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Type 2 innate lymphoid cells: new players in asthma and allergy

Seth T Scanlon and Andrew NJ McKenzie

Two years ago, T helper cells, including Th1, Th2 and Th17 cells, were considered to be the most significant sources of cytokine during the orchestration of immune responses in the lung. Following the discovery of innate lymphoid cells, we now know that these previously unappreciated cytokine-secreting cells, including ILC1 (IFN- γ -expressing NK cells), ILC2 (IL-5 and IL-13-expressing nuocytes) and ROR γ ILC (IL-17 and IL-22-expressing 'ILC3') are important mediators in immune processes. Herein we review the role of ILC2 specifically in inflammatory lung responses with special attention to allergen-induced and viral-induced type 2 lung disease.

Address

MRC LMB Hills Rd, Cambridge CB2 0QH, UK

Corresponding author: McKenzie, Andrew NJ (anm@mrc-lmb.cam.ac.uk)

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Introduction

An essential component of effective host cell-mediated immunity is the co-ordinated crosstalk between its innate and antigen-specific adaptive arms. Nowhere is this more crucial than at mucosal surfaces, such as the lung, which serve as the barrier between the external and the sterile internal environments, where both pathogenic microorganisms and innocuous substances such as commensal bacteria and inhaled antigens are frequently encountered. Several different populations of innate-like lymphocytes, including natural killer (NK) cells [1], $\gamma\delta$ T cells [2] and CD1d-restricted NKT cells [3] have been previously implicated in the regulation of immune responses in the respiratory tract. This review will focus on the roles of the recently discovered population of type 2 innate lymphoid cells (ILC2), which reside at the nexus between innate and adaptive immunity in directing type 2 inflammatory responses and may additionally participate in lung remodelling and repair (Figure 1).

Definition

Innate lymphoid cells (ILCs) have a morphology typical of lymphocytes, but lack rearranged antigen receptors, and are currently grouped into three known subsets: NK cells, ROR γ t-dependent ILCs and ROR α -dependent ILCs (referred to herein as ILC2) [4[•],5]. The latter two populations lack cell surface markers associated with other major hematopoietic lineages and express CD25 (IL-2R α), CD90 (Thy1), CD117 (c-Kit) and CD127 (IL-7R α). Additionally, ILC2 express CD278 (ICOS), ST2 (IL-33R) and IL-17BR, and are IL-25-responsive (IL-17E) and IL-33-responsive. Importantly they also secrete large quantities of cytokines such as IL-5, IL-9 and IL-13 that are part of the type 2 immunological response underlying allergic asthma and helminth–host defence. Several groups have reported ILC2 populations including nuocytes [6,7^{••}], natural helper cells (NHCs) [8^{••}] and innate helper 2 cells (Ih2s) [9]. Using IL-5-reporter [10] and IL-9-reporter [11] mice, respectively, cells with a similar cell surface and functional phenotype have also been described.

Whether these cells are identical, different subsets or the same cell at different stages of development remains an open question. ILC2 arise from a common lymphoid progenitor [12[•],13] in the bone marrow and have been shown to require IL-7 and IL-33 for their development. The transcription factors Id2 and ROR α are essential for their development and function, and Notch signals may also be necessary [12[•],13]. The cells proliferate in response to IL-25 and IL-33 administration and in response to pathogens such as helminths, viruses and fungi [7^{••},9] and play a central role in type 2-mediated immunity through the cytokines they secrete.

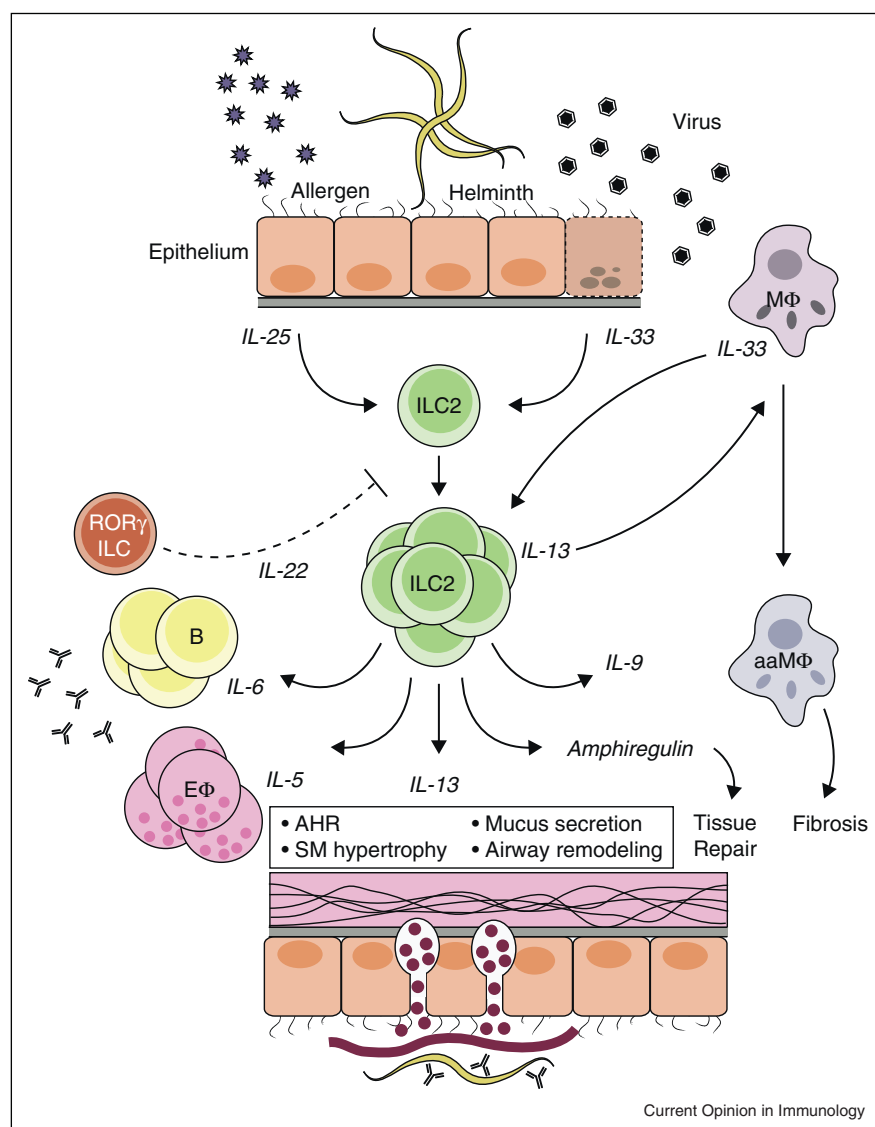
ILC2 in allergic airway disease

Multiple groups have observed ILC2 in the lungs and mediastinal lymph nodes of mice [4^{••},12[•],14^{••},15–19], and lineage[–]CD127⁺ ILCs in the guts, lung parenchyma and airways of foetal and adult humans [12[•],20^{••}].

The functions of ILC2 in the lung are a subject of ongoing study, but given their potential to direct type 2 responses, it is reasonable to believe that they may play a direct role in type 2 immune pathologies. Increased serum and tissue expression of IL-33 and ST2 has been noted in rhinitis patients [21–23], and epithelial and airway smooth muscle cells appear to represent two major sources of IL-33 in asthmatics [24]. Allergen challenge in asthmatics was also associated with increases in IL-25 and IL-25R expression [25,26] with basophils and eosinophils as possible sources [25]. In human patients with chronic

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Figure 1



ILC2 are central mediators of type 2 immune responses in the lung. After interaction with certain noxious agents, including helminths, allergens, viruses, and proteases, pulmonary epithelium and other cells such as alveolar macrophages, can produce IL-33 and IL-25 which drive the expansion of ILC2. Once activated, these cells can produce important type 2 cytokines including IL-6 (B cell growth factor), IL-5 (eosinophil proliferation), IL-9 (mast cell growth factor), and IL-13 (AHR, mucus production, smooth muscle contractility, alternative activation of macrophages and airway remodelling). ILC2 may also have an important role in wound healing and remodelling, through amphiregulin.

rhinosinusitis, a disease dominated by eosinophils, increased proportions of ILC2 were observed in nasal polyps compared to the uninfamed nasal tissue of non-allergic controls [20^{••}].

Several studies have found evidence that ILC2 participate in mouse models of type 2 allergic airway inflammation. Intranasally administered recombinant IL-25 or IL-33 induced the expansion of an ILC2 population recovered from the lungs, bronchoalveolar lavage (BAL) and mediastinal lymph nodes [4^{••}]. Intranasal IL-33 was able to drive airway eosinophilia and the

production of lung IL-5 and IL-13 in both wildtype and Rag1^{-/-} mice [16]. Transfers of wildtype ILC2 into IL-13-deficient mice showed that they were sufficient to restore IL-25-induced or IL-33-induced airway hyper-reactivity (AHR) [4^{••}].

Additionally, ILC2 infiltrate the lungs in the challenge phase of an ovalbumin-alum model and were found to be a substantial population within lung IL-13⁺ cells [4^{••}]. Inhalation of the clinically relevant fungal allergen *Alternaria alternata* was able to induce IL-33, the expansion of ILC2, the subsequent production of IL-5 and IL-13 and

eosinophilia, a chain of events not observed in ST2^{-/-} mice [16]. In another study, inhalation of the Vα14-iNKT cell-activating glycolipid antigen α-galactosylceramide resulted in increased production of IL-33 in the lung, possibly through increased production by alveolar macrophages [14^{••}]. Using transfers of wildtype Vα14-iNKT cells and ILC2, respectively, into IL-13^{-/-} mice, it was found that either cell population was sufficient to restore glycolipid-induced AHR. Finally, in papain-induced and house dust mite models of allergic airway disease, ILC2 were also found to be necessary for eosinophilia and mucus secretion via their production of IL-5 and IL-13 [18]. Wilhelm *et al.* took this work further, and found in the papain-induced model the presence of IL-9-producing ILC2 [13]. Indeed, IL-2 and IL-33 (but not IL-25) were required to induce IL-9 by ILC2 in this model, while blockade of IL-9 using neutralizing antibodies resulted in reduced expression of IL-5 and IL-13, suggesting that ILC2 may be the link between IL-9 and its established role in mediating type 2 immune responses.

Two recent studies have examined the role of IL-22, a molecule ostensibly antagonistic to IL-25 and IL-33, in models of Th2 airway inflammation. IL-22, an IL-9-inducible cytokine structurally homologous to IL-10 [27] is produced in normal human lung tissue and is found to be downregulated in individuals with sarcoidosis and acute respiratory distress syndrome (ARDS) [28]. Taube *et al.* used an ovalbumin-alum model of allergic airway inflammation, and found a population of CD25⁺CD44⁺IL-17^{+/+} ILC that secreted IL-22. In *Rorc*-Cre mice crossed with *Rosa26*-stop-eYFP mice, the vast majority of these cells fate-mapped to RORγt [29[•]]. Knocking out IL-22 in this model was correlated with an increase in lung IL-33 that correlated with a more severe form of allergic inflammation and AHR. Conversely, administration of recombinant IL-22 inhibited AHR, cellular infiltration, Th2 cytokine production and IL-13-responsive chemokine production [29[•]].

Using a similar ovalbumin-alum model, Takahashi *et al.* found that anti-IL-22 therapy produced similar effects as the IL-22 knockout: an exaggeration of AHR and inflammation. Notably, recombinant IL-22 administered intranasally led to decreased IL-25 expression and the amelioration of eosinophil recruitment and AHR, effects that were reversed if anti-IL-25 antibodies were also administered [30]. However, this report did not specifically demonstrate that ILC were the main source of the IL-22.

Together, these data suggest the possibility that other subsets of ILCs, including IL-22-producing RORγt-dependent ILCs, may be able to regulate ILC2 behaviour and function *in vivo*, a situation reminiscent of the counter-regulation of Th1 and Th2 cells.

ILC2 during influenza infection

Viral respiratory tract infections are a major trigger for asthma exacerbations, although the underlying mechanisms remain poorly understood. Such responses can be modelled in mice, with rhinovirus infection enhancing type 2 responses to allergens and increasing lung inflammation and AHR [31]. Notably, two recent studies have highlighted important roles for ILC2 in experimental mouse models of influenza virus infection [12[•],14^{••}]. These reports focused on a lung-resident ILC2 population, which increased in frequency during infection and expressed IL-13. Chang *et al.* reported a role for ILC2 in influenza subtype H3N1 virus-induced acute AHR [14^{••}]. This occurred in the absence of adaptive immunity and required the IL-33-ST2 signalling pathway. IL-33 was induced upon viral infection during the first 24 hours of the response and it was suggested that alveolar macrophages might represent a major cellular source of this cytokine. Virally induced AHR was dependent on IL-13 and adoptive transfer experiments demonstrated that only IL-13-secreting ILC2 were capable of restoring AHR to IL-13^{-/-} hosts. This reliance upon IL-13 is similar to the situation observed in models of allergic asthma [32].

Interestingly, Monticelli *et al.* reported that ILC2 were important for restoration of lung-tissue homeostasis after influenza H1N1 infection. By depleting CD90.2 expressing cells in Rag1^{-/-} mice, which include the ILC2 population, it was suggested that ILC2 play a key role in the maintenance of epithelial integrity and lung function following viral infection [12[•]]. Crucially, adoptive transfer of allotypic CD90.1⁺ ILC2 restored lung repair. This was independent of IL-13 and IL-22, and gene expression profiling identified amphiregulin, a member of the epidermal growth factor family, as a potential key player. Administration of amphiregulin was sufficient to restore epithelial cell integrity in influenza-infected mice, highlighting a mechanism by which ILC2 might promote tissue repair.

Pulmonary ILC2 in helminth infections

Several species of helminth migrate to the lungs as part of their normal life cycle where they penetrate the alveoli and are responsible for extensive tissue destruction. Type 2 cytokines are a crucial lynchpin in the fast and effective as evidenced in mice with impaired type 2 immunity [33]. Two recent reports have shown that accumulation of *Nippostrongylus brasiliensis* or *Strongyloides venezuelensis* in the lungs of mice results in cytokine-producing ILC2 [17,34]. In the latter case, this expansion correlated with the production of IL-33 and was IL-33-dependent [16]. The fact that chitin was able to induce similar patterns of IL-33 production suggests that the interaction of helminth antigens with innate receptors on the epithelial cell surface is required for IL-33 release [34].

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The modulation of ILC2 as therapy

Given that ILC2 are major producers of IL-5 and IL-13 in several models of airway allergic inflammation and infection, and that IL-13 is a major factor underlying the type-2-induced AHR, goblet cell metaplasia, mucus hypersecretion and inflammatory chemokines that characterize human asthma [32], it is tempting to speculate whether modulation of ILC2 development and function may be of use in the clinic.

Several groups have targeted IL-25 and IL-33 and their receptors, which are the primary pathways responsible for the expansion of ILC2 in the lung. Blockade of IL-33 with a neutralizing antibody in an ovalbumin-alum model resulted in significantly reduced inflammatory cell infiltrates, BAL IL-4, IL-5 and IL-13, and serum anti-ovalbumin IgE [35]. Both anti-IL-33 and anti-ST2 neutralizing antibody therapies were also effective in an *Aspergillus fumigatus* model of airway inflammation. Anti-ST2 treatment resulted in an abrogation of mucus secretion, lung Th2 cytokine mRNA expression, cellular inflammation and methacholine-induced AHR compared to controls [36].

In a similar fashion, targeting IL-25 expression in a mouse ovalbumin-alum model with a monoclonal antibody during sensitization and challenge prevented the development of allergic inflammation, an IgE-immune response and AHR. Interestingly, neutralization of IL-25 at the time of challenge but not sensitization had no effect on lung cellularity or immunoglobulin production, but, nevertheless, resulted in a significant reduction of AHR. Notably, antigen-restimulated mediastinal lymph node cells retained their ability to produce large quantities of IL-5 and IL-13 if IL-25 was neutralized during challenge but not when therapy was extended to include both sensitization and challenge [37].

IL-25-neutralizing therapy has also been employed in pneumonia virus of mice (PVM) model of respiratory syncytial virus (RSV)-associated asthma. Treatment with anti-IL-25 during the challenge phase resulted in significantly reduced lung Th2 cytokine mRNA expression and reduced airway remodelling [38].

Thus, targeting the cytokines that lie upstream of ILC2 activation appears beneficial, at least in mouse asthma models. The recent identification of ROR α as a key transcription factor involved in ILC2 development raises the possibility of manufacturing therapeutic ROR α inhibitors that would specifically block the production of ILC2 in lung type 2 inflammatory disease.

Future directions

ILC2, a cell population that serves as a crucial link between innate immunity and the type 2 adaptive immune response, appears to play important roles in the lung including responses to parasitic helminths, tissue

repair and the pathogenesis of allergic asthma. In order to effectively design therapeutic agents, further studies are needed in several areas to better understand ILC2 function.

Trafficking: What are the signals that are responsible for the transit of ILC2 into the lung? It has been previously reported that expanded ILC2 express high levels of CCR9, CXCR4 and CXCR6 [7^{••}]. It is currently unknown which chemokine receptors are expressed in lung-homing ILC2. Interestingly, Barlow *et al.* demonstrated that ILC2 do not expand into the lungs of IL-13^{-/-} mice that received IL-25 intranasally but do expand into the mesentery after IL-25 administration intraperitoneally, suggesting that IL-13 or IL-13-downstream chemokines are required for ILC2 trafficking into the lung but not into the peritoneum [4^{••}].

Function: While initial studies clearly show that ILC2 can play a role in the pathogenesis of asthma along the IL-25/33-ILC-IL-5/13 axis, several gaps remain in our understanding. As more information on the signals required for ILC2 development and differentiation become available, conditional knockout and/or depletion strategies would allow testing of their role in the sensitization and challenge phases, respectively. Questions remain about the function of ILC2 in the draining lymph nodes — are these cells an identical population to lung ILC2? What part do they play in the differentiation of Th2 cells? Additionally, *in vivo* microscopic techniques [39,40] would help reveal their spatial and temporal distribution and potential interaction partners.

Human relevance: Studies looking at segmental allergen challenged asthmatics would be useful in determining how relevant ILC2 are in the pathogenesis of disease. Additionally, the role of ILC2 in other diseases of the lung, including chronic obstructive pulmonary disorder (COPD), pulmonary fibrosis, acute lung injury and bronchitis should be investigated in experimental animal models and human patients.

Conclusion

After so long in obscurity, the discovery of ILCs has changed our perception of T cells as the major cytokine-secreting regulators of immunity and made us aware of completely unappreciated innate immune cell sources of regulatory cytokines. The goal is now to define their place in immunity and disease.

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