



COMMENT

Factors affecting the migration of ILC2s in allergic disease

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It is well known that group 2 innate lymphoid cells (ILC2s) are enriched in mucosal tissues and respond to epithelial cell-derived cytokines, initiating and maintaining type 2 inflammation. Although an increased number of ILC2s has been observed at sites of allergic inflammation and during helminth infection, some studies have shown that ILC2s are largely tissue-resident cells seeded in the tissue early in life,¹ suggesting that such accumulation may be due to local proliferation of ILC2s. However, other studies indicate that ILC2s are able to migrate into tissues from the circulation during inflammation.^{2–4} In this case, the mechanisms that control ILC2 accumulation in tissues and the contribution of ILC2 migration into and between tissues during allergic inflammation remain unclear.

Stier et al. showed that administration of IL-33 in mice alters the expression of chemokine receptors, including C-X-C motif chemokine receptor 4, on bone marrow ILC2 progenitors (ILC2Ps), which account for this cell translocation, while mice lacking IL-33 signaling have a significant accumulation of ILC2Ps in the bone marrow and a marked reduction in the number of ILC2s in peripheral tissues.⁴ In addition, exposure to exogenous IL-33 and the fungal allergen *Alternaria alternata* (Alt) rapidly and significantly mobilized ILC2Ps to egress from the bone marrow.⁴ Furthermore, using IL-13-enhanced green fluorescent protein reporter mice and elegant imaging techniques, Puttur et al. found that ILC2s exhibit amoeboid-like movement and accumulate in the extravascular tissue surrounding large blood vessels rather than alveolar capillaries during IL-33-induced lung inflammation, although ILC2s exist in relatively low numbers in the lungs under steady conditions.⁵ These data suggest that the rapid expansion of ILC2 numbers in the lung tissues of the mice challenged with IL-33 or Alt could result as a consequence of recruitment of ILC2Ps from the bone marrow rather than in situ proliferation of a small population of resident precursors at steady status. Therefore, it is critical to define the pathways controlling ILC2 migration to and within tissues.

Tissue environments critically regulate optimal immune responses, coordinating timely and proportionate recruitment, migration, chemotaxis, and positioning of leukocytes within inflamed tissues. Numerous factors, including lipids, cytokines, the distribution of adhesion molecules, and chemotactic signals controlling migratory patterns of ILC2s in the bone marrow, gut, mesenteric lymph nodes, lung, and skin, have been identified. For example, CCR2 expressed on human and murine ILC2s is in charge of migration toward PGD2 in vitro, as well as the accumulation of the cells in the lung in response to PGD2 in vivo.⁶ Similarly, although high levels of $\beta 1$ and $\beta 2$ integrin adhesion receptors can be expressed on lung ILC2s of humans

and mice, ILC2s increase in number in the mouse lung through trafficking from the circulation into the lung tissues using $\beta 2$ rather than $\beta 1$ or $\alpha 4$ integrins after Alt challenge.² Moreover, in vivo blockade of $\beta 2$ integrins significantly decreased the number of ILC2s in the lung without affecting their proliferation, apoptosis, and function.² In addition, IL-25- or helminth-induced inflammatory ILC2s expressed S1PR1 and S1PR4. Through sphingosine 1-phosphate (S1P)-mediated chemotaxis, these ILC2s can migrate to diverse tissues, which promotes lymphatic entry, blood circulation, and accumulation in peripheral sites, in a similar mechanism to T-cell egression from secondary lymphoid organs and the thymus.³ Blockade of the S1P signaling pathway markedly reduces ILC2 accumulation in peripheral sites, including the lung, liver, spleen and mediastinal lymph nodes, but does not affect IL-25-induced intestinal ILC2 proliferation.³

A few chemokine receptors, including CXCR6, CCR1, CCR4, CCR6, CCR8, and CCR9, have been reported to be expressed by ILC2s, while the migration of ILC2s in different tissues is partially mediated by distinct chemokines. Our study has shown that CXCL16 is able to induce chemotaxis of murine ILC2s in vivo and in vitro and that a specific anti-CXCL16 neutralizing antibody significantly attenuates ILC2 accumulation and inhibits airway hyperresponsiveness in IL-33- and HDM-induced airway inflammation.⁷ Furthermore, the expression of CXCL16 is elevated in the airway mucosa of mice, which might favor ILC2 migration into the airway lumen.⁷ Correspondingly, it has been noted that the number of ILC2s is significantly reduced in CXCR6^{GFP/GFP} mice compared to their CXCR6-sufficient counterparts in a papain-challenged allergic mouse model.⁸ In addition, CCL8 is also able to induce human and murine ILC2 chemotaxis, and blocking CCR8 significantly reduces ILC2 accumulation in IL-33-induced pulmonary inflammation.⁵ Conversely, a recent study has shown that CCL8 does not trigger mouse ILC2 migration in vitro, and Ccr8^{-/-} ILC2s do not display lung homing defects in an in vivo adoptive transfer model during helminth infection.⁹ Similarly, CCL25 induces the migration of mouse nasal-associated lymphoid tissue-derived ILC2s via activation of CCR9 on ILC2s in vitro.¹⁰ In contrast, our published data show that CCL25 could not induce the accumulation of ILC2s in the lungs of mice, either in vitro or in vivo.⁷ CCL22, a high-affinity ligand of CCR4, recruits ILC2s in lung tissues compared to wild-type mice in the context of systemic IL-25 abundance, and CCR4-deficient mice display impaired migration of ILC2s to the lung.⁹ In addition, CCL20, a ligand of CCR6, has been identified as a potent promoter of lung-directed ILC2 migration under inflammatory conditions in vitro and in vivo using a humanized mouse model treated with papain.¹¹ Obviously, these data suggest that the microenvironment in local tissues might also

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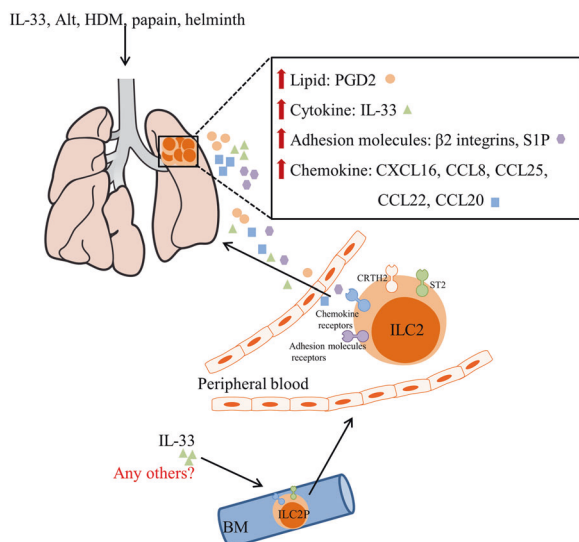


Fig. 1 Experimentally proposed diagram of the accumulation of ILC2s in IL-33-, allergen-, and helminth-induced lung inflammation. Exposure to IL-33 (and any other unknown factors) rapidly and significantly mobilizes ILC2Ps to egress from the bone marrow. In IL-33-, allergen- (Alt, HDM), papain-, and helminth-induced lung allergic inflammation, elevated expression of PGD2, IL-33, adhesion molecules (β 2 integrins, S1P), and various chemokines (CXCL16, CCL8, CCL25, CCL22 and CCL20) promote and/or enhance the migration of ILC2s from the peripheral bloodstream into inflamed lung tissue. Accumulated ILC2s likely play an important role by producing various mediators in the type 2 immune response, including allergic lung inflammation

affect ILC2 accumulation, while distinct models might have obtained different observations.

Previous studies have revealed that IL-33 promotes the egress of ILC2s from the bone marrow,⁴ and our studies have further demonstrated that IL-33 is able to induce the accumulation of ILC2s in the lung tissue *in vivo* and directly induce ILC2 chemotaxis *in vitro*.⁷ Recent studies have shown that IL-33 can promote the capacity of ILC2s to produce PGD2, which in turn regulates ILC2 migration via CRTH2, while IL-33-elicited ILC2 accumulation in the lung is partially attenuated in CRTH2-deficient mice compared with wild-type mice but does not affect the proliferation or apoptosis of ILC2s.¹² An increased understanding of the networks that control ILC2 accumulation will inform the use

and development of drugs specifically targeting these factors in type 2 inflammation.

Apart from migration, ILC2s recruited into inflammation sites might further undergo proliferation through stimulation with various cytokines, neuropeptides, and lipid mediators.¹³ Therefore, to effectively decrease ILC2 numbers at inflammation sites, it is also important to consider not only inhibiting the migration of ILC2s but also blocking the proliferation of ILC2s (Fig. 1).

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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