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# Role of Innate Lymphoid Cells in Lung Disease

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## ABSTRACT

Innate lymphoid cells (ILCs) are identified as novel population of hematopoietic cells which protect the body by coordinating the innate immune response against a wide range of threats including infections, tissue damages and homeostatic disturbances. ILCs, particularly ILC2 cells, are found throughout the body including the brain. ILCs are morphologically similar to lymphocytes, express and release high levels of T-helper (Th)1, Th2 and Th17 cytokines but do not express classical cell-surface markers that are associated with other immune cell lineages.

Three types of ILCs (ILC1, 2 & 3) have been reported depending upon the cytokines produced. ILC1 cells encompass natural killer (NK) cells and interferon (IFN)-γ releasing cells; ILC2 cells release the Th2 cytokines, IL-5, IL-9 and IL-13 in response to IL-25 and IL-33; and ILC3 cells which release IL-17 and IL-22. ILC2 cells have been implicated in mucosal reactions occurring in animal models of allergic asthma and virus-induced lung disorders resulting in the regulation of airway remodeling and tissue homeostasis.

There is evidence for increased ILC2 cell numbers in allergic responses in man but little is known about the role of ILCs in chronic obstructive pulmonary disease (COPD). Further understanding of the characteristics of ILCs such as their origin, location and phenotypes and function would help to clarify the role of these cells in the pathogenesis of various lung diseases.

In this review we will focus on the role of ILC2 cells and consider their origin, function, location and possible role in the pathogenesis of the chronic inflammatory disorders such as asthma and COPD.

**Keywords:** Cytokines; IL-17; IL-22; ILCs; Respiratory tract

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## INTRODUCION

Innate lymphoid cells (ILCs) are a newly identified population of immune cells which have been found in a variety of organs such as the gut, the lung and mucosal membranes.[1-4] ILCs share many phenotypic, morphological, developmental and functional features with CD4+ T helper cells[1,3-6] but do not express the characteristic adaptive immunity receptors/lymphoid lineage (Lin-) markers expressed on T-helper (Th) cells. ILCs are able to react to a wide array of stimuli [5,7-9] and play critical roles in lymphoid tissue formation and repair and in immune reactions against helminthic infections in several disease models.

Although ILCs do not express Lin markers, they commonly express IL-2Rα (CD25), the IL-7 receptor α chain (IL-7Rα, CD127) and the common γ chain (CD132) (Table 1).[10] However, NK cells do not express CD127. ILCs are divided into 3 different classes depending upon their ability to synthesize and release Th1, Th2 and Th17 cytokines. Thus, type1 ILC (ILC1) cells produce interferon (IFN)-γ, type 2 ILC (ILC2) cells produce IL-5, IL-9 and IL-13 and type 3 ILC (ILC3) cells produce IL-17A and IL-22.[10] Conventional and IFN-γ-producing non-natural killer (NK) cells are the predominant examples of ILC1 and produce IFNγ under the control of the transcription factor T-bet as an innate counterpart to Th1 CD4+ cells.[10] ILC3 cells, which include ILC17 and lymphoid tissue inducer cells (LTi cells) have been known for two decades [5,11,12] and have the ability to promote the formation of secondary lymphoid nodes in addition to Peyer's patches during embryonic development.[5,10,11,13-16]

The expression of IL-17A by ILC3 cells and their subsequent function is dependent upon Th17-associated transcription factors such as RORγt and the aryl hydrocarbon receptor (AhR).[5,10,17-24] RORγt positive ILCs represent three subsets of cells namely LTi, ILC22 (IL-22 producing ILCs) and ILC17 (IL-17 producing cells) (Table2). LTi cells are believed to be related to CD4+ cells [5,25,26] and produce cytokines such as TNF-α[5,27] and IL-17A.[5,28] ILC3 cells which produce equal amounts of IL-17A and IL-22 are often considered a fourth ILC3 subset. There is debate as to whether these subsets represent distinct cell types or whether they are the result of local environmental stimuli on a single plastic cell type. In addition, a progenitor ILC population exists in blood which is capable of differentiating into RORγt- or RORα-dependent ILCs which are able to release IL-22 (ILC22) or IL-13 (ILC2), respectively depending upon the local microenvironment.[1,28]

ILC2 cells include nuocytes; natural helper cells (NH) and innate helper type 2 cells (Ih2) [10,29-35] which compose the third group of ILCs. These cells express CD127 (Lin-CD127+), T1-ST2, IL-17RB (a receptor for IL-25) and are dependent upon RORα and GATA3 for their development (RORγt-independent ILCs) [10,28,32,36-39]. These ILCs are derived from the common lymphoid progenitor cells in the bone marrow and require IL-25 and IL-33 for their development.[33,36,40]

### Development of ILCs

RORγt-dependent ILCs are found in fetal liver in mice[5,41] and after adoptive transfer are able to develop into several ILC lineages[5] although this has not been formally confirmed for ILC3 cells. These ILC3 cells from fetal liver in mice are phenotypically similar to the common lymphoid precursor (CLP) cells found in adult bone marrow.[5]

**Table1. The ILC family**

| Cell type | Function | Signature cytokine produced | Major stimulating cytokines |
|---|---|---|---|
| ILC1 cells (cytotoxic ILCs include NK and IFNγ-producing non-NK cells) | Innate immunity against viral infections, tumor immunosurveillance | IFN-γ | IL-18, IL-12, IL-15 |
| ILC2 cells | Innate immunity against extracellular parasites | IL-5, IL-13 | IL-25, IL-33 |
| ILC3 cells (RORγt+ cells) | Lymphoid tissue formation and repair, innate immunity against bacteria | IL-17, IL-22 | IL-1β, IL-23 |

ILC: innate lymphoid cell, IFN: interferon, IL: interleukin, NK: natural killer, ROR: retinoic acid orphan receptor


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**Table 2. The retinoic acid orphan receptor (ROR)γt+ ILC populations**

| Subset | Name | Species | Tissue distribution | Function |
|---|---|---|---|---|
| LTi cells | LTi (fetal) | Humans, mice | Fetal lymphoid organs | Lymphoid organ development |
| LTi cells | LTi-like (adult) | Humans, mice | Tonsil, adult mouse intestine, spleen | Mucosal immunity, ILF formation, tissue modeling |
| IL-22-producing ILCs | NK22 | Humans | Tonsil, intestine, Peyer's patches | Epithelial homeostasis, intestinal immunity |
| IL-22-producing ILCs | NCR22 | Mice | Intestines, Peyer's patches, spleen | Epithelial homeostasis, intestinal immunity |
| IL-22-producing ILCs | NKR-LTi | Mice | Intestine | Intestinal immunity |
| IL-22-producing ILCs | ILC22 | Humans, mice | Intestine, tonsil, Peyer's patches | Epithelial homeostasis, intestinal immunity |
| IL-17 producing, IL-17/IL-22 producing ILCs | ILC17 | Humans, mice | Intestine, mouse spleen, tonsil | Yeast immunity, intestinal pathology |

IL: interleukin, ILC: innate lymphoid cell, LTi: Lymphoid tissue-inducer cells, NCR: natural cytotoxicity receptors, NK: natural killer, NKR: NK cell receptor

The expression of natural cytotoxicity receptors (NCRs) on ILC3 cells and NK cells in mouse and man initially suggested that ILC3 cells were a subpopulation of NK cells but recent evidence suggests that they are both derived from a common precursor cell following distinct developmental pathways.[5,42,43] It is possible that the expression of RORγt follows the commitment to the ILC3 lineage.

IL-22 producing immature NK cells can differentiate into mature cytotoxic NK cells under the control of IL-1β [46-49] suggesting a precursor role for immature NK cells in the induction of CD127+ IL-22 producing ILCs. Further evidence for a developmental link between NK cells and LTi cells is that they both require the common cytokine receptor γ-chain (γc; also known as IL-2Rγ) and the transcriptional repressor inhibitor of DNA binding 2 (ID2) to develop. In contrast, ILC3 and LTi cell-like NKp46+ cells isolated from the gut express RORγ indicating that they probably develop independently from NK cells.[44,45]

In terms of ILC2 development, exposure to IL-7 is critical since ILC2 cell numbers are reduced in IL-7 deficient mice.[5,30] IL-2Rγ is also present in ILC2 cells and in vitro evidence highlights key roles for IL-2 in ILC2 cell development, survival and expansion.[5] It is likely, therefore, that ILC2 development is absolutely dependent upon the presence of at least two cytokines: IL-7 for ILC2 cell development and IL-25, IL-33 and indirectly IL-2 for the ILC2 recruitment, expansion and activity (Figure 1).[5]

## Function of ILCs

### A) Mediator and Cytokine Release

As described above, the three types of ILCs include NK cells (ILC1), RORα-(ILC2) and RORγt-dependent ILCs (ILC3).[40,50] Two latter types of ILCs do not express surface markers associated with the major hematopoietic lineages but they do express CD25 (IL-2Rα); CD90 (Thy1); CD117 (c-Kit) and CD127 (IL-7Rα).[40] ILC2 cells express and produce ICOS (CD278); ST2 (IL-33R) and IL-17BR in response to IL-25 and IL-33 exposure.[51] The same stimulus results in high levels of IL-5, IL-9 and IL-13 expression which is characteristic of these cells (Figure 2).[10,40,51-54]

In contrast, ILC3 cells in fetal lymph nodes (LN) and other tissues respond to IL-23 by secreting IL-17A and IL-22.[7,9,10,14,55] ILC22 cells, despite being a member of the LTi group of ILCs, produce large amounts of IL-22, and to a lesser extent IL-26, in response to IL-23.[7,10,55-57] However, it is evident that the local environment can also affect the cytokine profile produce by ILC22 cells. Thus, ILC22 cells also synthesize cytokines and chemokines such as IL-2; IL-13, CXCL8, GM-CSF, and BAFF[5,8,58] depending upon the local mucosal immune system and this is particularly evident in the intestine.[5,7,55,56,59,60] The expression of inflammatory mediators and subsequent function by other ILC3 subsets also varies depending


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upon context. Hence, whilst ILC17 cells have a critical role in the pathogenesis of intestinal diseases in mice where they co-produce IFN-γ, IL-22 and IL-17,[10] ILC3 are also involved in several aspects of tissue and mucosal functions such as organogenesis, tissue repair, mucosal immunity, homeostasis and pathology as well as modulating cancer progression in the absence of IFN-γ production.[5] Deep immunophenotyping of human circulating blood ILC subsets indicated that patients with psoriasis have much greater numbers of IL-17A and IL-22 producing NKp44+ ILC3 cells than healthy individuals. The numbers of these cells was further increased in the skin of these patients suggesting a possible role for these cells in the pathogenesis of psoriasis.[61]

**B) Lymphoid Organogenesis**

It is clear from their name that LTi cells are involved in the induction of lymphoid tissue organogenesis. This occurs mainly during fetal development even though LTi cells are present throughout life.[5,6] The appearance of these Lin-RORγt+ ILCs expressing high levels of CD117 and CD127 in human fetal lymph nodes occurs well before that of T cells.[5,6] Mouse LTi cells express CD4 whereas this is not expressed on human LTi cells. However, lymphoid organogenesis is not affected in CD4 knockout mice.[14, 62]

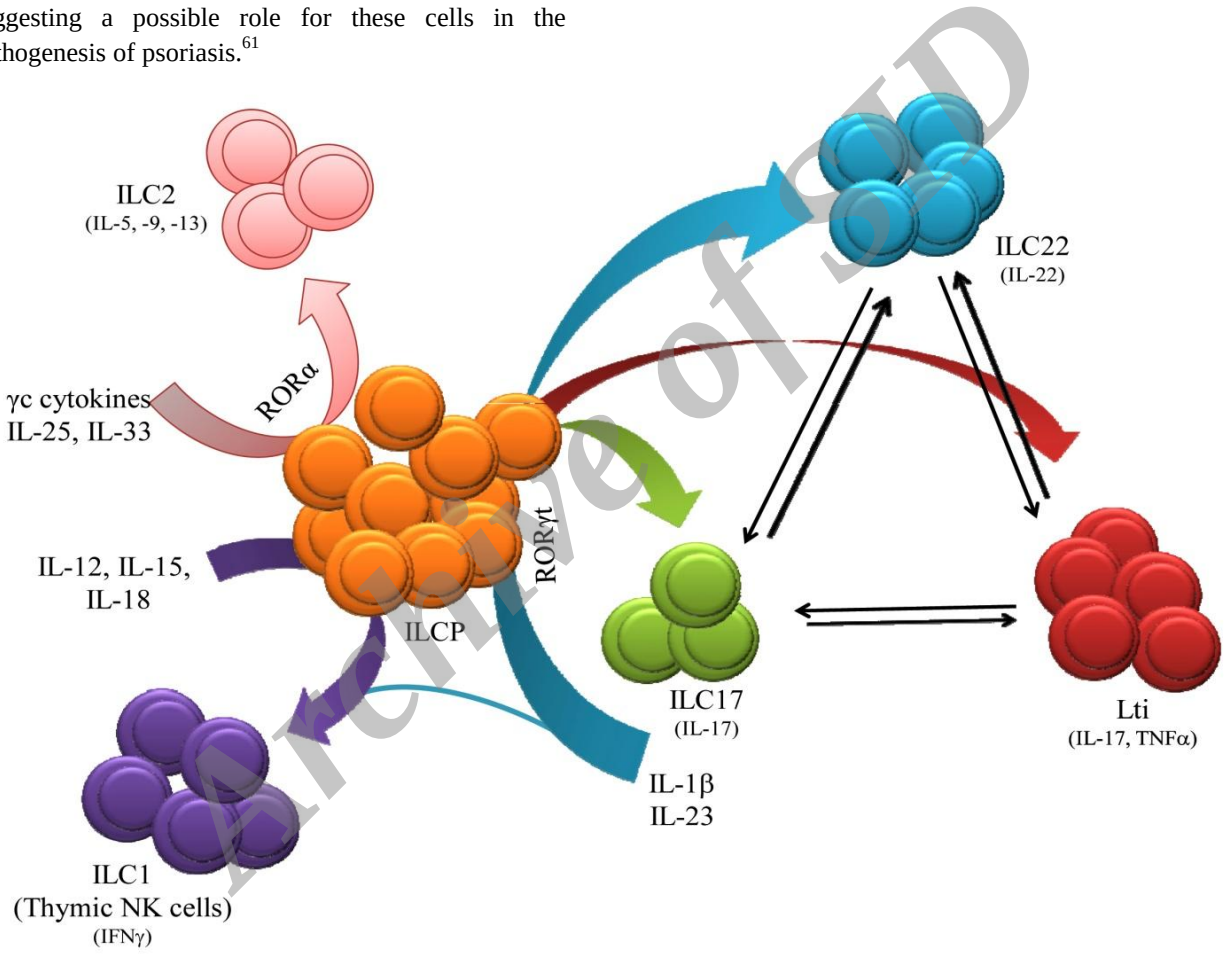


**Figure 1. Simplified cartoon to indicate the drivers that regulate the production of the various innate lymphoid cell (ILC) subtypes. When exposed to interleukins (IL)-12, -15 or -18, ILC precursor (ILCP) cells are driven to produce ILC1 cells such as natural killer (NK) cells which produce interferon (IFN)-γ. In contrast, exposure of ILCP cells to γc cytokines such as IL-25 and IL-33 induces IL-5-, -9- and -13-producing ILC2 cells. The transcription factor retinoic acid receptor orphan receptor (ROR)α is required to enable Th2 cytokine production. ILC3 cells are produced from RORγt-containing ILCP cells under the control of IL-1β and IL-23. Subpopulations of ILC3 cells are found which predominantly express IL-22 (ILC22), IL-17 (ILC17) or both IL-17 and TNF-α (lymphoid tissue-inducer, LTi) cells. Some ILC3 cells produce equal amounts of both IL-17A and IL-22.**

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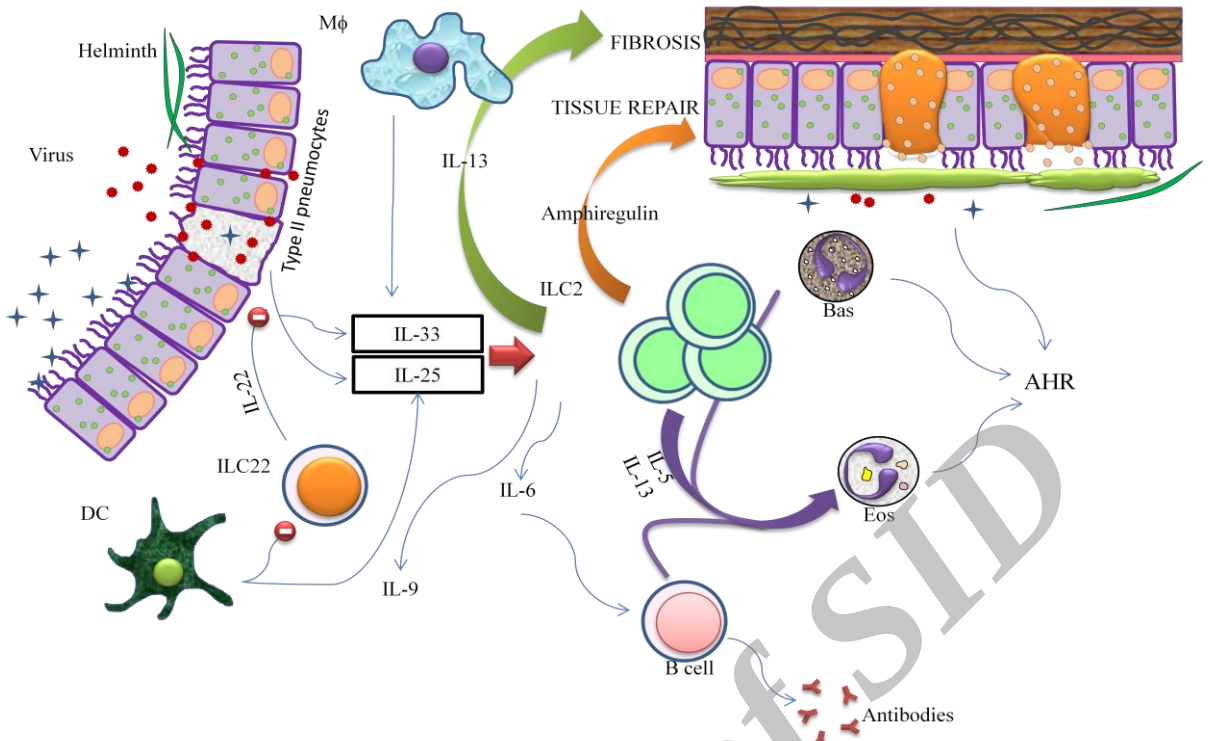


**Figure 2. The role of ILC2 cells in the lung. IL-25 and IL-33 are produced by a diverse array of cell types including epithelial cells, alveolar macrophages (mϕ) and dendritic cells (DC) in response to allergens, viruses and other parasitic stimuli e.g. helminthes within the lung. These cytokines activate type 2 innate lymphoid cells (ILC2) to produce large amounts of interleukin (IL)-5 and IL-13. This has profound effects in the lung causing the proliferation and survival of eosinophils (IL-5), goblet cell differentiation and mucus production (IL-13), epithelial cell hyperproliferation (IL-13), airway smooth muscle hypercontractility and airway fibrosis (IL-13). Overall, this results in the impairment of airways hyperresponsiveness. Cross-talk exists between ILC2 and other lymphocyte subsets including IL-22 producing ILC22 cells, Th2-cells and B-cells to enhance and maintain the interface between the innate and adaptive inflammatory/immune response in asthma.**

LTi cells are also required for the development of secondary lymphoid organs specifically lymph nodes and Peyer's patches but not the spleen.[5,6] In all cases of lymphoid organogenesis the key effector proteins are the TNF super family members lymphotoxins (LT)-α and -β and and TNF-α. Lymphotoxin binding to the LTβR on stromal cells leads to the production of CXCL13 and of adhesion molecules providing a feed-forward mechanism to recruit more LTi cells and the eventual formation of a lymphoid organ.

RORγt-positive ILC3-induced lymphoid organogenesis also occurs in the adult intestine.[63-66] ILC3 cells are important for the formation of small lymphocyte clusters in the gut, known as crypto patches, which contain ILCs, a small number of DCs but almost no T or B cells. [63-66] In addition, ILC3 cells also drive crypto patch transformation into isolated lymphoid follicles (ILFs) in response to microbial-derived signals and high local IgA levels. These ILFs are important for the generation of IgA-producing plasma cells in the gut.[63-66]

### C) Tissue and Mucosal Repair

The most important role of ILC3 cells with respect to tissue damage and repair is the reconstitution of the damaged spleen architecture resulting from infection by lymphocytic choriomeningitis virus (LCMV). This leads to a complete loss of B and T cell segregation and disrupts germinal center formation in adult human.[67] RORγt positive ILCs show a capability of rebuilding in



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these aspects.[67]

IL-22 and IL-17 are absolutely essential in mucosal immunity, homeostasis and pathology.[5] For example, IL-17-producing ILCs have been implicated in the pathology of intestinal infections and Crohn's disease.[57,68] RORγt$^+$ NKp46$^+$ILCs are the major source of IL-22 in the mouse intestine and they reside mainly in intestinal mucosal tissue and palatine tonsils.[6, 55, 56, 60, 69] Cross-talk between these cells and epithelial cells, immune cells and the gut microflora is essential for gut homeostasis. For example, IL-22 can act directly on epithelial cells to induce the release of antimicrobial proteins and IL-23 release from DCs can modulate IL-22 production from ILCs in an LTβR-mediated manner.[70,71]

In adults, the major sites of CD4+ ILC localization is within secondary lymphoid tissues particularly Peyer's patches.[25] NKp46$^+$ ILCs also reside within the lamina properia of the intestine where they also produce large quantities of IL-22 and regulate mucosal homeostasis including mucus production.[69,72] As described before, CD4$^+$ RORγt$^+$ ILC3 cells are strongly associated with crypto patches, ILFs and the mesenteric lymph nodes in the murine intestine.[25,55,59,60]

Human tonsil-derived ILC3s have similar characteristics to those from the murine gut. These cells also secrete IL-22 in response to IL-23 but this process requires a co-stimulus such as IL-2 or TLR activation.[5] Interestingly, human ILC3 cells can produce IL-2 raising the possibility of autocrine cell activation. IL-1β can also modulate IL-22 production in conjunction with IL-2 and IL-15.[5]

**D) Role of ILCs in Cancer and Immunomodulation**

"The immune system plays a dual role in cancer" as Spits and Cupedo quote from de Visser et al.[5] On one hand, the immune system may attack tumor cells leading to cancer regression whilst on the other hand, the same system can promote tumor growth through providing an immunosuppressive milieu within the tumor microenvironment.[5] In a murine model of melanoma, RORγt knockout mice did not show CCL21-mediated tumor growth due to a lack of CCR7$^+$CD4$^+$RORγt$^+$ cells. This effect is due to these cells facilitating the recruitment and differentiation of suppressive cells such as Treg cells.[73] However, in other murine melanoma models, NK46$^+$RORγt$^+$ cells had the opposite effect.[74] Similarly, ILCs may have a dual effect in the regulation of inflammation depending upon the local conditions and cellular targets.[75]

ILCs also modulate adaptive immune responses within the airway by controlling Th2[76-81] and memory T cell [82, 83] survival. This process is mediated via direct interaction between ILCs and T-cells utilizing the expression of the T-cell costimulatory molecules OX40 ligand and CD30 ligand on the ILC3 cell surface. The expression of these co-stimulatory molecules is regulated by the TNF family member TL1A and by IL-7R signaling for OX40L and CD30L, respectively.[76-83] In addition, ILCs also drive the production of ILFs and IgA in the gut (see above). ILC3s activate latent Transforming growth factor beta

Transforming growth factor beta (TGF-β) and induce IgA synthesis via stimulation of matrix metalloproteinases. [64] Together this highlights the importance of RORγt$^+$ILCs in immune homeostasis in response to commensal bacteria in the gut [64] and potentially many other tissues.[75] Interestingly, the circadian rhythm of blood eosinophilia may also be under ILC control.[84] Long-lived tissue resident ILCs maintain blood eosinophil levels under the control of the vasoactive intestinal peptide (VIP). VIP is released in a circadian manner and stimulates ILCs to increase IL-5 expression.

**E) Role of ILCs in Respiratory Systems**

As described earlier, ILCs represent distinct immune cell populations which perform key immune functions throughout the body. They are classified into three categories depending upon their developmental origins: Type 1 cells are represented by IFN-γ-producing NK cells, Type 2 cells are RORα$^+$ Th2 cytokine producing cells and Type 3 cells are RORγt$^+$ cells that produce IL-17A, IL-22 and TNF-α depending upon the subset.[1-4] Many allergic or noxious challenges to the respiratory system may trigger airway epithelial cells to release cytokines such as IL-25 and IL-33.[1,29,85] These cytokines, in turn, can act on ILC2 or ILC-precursor cells to express Th2 cytokines such as IL-5 and IL-13[1,29,85] rather than IL-22, IL-17A or IFN-γ.[31,86] Non-lineage-expressing (Lin-) cells which express CD25 and CD127 markers are found in the lung parenchyma and bronchoalveolar lavage (BAL) fluid of subjects undergoing lung transplantation.[1,39,86,87] These cells are analogous to murine ILCs and have previously been found in gut-associated lymphoid tissue (GALT), fat-associated lymphoid clusters (FALC) and in the spleen.[29, 30, 32]


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Animal models, and to a much lesser extent studies in human tissue, have begun to reveal the critical role of ILC2 cells in the respiratory tract during asthma and chronic rhino-sinusitis, in protease-allergen-induced airway inflammation and in parasitic and fungal infections.[10, 28-32, 39, 50, 53] These challenges result in the increased production of Th2 cytokines which is characteristic of the pathogenesis of these disorders.[10, 28-32, 39, 50, 53, 88] Not surprisingly, the most common ILC reported in the human respiratory tract are RORγt-independent ILC2 cells which, as detailed above, produce Th2 cytokines in response to IL-25, IL-33 and IL-2 exposure.[28] The local airway environment may affect the expression of ILC2 cell surface markers such as CD117 and CD45 which may have functional consequences.[89]

ILC2 cells represent less than 1% of all $CD45^+$ cells in tissues and only 0.01-0.03% of cells in circulating blood of healthy people. However, cell numbers are increased in human lung, intestine and palatine tonsils.[5] Table 3 describes the distribution and function of ILC2 cell in mouse and man. Studies have also established that ILC2 cells from human peripheral blood have a more plastic phenotype regarding their IL-22 production compared to tissue-localized ILC2 cells with some expressing low levels of, or even no, IL-22.[28]

ILC2 cells accumulate in the lung following H1N1 influenza virus infection. ILC2 cells do not directly affect immunity against the virus since depletion of ILC2 after H1N1 infection did not affect viral load. Rather, ILC2 cells are likely to play a major role in maintaining the epithelial cell barrier since ILC2 depletion had profound effects on epithelial cell damage following viral infection.[90] This effect was not mediated by IL-22 but by the release of amphiregulin, a member of the epidermal growth factor (EGF) family, from ILC2 cells.[33] IL-22 may also be important in epithelial cell damage/repair processes in ovalbumin-challenge models [33] through promoting epithelial cell proliferation following IL-13 release from ILC2 cells.[39, 91-94]

**F) ILCs in Pathogenesis of Asthma**

The possible role of ILC2 in the pathogenesis of human allergic asthma recently has been appreciated.[95] Allergic asthma is a chronic inflammatory condition of the airways which is characterized by airway hyperreactivity (AHR), bronchoconstriction, increased mucus secretion and limited airflow. This is usually associated with elevated serum IgE, eosinophilia and goblet cell hyperplasia in those patients with a clear allergic disease with heightened expression of Th2 cytokines.[52, 96-103] ILC2 cells identified in the human lung resemble their intestinal counterparts as they express ICOS, ST2, CD25 and CD44 on the cell surface.[28, 33, 40, 102, 103]

Both NK cells and ILC2s are found asthmatic and healthy volunteer lung and peripheral blood. Severe asthma patients had evidence for activated NK cells which were able to promote eosinophil apoptosis.[104]

**Table 3. ILC2 cell populations/subtypes**

| Cell | Species | Tissue distribution | Function/pathology |
|---|---|---|---|
| Natural helper cells (NH) | Wild type mouse | Fat associated lymphoid tissue, lung | Nematode expulsion, airway pathology/tissue repair following viral infection |
| Nuocytes | IL-13-GFP reporter mouse | Intestine, mesenteric lymph nodes | Nematode expulsion |
| Innate helper 2 cells (ih2) | IL-13-GFP and IL-14-GFP reporter mice | Broad, spleen, liver, mesenteries | Nematode expulsion |
| Multi-potent progenitor population (MPP) 2 | IL-25 knock out mice | Gut-associated lymphoid tissue | Promotes Th2 cytokine responses in response to IL-25 and confers protective immunity to helminth infection |
| ILC2 | Humans | Fetal and adult gut and lung, adult peripheral blood | Chronic rhinosinusitis |

IL: interleukin, ILC: innate lymphoid cell, GFP: green fluorescent protein.



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In addition, the combination of mast cell-derived prostaglandin D2 and epithelial cell-derived IL-25 and IL-33 resulted in enhanced ILC2 production of IL-13. Since the expression of lipoxin A4 is reduced in severe asthma, ILC activation may not be regulated in these patients.

In animal models of allergic asthma, IL-13 release from ILC2 cells has been shown to be an essential director of AHR, mucus hyper secretion and inflammation.[39, 40, 50, 52, 98,105-107] These studies indicate that activation of ILC2 occurs not only following intranasal IL-25 or IL-33, as the main stimulators of ILCs, but also following the exposure to fungal aeroallergens such as *Alternariaalternata*.[31, 35, 39, 40, 50, 52, 87, 108] Alternaria exposure, in turn, results in an increase in the expression of IL-5, IL-13, IL-6, IL-9, and IL-10.[29, 35, 108] IL-33 is also released from alveolar macrophages, (DCs) and type 2 pneumocytes following infection or exposure to allergens [31, 87, 103, 109-112] and would be able to activate ILC2 cells.[1, 31, 52] In addition, IL-25 may also be released from basophils and eosinophils following allergen challenge in animal models of asthma.[113, 114] Furthermore, infection by parasites and by viruses also leads to the production of IL-5 and IL-13 from ILC2 cells.[115, 116] In all cases the level of Th2 cytokines released from ILC2 cells into the lungs is at least similar to that released from Th2 cells and is often much greater than the Th2-dependent release.[95] In contrast, ILC2 cells produce little IL-4 and most IL-4 is derived from Th2 cells in animal models of asthma.[50, 98]

Chronic rhinosinusitis is an inflammatory disease associated with high levels of IL-13, IgE, eosinophils and the presence of nasal polyps. Human ILC2 express a prostaglandin D2 receptor named chemoattractant receptor expressed on Th2 cells (CRTH2) and elevated numbers of $CRTH2^+$ ILCs were found in nasal polyps of chronic rhinosinusitis patients compared to control subjects.[28] The authors did not measure IL-25 or IL-33 levels in the polyps. In addition, the utility of anti-IL-13 treatment in patients with severe asthma.[117]

New therapeutic strategies targeting ILCs may therefore be important for allergic airway diseases.[28]

In addition to ILC2 cells, IL-22-producing ILCs have also been recently found in the lung parenchyma of mouse models of allergic asthma.[118, 119] As described above, ILC22 cells play important roles in tissue repair and epithelial integrity in the respiratory tract and may, as reported for IL-17A, also have a protective effect on inflammation through effects on DCs.[120-122]

**G) ILCs in COPD**

Chronic obstructive pulmonary disease (COPD) is characterized by a chronic inflammation of the airways triggered by inhaled noxious particles and gases, mostly cigarette smoke (CS), leading to progressive bronchitis and/or emphysema that causes an irreversible airflow limitation of the lungs.[123-125] COPD-induced lung inflammation involves neutrophils, $CD4^+$ and $CD8^+$ lymphocytes, macrophages and DCs. Although eosinophils are not usually present in stable disease, increased numbers have been observed during acute exacerbations of COPD (AECOPD) in a large (30%) subgroup of patients.[126] Liesker et al.[127] demonstrated that sputum eosinophil numbers are significantly increased during AECOPD which coincides with a significant 30-fold increase in IL-13 mRNA levels.[127, 128] At present, the trigger and cellular source for IL-13 gene expression in AECOPD is unknown. Although Th2 lymphocytes express IL-13, these cells are not considered to be implicated in COPD pathogenesis. It is tempting to speculate that ILC2 cells may play a role in this scenario.

Interestingly, respiratory viral infection, important triggers of AECOPD, induces the accumulation of ILCs in lung tissue of mice.[129] Depletion of ILCs with anti-CD90.2 antibody strongly reduced BAL eosinophil numbers and IL-5 and IL-13 mRNA expression in lung tissue upon respiratory viral infection.[130] Since IL- 33 is a critical trigger for ILC activation after respiratory viral infection in mice, it is tempting to speculate that IL-33 release and subsequent ILC2 activation results in the enhanced IL-5/IL-13 expression and eosinophilia seen in AECOPD.

IL-33 is a chromatin-associated nuclear cytokine that is abundant in epithelial and endothelial cells and is considered not to be actively secreted but only released upon cellular damage or necrotic cell death.[131] NALP3 inflammasome-mediated activation of caspase-1 activity results in the release of an inactive form of IL-33 in contrast to the production of active forms of IL-1β and IL-18.[131] Interestingly, full-length IL-33 is processed into a mature form with superior biological activity (10-fold higher than full-length IL-33) by neutrophil elastase and cathepsin G.[132] Neutrophilic


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airway inflammation is a characteristic of COPD patients and neutrophil elastase and cathepsin G levels are increased in sputum from AECOPD patients.[133] Therefore, neutrophil elastase and cathepsin may induce maturation of IL-33 released from necrotic epithelial or endothelial cells into a molecule with superior biological activity.

ILCs may not only play a role in AECOPD but also in the early development of COPD[129] since cigarette smoke extract (CSE) switches airway epithelial cell apoptosis into necrosis.[134] Furthermore, CSE-induced necrosis of airway epithelial cells was associated with the release of various damage-associated molecular patterns (DAMPs).[135] In a mouse model of cigarette smoke-induced neutrophilic airway inflammation, a model of COPD inflammation, we have demonstrated that the inflammation is preceded by epithelial sloughing and the presence of DAMPs in BAL fluid, indicating necrosis of airway epithelial cells.[135] Although we have not measured the levels of IL-33 in this model, it is tempting to speculate that ILC17 and ILC2 cells have been activated since serum IL-17 and BAL IL-5 levels were significantly increased.

These increases in IL-5 and IL-17 levels occur too early to be produced by differentiated Th17 cells and point to a role for ILC2 and ILC17 cells. However, a role for other IL-17-producing innate immune cells or even epithelial cells[136] cannot be excluded. Interestingly, there is evidence that IL-17 is produced by innate immune cells in COPD patients. Chang et al.[31] demonstrated that 80% of the $IL17^+$ cells in the airways of COPD patients were not $CD4^+$ or $CD8^+$ lymphocytes.

**Future Perspectives on the Roles of ILCs in Lung Disease**

Although the role of ILC cells in animal models of asthma and COPD are clear, there is little evidence in human disease. It is important that future studies examine the expression of these cells in human airways, sputum and bronchoalveolar lavage for example and determine how they link with the adaptive immune system within the human lung. It is also unclear what effects anti-inflammatory agents such as steroids have on the number and function co these cells.

In addition, it is unclear whether ILC subsets represent truly distinct populations of cells or merely reflect different states of a plastic precursor cell exposed to a specific local microenvironment. More sophisticated analysis of the gene expression and regulatory patterns are needed in these cells. The critical signaling pathways or proteins that control cell-cell interactions are also areas that need to be elucidated. This is even more evident in the case of human airways disease where these may provide important novel therapeutic targets particularly in relation to viral and bacterial infections and the maintenance of an intact epithelial barrier.

The discovery of the role of these cells in mouse models of asthma and COPD has opened up an exciting era of research which may explain the anomalies reported to date regarding the presence of Th2 cells and markers in asthma for example. It is hoped that further understanding of the functions of these cells in human disease will lead to novel anti-inflammatory approaches in severe asthma and COPD where there is a major unmet clinical need.

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