



Innate lymphoid cells in asthma: when innate immunity comes in a Th2 flavor

Donata Vercelli^{a,b,c}, Justyna Gozdz^{a,b}, and Erika von Mutius^d

Purpose of review

Asthma is typically considered as an immunologic Th2 cell-mediated disease, a notion that is still inspiring many therapeutic strategies. In the past years, however, an innate immune cell type has been discovered in mice that resides in the mucosa and secretes the Th2 cytokines IL-13 and IL-5 in response to IL-33 and IL-25 released by a damaged epithelium. These cells [now named group 2 innate lymphoid cells (ILC2s)] are rare, systemically dispersed, long-lived, and exist in humans. Recent work shows that ILC2s are critical for the development of asthma and related phenotypes in mice. Their role in human asthma remains unknown.

Recent findings

This article reviews the most recent work that highlights ILC2s and the mechanisms underlying their critical role in experimental asthma. We also review the results of asthma therapeutic trials that targeted IL-13 and IL-5, the products of both Th2 cells and ILC2s.

Summary

Although the limited success of these trials is often quoted to dismiss the role of Th2 immunity as a whole, we propose that Th2 cytokines released by ILC2s may be critical for human asthma, but are not adequately neutralized because they are not readily accessible in peripheral tissues.

Keywords

asthma, ILC2, innate immunity, Th2 cytokines

INTRODUCTION

For a while now, asthma has been widely considered as an immunologic disease mediated by Th2 cells and adaptive immunity. This notion has inspired not only multiple research efforts but also a number of anti-Th2 therapeutic strategies. In the past couple of years, however, it has become clear that a Th2 cytokine signature does not necessarily reflect an adaptive Th2 cell-orchestrated response. This appears to be the case in a rapidly increasing number of conditions [1], including atopic dermatitis [2], hepatic fibrosis [3] and, in humans, chronic rhinosinusitis with nasal polyps [4]. Asthma, particularly in its experimental mouse version, is also experiencing a revisionist sweep based on the concept that there is more to this disease than just Th2 cell-dependent, IgE-mediated allergic inflammation [5].

This paradigm shift has occurred primarily, thanks to the discovery of a new innate lineage-negative cell type variously named natural type 2 helper cells, I_H2 cells or nuocytes [6^{••}–9^{••}] and finally, following a nomenclature proposed by a consortium of experts [10[•]], group 2 innate

lymphoid cells (ILC2s). These previously unappreciated ILCs produce Th2 cell-associated cytokines, but they do not express cell surface markers typically associated with other immune cell lineages. Furthermore, like the ILCs expressing other cytokines, this ILC subset does not express a T-cell receptor and thus does not respond in an antigen-specific manner [1]. Even though most studies on ILC2 have been performed in mice, these cells have also been found in the human fetal and adult lung, and even in human peripheral blood [4].

We now know that ILC2s arise in the bone marrow and differentiate from a common Id2+ lymphoid progenitor, indicating that they are

^aFunctional Genomics Laboratory, Arizona Respiratory Center,

^bDepartment of Cellular and Molecular Medicine, ^cThe BIO5 Institute, University of Arizona, Tucson, Arizona, USA and ^dDr von Hauner Children's Hospital, Ludwig Maximilians University, Munich, Germany

Correspondence to Donata Vercelli, MD, The BIO5 Institute, Rm. 339, 1657 E. Helen Street, Tucson, AZ 85719, USA. Tel: +1 520 626 2567; fax: +1 520 626 6623; e-mail: donata@email.arizona.edu

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KEY POINTS

- ILC2s are innate lymphoid cells that reside in the mucosa and respond to epithelial distress signals by releasing IL-13 and IL-5.
- Recent work unambiguously shows that IL-13 and IL-5-secreting ILC2s play a major role in experimental asthma. Their role in human asthma has not yet been explored.
- Human studies using biologicals targeting IL-13, IL-5 and IL4-R α have shown only limited success in disease control for patients with asthma.
- These somewhat disappointing findings may result from the limited access antibodies have to ILC2-derived cytokines in the mucosa.

distinct, previously unknown members of the lymphoid lineage [11]. At least three transcription factors appear to be essential for ILC2 differentiation: RAR-related orphan receptor (ROR) α [11], T cell factor-1 [12] and GATA binding protein 3 [13]. ILC2s reside primarily in the mucosa and behave as innate tissue sentinels. One of their main jobs is to rapidly secrete large amounts of the Th2 cytokines IL-13 and IL-5 when stimulated by IL-33 and IL-25 released by the epithelium in response to damage by proteases, viruses or other environmental insults. ILC2s are extremely rare, but on a per-cell basis, their ability to secrete Th2 cytokines is several-fold higher than that of classical polarized Th2 cells [1,10¹⁴] (Fig. 1).

The identification of innate lymphoid cells that secrete Th2 cytokines in response to epithelial damage fills a critical gap in our understanding of asthma pathogenesis by providing a long-sought link between Th2 inflammation and lung-based innate mechanisms of disease initiation and maintenance [5]. Not by chance, unbiased genome-wide association studies [15,16] independently pointed to the epithelium/ILC2 axis as a critical player in asthma by identifying IL33, the IL33 receptor IL1RL1/ST2, thymic stromal lymphopoietin (TSLP), RORA and IL13 as major asthma-susceptibility genes. But there may be even more to ILC2s. For instance, recent work demonstrated that these cells regulate eosinophil homeostasis and circadian cycling in response to nutrient intake [17¹⁸] and skeletal muscle regeneration after injury [18], roles that go well beyond purely immunological, defense-related properties. Below we discuss how the discovery of ILC2s and the growing appreciation of their functional properties add to our understanding of asthma pathogenesis and create a novel framework to design more effective treatments.

GROUP 2 INNATE LYMPHOID CELLS AND ASTHMA PATHOGENESIS

Probably for technical and logistical reasons, most if not all of the studies that link ILC2s to asthma have been performed in mice. This is also true of the work published over the past year. For instance, adoptive transfer of innate IL-13-producing cells isolated from il4/il13 reporter mice was used to investigate the role of ILC2s in airway hyper-reactivity (AHR). Transfer of wild-type but not Il13^{-/-} ILC2s into Il13^{-/-} mice, which are normally resistant to IL-25-induced AHR, restored airway resistance and lung cell infiltration, demonstrating ILC2s are an innate source of IL-13 that can directly induce AHR in the absence of IL-13-producing CD4⁺ T cells [19].

Because natural allergens often contain proteases, the role of ILC2s in allergen-induced lung inflammation was characterized in a model that relies on intranasal sensitization with the protease papain [20²¹]. Eosinophil infiltration and mucus hyperproduction were detected in the lungs of wild-type and Rag1^{-/-} mice, but not in Rag2^{-/-} Il2rg^{-/-} mice that lack ILC2s. Moreover, ILC2 depletion inhibited papain-induced airway inflammation in Rag1^{-/-} mice, whereas adoptive transfer of ILC2s enabled Rag2^{-/-} Il2rg^{-/-} mice to respond to papain. Finally, treatment of lung explants with papain-induced IL-33 and TSLP production by stromal cells, and IL-5 and IL-13 production by ILC2s, establishing ILC2s as a critical T-cell-independent source of Th2 cytokines in protease-dependent airway inflammation. Interestingly, heat-inactivated papain had no activity in this model.

More recent work focused on the contributions of ILC2s to the development of allergic asthma in response to natural allergens. Airway exposure of naive mice to the asthma-associated fungal allergen *Alternaria alternata* increased bronchoalveolar lavage levels of IL-33, followed by IL-5 and IL-13 production and airway eosinophilia without T or B cells. This innate type 2 response to the allergen was nearly abolished in mice deficient in IL-33R/ST2, and ILC2s in the lungs were necessary and sufficient to mediate the response to *Alternaria* [21]. ILC2s are also critical for the response to house dust mite (HDM) and peanut. When mice deficient in TSLP, IL-25 or IL-33 signaling were exposed to HDM intranasally or to peanut intragastrically, HDM-induced allergic asthma and peanut-induced food allergy/anaphylaxis required IL-33 but not IL-25 or TSLP signaling, likely because of the superior ability of IL-33 to expand ILC2s *in vivo* [22].

Because asthma is not invariably associated with allergic sensitization, a recent study sought to model conditions that might lead to AHR, a cardinal

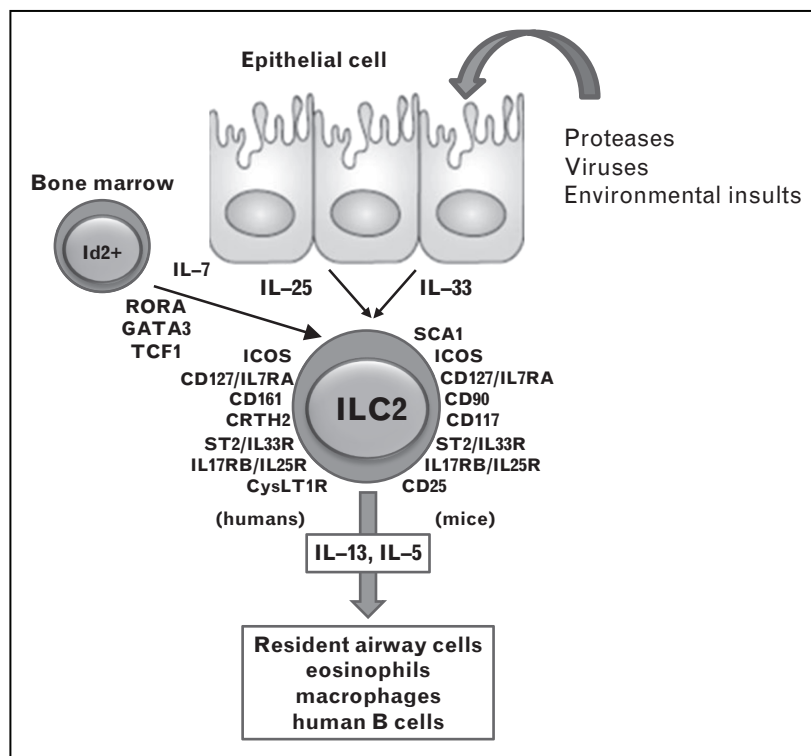


FIGURE 1. ILC2s: development, functional properties and phenotypic characteristics in humans and mice. ILC2s, group 2 innate lymphoid cells.

feature of asthma, through Th2 cell-independent mechanisms. To this end, AHR was induced with glycolipid antigens, which activate natural killer T (NKT) cells. AHR developed rapidly when mice were treated with glycolipids, even in the absence of conventional CD4⁺ T cells. The activated NKT cells directly induced alveolar macrophages to produce IL-33, which in turn activated NKT cells, as well as ILC2s, to increase production of IL-13. This glycolipid-induced AHR pathway required not only IL-13, but also IL-33 and its receptor, ST2. When adoptively transferred into IL-13^{-/-} mice, both wild-type ILC2s and NKT cells were sufficient for the development of glycolipid-induced AHR [23]. AHR induced by the *Aspergillus fumigatus*-derived glycosphingolipid, asperamide B, through invariant NKT cells also required IL-33/ST2-dependent mechanisms [24]. Because plant pollens, house dust and some bacteria contain glycolipids that can directly activate NKT cells, these studies suggest that AHR and asthma can fully develop or be greatly enhanced through innate immune mechanisms involving IL-33, natural helper cells and NKT cells.

Even though IL-25 and IL-33 play closely overlapping roles in type 2 immunity, only polymorphisms in IL-33 pathway genes (IL1RL1 and IL33) are associated with asthma in genome-wide association studies [15,16]. Recent work addressed this

discrepancy by directly comparing IL-25 and IL-33 pathway-deficient mice. IL-33 signaling was found to play a more important in-vivo role in AHR than IL-25. Furthermore, methacholine-induced airway contraction *ex vivo* increased after treatment with IL-33 but not IL-25. This effect was dependent on expression of the IL-33 receptor and type 2 cytokines. Most importantly, IL-33 more potently induced expansion of IL-13-producing ILC2s, correlating with airway contraction. The study concluded that predominant IL-33 activity is enforced *in vivo* because IL-33 is expressed and released more rapidly than IL-25 [25].

Finally, an interesting mechanistic link between ILC2s, asthma pathogenesis and asthma treatment recently emerged from the demonstration that lung ILC2s are activated by leukotrienes through cysteinyl leukotriene receptor 1 (CysLT1R). CysLT1R was found to be expressed on lung ILC2s from wild-type, RAG2^{-/-} and STAT6^{-/-} naive and *Alternaria*-challenged mice. *In vitro*, LTD₄ induced ILC2s to generate high levels of IL-5 and IL-13 within 6 h of stimulation. Interestingly, LTD₄ but not IL-33 induced high levels of IL-4 by ILC2s. In-vivo LTD₄ administration rapidly induced ILC2-derived IL-5 production that was significantly reduced by the CysLT1R antagonist montelukast. Finally, LTD₄ potentiated

Alternaria-induced eosinophilia as well as ILC2 accumulation and proliferation [26[¶]].

HUMAN STUDIES

A curious dissociation exists between mouse and human studies of ILC2s in asthma. These cells have literally taken mouse immunology by storm, but as yet, there are very few studies explicitly investigating their role in the onset, progression or exacerbation of human asthma, or their adequacy as a therapeutic target. Only recently Saglani *et al.* [27] showed that IL-33 was associated with increased reticular basement membrane thickness in endobronchial biopsy specimens and promoted collagen synthesis from fibroblasts of children with severe therapy-resistant asthma. We suspect that this state of affairs is largely due to the technical problems inherent to characterizing the function of cells that reside in difficult-to-access tissues, are (if mouse data apply) extremely rare and still lack robust phenotypic markers (even though CRTH2 is a promising one [4]). But we also suspect that the lukewarm (if any) interest of asthma clinical researchers in ILC2s may reflect the still prevailing notion that Th2 cytokines are the product of Th2 cells and Th2 cells only [28]. And – the argument goes – because a number of treatments that target Th2 cells and their cytokines have been attempted but none has drastically altered the natural history of asthma, why not look elsewhere in our quest for determinants of asthma pathogenesis and targets for effective therapies? In response to this argument, we would like to suggest that whereas the success achieved by anti-Th2 cytokine treatments is indisputably modest, the reasons behind this limited success may have been misinterpreted.

Let us first look at the most recent data (Table 1) [29[¶],30–34]. A number of research groups have used biologicals targeting Th2 cytokines in selected groups of patients with asthma. The first studies targeted IL-5, which has been shown to induce eosinophilic airway inflammation, a characteristic feature of some, but not all, asthma phenotypes. In first studies of unselected patients with asthma, the blockade of IL-5 did not significantly improve outcomes. Subsequent studies addressed preselected patient populations with the eosinophilic phenotype. A recent meta-analysis [29[¶]] summarized the effect of intravenous infusion of mepolizumab, a monoclonal antibody against IL-5. In the pooled analyses of seven included studies, mepolizumab significantly reduced eosinophils in blood and sputum. The drug was also associated with significantly decreased exacerbation risk than placebo. Finally, a significant improvement in the scores

on the Asthma Quality of Life Questionnaire was found in patients with eosinophilic asthma. However, there were no statistical differences between the groups with respect to lung function and airway hyperresponsiveness [forced expiratory volume in 1 s (FEV1), peak flow or histamine provocative concentration causing a 20% fall in FEV1]. Another recent study [30] investigated the effect of reslizumab, an IgG4/k humanized monoclonal antibody composed of the complementarity-determining regions of a murine antibody to human IL-5 that has been grafted onto human frameworks. Reslizumab has been shown to neutralize circulating IL-5 by preventing it from binding to eosinophils. Patients receiving reslizumab showed significantly greater reductions in sputum eosinophils, but also improvements in airway function, and a trend toward greater asthma control than those receiving placebo.

With respect to IL-13, a first study [31] has used IMA-638 and IMA-026, which are fully humanized IgG1 antibodies that neutralize IL-13 bioactivity. The investigators did not find consistent improvements in lung function parameters. A subsequent study [32] targeted inadequately controlled asthma patients on glucocorticoids and a pretreatment profile consistent with IL-13 activity. Patient subgroups were prespecified according to baseline type 2 helper T-cell (Th2) status assessed as serum periostin level. Among patients in the high-periostin subgroup, the increase from baseline FEV1 was 8.2% points higher in the lebrikizumab group than in the placebo group, whereas no effect was seen in the low-periostin subgroup. In a population of mild asthmatic patients not receiving inhaled corticosteroids, lebrikizumab, however, did not improve lung function [33]. There was some evidence that this IL-13 blockade may improve disease control, since it was associated with less protocol-defined treatment failure in these patients.

IL-4 and IL-13 signal through two different but overlapping receptors, each containing the alpha subunit of the IL-4 receptor. Therefore, antibodies targeting IL-4 receptor α may inhibit downstream pathways engaged by both cytokines and improve asthma control. A recent study [34] evaluated the efficacy of dupilumab, a fully human monoclonal antibody to the alpha subunit of the IL-4 receptor, in 112 patients with persistent, moderate-to-severe asthma and elevated eosinophil levels who used inhaled glucocorticoids and long-acting beta-2 agonists (LABAs). Dupilumab therapy, as compared with placebo, was associated with fewer asthma exacerbations when LABAs and inhaled glucocorticoids were withdrawn, with improved lung function and reduced levels of Th2-associated inflammatory markers.

Table 1. Overview of human studies using anti-IL-5, anti-IL-13 and anti-IL4R α therapies

Author	Patient characteristics	Target	Treatment regimen	Main effect
Liu <i>et al.</i> [29 [¶]]	Meta-analysis of $n = 1131$ patients with mild atopic asthma (2 studies); mild or moderate asthma (2 studies); eosinophilic asthma (3 studies)	IL-5	Mepolizumab i.v. 750 mg from 1 day to 52 weeks	Decreased exacerbation risk (OR 0.30, 95% CI 0.13–0.67, $P = 0.004$), improvement in Asthma Quality of Life Questionnaire (AQLQ) (MD 0.26, 95% CI 0.03–0.49, $P = 0.03$)
Castro <i>et al.</i> [30]	106 patients with eosinophilic asthma poorly controlled with high-dose inhaled corticosteroid	IL-5	Reslizumab at 3.0 mg/kg at baseline and weeks 4, 8, and 12	Mean changes from baseline to end of therapy in ACQ score were -0.7 with reslizumab and -0.3 with placebo ($P = 0.054$); in FEV1 0.18 and -0.08 L, respectively ($P = 0.002$)
Gauvreau <i>et al.</i> [31]	56 patients with mild atopic stable asthma	IL-13	Either IMA-638 or IMA-026, 2 mg/kg on days 1 and 8	No significant effect on lung function parameters
Corren <i>et al.</i> [32]	219 patients with inadequately controlled asthma despite inhaled glucocorticoid therapy; stratified by Th2 status (high vs. low)	IL-13	Lebrikizumab 250 mg s.c. once a month for 6 months	FEV1 increase from baseline 8.2% points higher with lebrikizumab ($P = 0.03$) in the high-periostin group. No effect in the low-periostin group
Noonan <i>et al.</i> [33]	212 asthmatic patients not receiving inhaled corticosteroids	IL-13	Lebrikizumab 125, 250, or 500 mg s.c. monthly for 12 weeks	No significant differences in changes in FEV1 between the dose groups and between group with high and low periostin levels
Wenzel <i>et al.</i> [34]	104 patients with persistent, moderate-to-severe asthma and blood eosinophil count >300 cells/ μ L or sputum eosinophil $>3\%$ with medium-high-dose inhaled glucocorticoids and long-acting beta-agonists	IL4R α	Dupilumab, 300 mg, s.c. weekly for 12 weeks or until exacerbation occurred	87% reduction of exacerbations (OR = 0.08, 95% CI 0.02–0.28, $P < 0.001$). Change in FEV1, baseline to week 12: 0.27 (0.11 to 0.42) $P < 0.001$

ACQ, Asthma Control Questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 s; IL-13, interleukin 13; IL4R α , interleukin 4 receptor alpha; IL-5, interleukin 5; MD, mean difference; OR, odds ratio.

CONCLUSION

Overall, like their predecessors, the most recent trials with antibodies that target Th2 cytokines or their receptors have been only modestly successful. Thus one may be tempted to write off Th2 responses as major players in human asthma because they have failed the ultimate intervention test. But the discovery of ILC2s puts these results in a somewhat different perspective. Perhaps IL-13 and IL-5 (as well as IL-33, still untested but seemingly ideal) are indeed good targets, but we need to keep in mind that important sources of these cytokines in asthma are highly dispersed, long-lived [17^{¶¶}] innate cells that are constitutively active and hide deep inside mucosal tissues. And perhaps the problem with anti-Th2 cytokine antibodies is smaller in the identity of their targets than in their limited ability to reach

these targets deep in the tissues in which they are hiding.

Thus, there are lessons to be learnt from the unfolding ILC2 story. From now on, for the sake of clarity, it might be wise to punctiliously distinguish between Th2 cells and Th2 cytokines, because the ones are not synonymous with the others: Th2 cytokines can have both adaptive and innate cellular sources. Agents inspired by the notion that therapeutic targets lie deep in mucosal tissues may prove much more effective than the current ones and targeting IL-33 may be more promising. And finally, as Andrew McKenzie – one of the researchers who put ILC2s on the map – nicely put it: ‘So, ILCs – how did we miss them? Well, we had just gated them out, assuming that we already knew all the players. Who knows what other

unknowns wait to be discovered within the lineage-negative population?" [1].

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Conflicts of interest

The authors declare no conflicts of interest.

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