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Innate lymphoid cells: critical regulators of allergic inflammation and tissue repair in the lung

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Abstract

Maintenance of epithelial barrier function in the skin, respiratory tract and intestine is critical to limit exposure to commensal and pathogenic microbes and to maintain tissue homeostasis. Innate lymphoid cells (ILCs) are a recently recognized innate immune cell population that plays critical roles in host defense, regulation of inflammation and promotion of wound healing and tissue repair at barrier surfaces. In this review we discuss recent advances in the understanding of how ILC populations in the respiratory tract impact allergic airway inflammation and lung epithelial repair.

Introduction

Recent studies have identified a previously unrecognized population of immune cells called innate lymphoid cells (ILCs) that serve as crucial regulators of immunity and inflammation at barrier surfaces [1–3]. ILCs are a heterogeneous cell population found in multiple tissue sites that share morphological, developmental, and functional similarities with CD4⁺ T helper cells, but lack antigen receptors. Although the cell lineage relationships between phenotypically distinct ILC populations are not yet fully understood, ILCs are thought to arise from a common bone marrow-derived lymphoid precursor that is dependent on the transcription factor inhibitor of DNA-binding 2 (Id2) [1]. Distinct phenotypic and transcriptional profiles and patterns of effector cytokine expression allow ILCs to be broadly divided into three classes: classical NK cells, ROR γ t-dependent ILCs and ROR γ t-independent ILCs [1–3]. Phenotypically, the latter two ILC populations can be broadly defined by the absence of expression of cell lineage makers associated with dendritic cells (DC), macrophages, granulocytes and lymphocytes but positively identified by expression of c-Kit, CD90 (Thy1), CD25 (IL-2R α) and CD127 (IL-7R α) [1–3]. The development, regulation and function of classical NK cells and ROR γ t-dependent ILCs at various tissue sites have been thoroughly reviewed elsewhere [1,3–6]. Therefore, this review will focus on recently identified roles for ROR γ t-independent ILC subsets in regulating immunity, inflammation and tissue homeostasis in the respiratory tract.

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Production of the Th2 cytokines IL-5 and IL-13 is a hallmark of both pathogenic allergic inflammation and protective anti-helminth parasite immune responses at mucosal sites [3,7–9]. Studies published in three independent laboratories identified populations of non-NK cell, ROR γ t-independent ILCs (termed Natural Helper cells (NHC), Nuocytes or Innate Helper Type 2 cells (Ih2)) that express a cytokine profile similar to CD4⁺ Th2 cells and could promote immunity against intestinal helminth parasites [10–12]. Development of these “Type 2” ILCs (also termed ILC2 [1]) requires the transcription factors Id2 and ROR α but is independent of ROR γ t [10,13], thereby distinguishing Type 2 ILCs from the ROR γ t⁺ ILC subset that expresses IL-22 and IL-17A. Type 2 ILCs express the receptors for the epithelial cell-derived cytokines IL-25 (IL-17Rb) and IL-33 (T1/ST2) and produce IL-5 and IL-13 upon IL-25 and/or IL-33 stimulation [6,11,13]. In parallel with these studies, a fourth report identified a population of IL-25-elicited, multi-potent progenitor type 2 cells (MMP^{type2} cells) which also promotes anti-helminth immunity, but are functionally distinct from other Type 2 ILCs due to their cell surface marker expression and ability to differentiate into cells of the myeloid lineage [14]. This review will discuss recent reports identifying lung-resident human and murine Type 2 ILCs and defining emerging roles for these ILCs in regulating inflammation and tissue repair in the lung.

Identification of ILCs in the respiratory tract of mice and humans

Recent studies from a number of laboratories identified a population of ILCs in murine lung parenchyma [15–22] analogous to the Type 2 ILC population previously reported in the gut-associated lymphoid tissue (GALT), fat-associated lymphoid clusters (FALC) and spleen [10–12]. Examination of the lung parenchyma of wildtype or *Rag1*^{−/−} mice in the steady-state revealed a constitutive population of Id2-dependent lineage-negative (Lin[−]) cells that expressed CD90, c-Kit, CD127 (IL-7R α), CD25 (IL-2R α), CD44, ICOS and T1/ST2 (IL-33R) but lacked expression of NK cell markers and ROR γ t, a phenotype consistent with Type 2 ILCs ([16]; Fig 1). Stimulation of lung ILCs with IL-33 in combination with IL-2 and IL-7 resulted in production of IL-5 and IL-13, but these cells did not produce IL-22, IL-17A or IFN γ [15,16], demonstrating that the ILC population in the lung resembles Type 2 ILCs that express Th2-associated cytokines and is distinct from ROR γ t-dependent populations that express the Th17-associated cytokines IL-17A and IL-22.

While previous studies have identified ROR γ t⁺ ILCs in human adult tonsil or intestinal tissue that produce IL-22 or IL-17A [23–27], until recently there were no reports of whether Type 2 ILC populations could also be detected in human tissue. In 2011, two independent studies identified a population of ILCs in human lung and intestine that is phenotypically and functionally analogous to Type 2 ILCs described in mice [16,28]. Examination of healthy human lung tissue or bronchoalveolar lavage fluid from lung transplant patients revealed a constitutive population of Lin[−] cells expressing CD25, CD127 and ST2, a cell surface phenotype shared by Type 2 ILCs in the murine lung parenchyma [16]. In a comprehensive characterization of human ILC populations at multiple tissue sites, Mjosberg *et al.* detected an ILC population in both adult and fetal lung and intestinal tissue that were identified by their expression of CD161 and CRTH2, a chemoattractant receptor previously reported to be expressed on CD4⁺ Th2 cells [28]. Human CRTH2⁺ ILCs were responsive to IL-25 or IL-33 in combination with IL-2, which allowed for the generation of long-term cultures and stable cell lines that were terminally differentiated [28]. Analogous to Type 2 ILC populations in mice, CRTH2⁺ ILCs isolated from fetal intestine produced IL-13, but not IL-22 or IL-17A [28]. Notably, Spits and colleagues were able to detect CRTH2⁺ ILCs in human blood, suggesting that these cells have the capacity to circulate throughout the body to traffic to different tissue sites. Interestingly, CRTH2⁺ ILCs in human blood displayed some level of plasticity not observed in tissue-resident ILC populations. CRTH2⁺ ILCs in the blood could produce IL-22 in addition to IL-13 [28], providing some evidence that the

blood may harbor a progenitor ILC population capable of differentiating into either an IL-22-producing ROR γ t-dependent ILC or an IL-13-producing Type 2 ILC depending upon the cytokine milieu in the tissue microenvironment.

Influence of Type 2 ILCs on regulation of allergic airway inflammation

The identification of Type 2 ILCs in respiratory tissue raises questions about their potential involvement in regulation of pulmonary immunity, inflammation or tissue homeostasis. Several recent studies have emerged demonstrating critical roles for lung ILCs in the development of allergic airway inflammation or promotion of airway epithelial repair. For example, Umetsu and colleagues observed that ILCs in the respiratory tract played a pathologic role in promoting airway hyper-reactivity (AHR) following viral infection. In these studies, infection with influenza A virus subtype H3N1 induced acute allergic airway inflammation characterized by a rapid AHR response that developed independently of adaptive immunity [15]. Following virus infection, macrophage-derived IL-33 induced expansion of Lin⁻ CD90⁺ ST2⁺ Sca-1⁺ ILCs that expressed high amounts of IL-5 and IL-13. Moreover, disruption of the IL-33/IL-33R signaling pathway or anti-CD90 monoclonal antibody-mediated depletion of ILCs resulted in protection from influenza virus-induced AHR [15], suggesting an essential role for ILCs in promoting airway inflammation (Fig 1). IL-13 has been shown to promote epithelial cell proliferation in multiple settings of airway injury or inflammation [8,29–31]. Strikingly, adoptive transfer of wildtype, but not IL-13-deficient ILCs, was sufficient to drive AHR responses in IL-13-deficient hosts [15], indicating that ILC-derived IL-13 is critical for induction of allergic airway inflammation following viral infection.

In addition to regulating virus-induced airway hyper-reactivity, further studies have defined roles for Type 2 lung ILCs in promoting allergic inflammation in response to a wide variety of antigenic stimuli. Using dual-reporter mice tracking expression of *Il4* and *Il13* transcripts, studies by McKenzie and colleagues demonstrated that IL-13-expressing ILCs accumulate in the lung following intranasal challenge with OVA antigen, IL-25 recombinant protein or IL-33 recombinant protein [18]. Furthermore, adoptive transfer of IL-13-sufficient ILCs, but not IL-13-deficient ILCs, promoted airway hyper-reactivity in response to IL-25 intranasal challenge, demonstrating that ILC-derived IL-13 is a crucial regulator of allergic airway inflammation in this setting. Supporting this, an additional study using intranasal challenge with NKT glycolipid antigen showed a similar dependence on ILC-derived IL-13 to promote airway hyper-reactivity [17]. A third study examining papain allergen-induced inflammation implicated Type 2 ILCs as essential mediators of eosinophilic infiltration and mucus production in the airways [22], providing further evidence that ILC-derived Type 2 cytokines are central to the promotion of allergic airway inflammation in multiple models of airway inflammation.

In addition to IL-5 and IL-13 production, one study by Wilhelm *et al.* also demonstrated that ILCs in the lung are capable of expressing IL-9, a cytokine linked to allergic airway inflammation [32]. ILC production of IL-9 in response to papain-induced airway inflammation was dependent upon IL-2 from adaptive immune cells, indicating an important link between adaptive immunity and regulation of ILC function. Critically, while IL-9 expression by ILCs was transient and decreased quickly after papain challenge, antibody-mediated neutralization of IL-9 resulted in reduced IL-5 and IL-13 expression in ILCs, suggesting that IL-9 acts to promote production of Type 2 cytokines involved in driving allergic inflammation [32] (Fig 1). Future studies are needed to determine the differential effects of IL-5, IL-13 and IL-9 in ILC-dependent regulation of allergic airway inflammation.

In addition to promoting allergen-induced Type 2 cytokine responses, recent studies identified that lung ILCs can produce IL-5 and IL-13 in the context of helminth infection. As part of the natural life cycle for many helminth parasites, the worms migrate through the lung where they cause substantial tissue damage before being coughed up and swallowed to complete maturation within the gut [9,33]. The cellular and molecular mechanisms that regulate worm exit from the lung and subsequent repair of the damaged respiratory tissue are not fully understood [9,33]. Two recent studies by Liang *et al.* and Yasuda *et al.* showed that IL-13-producing Type 2 ILCs accumulated in the lung in response to *Nippostrongylus brasiliensis* or *Strongyloides venezuelensis* helminth infection [19,34], presumably due to elevated IL-33 levels. The investigators hypothesize that production of IL-5 by Type 2 ILCs and subsequent recruitment of eosinophils to the airways may contribute to expulsion of the parasites [19] (Fig 1), although direct evidence supporting this remains to be determined. Additionally, the potential role of ILC-derived IL-13 in the lung during helminth infection is unknown. IL-13 is a potent inducer of epithelial hyperplasia characteristic of both injury repair responses and chronic pulmonary fibrosis [8,30,31]. Whether Type 2 ILCs are involved in regulating lung tissue repair in the early acute injury phase during larval migration or may contribute to the later development of chronic fibrosis remains to be determined.

Elevated levels of IL-5 and IL-13 are also associated with allergic airway disorders in human patients [8,29,35,36], but the potential contribution of ILCs to the development and/or progression of allergic inflammation in humans is unclear. In their recent study, Mjosberg and colleagues found elevated numbers of CRTH2⁺ ILCs in the nasal polyps of patients with chronic rhinosinusitis, an allergic Type 2 inflammatory disease characterized by high levels of circulating IgE and eosinophilia [28]. Based on these observations, it is possible that high amounts of IL-5 produced by CRTH2⁺ ILCs within the nasal polyps can contribute to the robust eosinophilia observed in this disease. Consistent with this hypothesis, patients with rhinosinusitis polyps have higher levels of IL-5 and IL-13 transcripts than patients without polyps [28], suggesting that CRTH2⁺ ILCs may be an important target in the development of new therapeutic strategies to ameliorate allergic airway inflammation.

Role of Type 2 ILCs in mediating airway epithelial repair

In addition to playing a pathogenic role in the context of allergic airway inflammation, a recent report demonstrated that ILCs could promote beneficial tissue repair responses in the lung following acute epithelial damage. In this study, genome-wide transcriptional profiling of lung-resident ILCs from naïve mice revealed a transcriptional signature that is strongly enriched in genes that regulate wound healing pathways, including the gene encoding the epidermal growth factor (EGF) family member amphiregulin [16]. Amphiregulin has been linked to tissue remodeling and repair in diverse settings of acute epithelial injury and asthma [30,31,37,38], although the hematopoietic sources of amphiregulin are poorly defined. Remarkably, lung ILCs produced amphiregulin in response to IL-33 stimulation and amphiregulin expression was elevated in the lung following exposure to H1N1 subtype of influenza A virus, which causes substantial damage to the respiratory epithelium [39]. However, unlike infection with influenza A virus subtype H3N1 discussed above, H1N1 is not known to cause an AHR response. Further, CD90⁺ CD25⁺ ST2⁺ ILCs accumulated in the lung parenchyma following H1N1 infection and depletion of ILCs in influenza virus-infected *Rag1*^{-/-} hosts using anti-CD90 monoclonal antibody treatment resulted in severely decreased lung function, compromised lung epithelial barrier integrity and increased host mortality, suggesting that lung ILCs are crucial regulators of lung epithelial repair and tissue remodeling [16]. Strikingly, treatment with recombinant amphiregulin, but not IL-13, effectively restored lung function and epithelial repair in ILC-depleted influenza virus-infected mice, suggesting that ILC-derived amphiregulin is one mechanism by which ILCs

can promote airway epithelial repair and lung tissue homeostasis following acute lung damage (Fig 1). Amphiregulin is widely expressed throughout multiple organs [40], raising the possibility that ILC-derived amphiregulin may influence tissue homeostasis at extra-pulmonary sites. The question of whether amphiregulin is uniquely expressed by lung-resident ILCs or alternatively represents a more generalized tissue-protective effector mechanism shared by Type 2 ILCs at other tissue sites remains to be determined.

The identification of distinct roles for lung ILCs in the promotion of airway inflammation or lung epithelial repair reveals a previously unrecognized degree of functional heterogeneity within the ILC population. Although the precise mechanisms underlying the dichotomy in ILC function observed under different inflammatory conditions is not yet understood, based on current data one could speculate that the ability of Type 2 ILCs to serve either tissue-protective or pathologic functions may depend upon the extent of tissue injury, the nature of the inflammatory or infectious stimulus and/or the local cytokine milieu. In addition, the same factors that are crucial for the effective restoration of tissue homeostasis after injury, including epithelial hyperplasia, mucus secretion and collagen deposition, can be deleterious to the host if induced in the absence of tissue damage [8,30,31]. Therefore, it is conceivable that while induction of ILC-derived IL-5/IL-13 and/or amphiregulin during lung injury can have a beneficial effect by promoting tissue repair, the initiation and subsequent dysregulation of these responses in uninjured tissue can be detrimental by contributing to pathogenesis of airway inflammation. Supporting this scenario, the inflammatory stimuli that results in ILC-dependent airway inflammation (papain allergen [22,32], H3N1 influenza virus [15], IL-25 or IL-33 protein [18], OVA antigen [18] and glycolipids [17]) are not known to cause substantial injury to the respiratory tissue as is observed during H1N1 influenza virus infection in which respiratory ILCs have beneficial effects in promoting repair of virus-damaged epithelium [16]. Future studies are needed to determine whether Type 2 ILCs can also serve tissue-protective functions in other models of lung tissue damage, such as LPS or Bleomycin-induced lung injury. A similar paradigm likely also applies to the intestinal mucosa, whereby strong Type 2 ILC responses are essential for helminth clearance [9,33] but high levels of ILC-derived cytokines could also cause intestinal pathology if induced in the absence of infection-induced tissue damage. Collectively, these studies suggest that Type 2 ILC populations can have either a protective or a pathogenic effect depending in part upon the state of the tissue microenvironment and the nature of the inflammatory signal (Fig 1).

Concluding remarks

The identification of previously unrecognized populations of Type 2 ILCs in human and murine lungs has advanced our understanding of the cellular and molecular mediators of allergic airway inflammation and airway epithelial repair and may provide potential new drug targets for improved immune-therapies. However, given the ability of Type 2 ILC responses to cause either beneficial or deleterious effects in different disease settings, caution must be applied when considering the development of therapeutics that target Type 2 ILCs in human disease. Future studies are needed to further define the signals that regulate the pathogenic versus protective functions of lung ILC populations in the context of distinct infectious or inflammatory conditions in order to design effective targeted therapeutic strategies that can ameliorate allergic inflammation or improve tissue repair following injury.

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Highlights

- Innate lymphoid cells (ILCs) have recently been identified in human and mouse lung.
- Lung ILCs produce IL-5, IL-13, IL-9 and amphiregulin in response to IL-33 stimulation.
- ILC-derived IL-13 can promote allergic airway inflammation.
- Production of amphiregulin by lung ILCs mediates epithelial repair after lung damage.
- Targeting lung ILCs may provide improved immuno-therapies in human diseases.

Figure 1. Regulation, phenotype and function of lung-resident Type 2 ILCs

In the lung, numerous infectious and allergic stimuli can promote epithelial cell and macrophage expression of IL-33. IL-33, IL-2 and IL-7 have been shown to act on Type 2 ILCs (defined as Lin⁻ cells that express ST2, CD127, CD25 and c-Kit) to induce expression of autocrine IL-9 and paracrine IL-5, IL-13 and amphiregulin (Areg) that, depending on the context, can induce either pathologic allergic airway inflammation or protective airway tissue repair.