 2 cytokines, including IL-4, IL-5, IL-13 and IL-9; and contribute to eosinophilic CRSwNP. As type 2 CRSwNP is usually accompanied by asthma comorbidity and recurrence after surgery, we have speculated that ILC2 may be one of the key cells that mediates disease refractoriness; however, this needs to be confirmed in future studies. This in turn should provide valuable information on the design of novel ILC2-targeting therapies for the management of these diseases. However, several questions still remain to be addressed. First, it is unclear how and when these cells evolve from serving a balanced homeostatic/reparative function to promoting an allergic pathology. Secondly, it is also unclear whether ILC2s inhibit the function of Tregs in CRSwNP. Thirdly, factors controlling the timing and extent of ILC2 tissue migration are not clear. Finally, we are just beginning to understand the cellular and molecular interactions of these cells with other cell types, and the dynamics of these cells within the NP tissue under inflammatory conditions. Although great effort are required to further elucidate the role of ILC2s in CRSwNP, it is likely that this will also lead to the development of novel therapies for the management of CRSwNP, and possibly other airway inflammatory diseases in the future.

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