


Role of myeloid cells in the regulation of group 2 innate lymphoid cell-mediated allergic inflammation

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Introduction

Allergic diseases such as asthma and atopic dermatitis are common inflammatory disorders characterized by the dysregulated type 2 immune responses to environmental antigens. It is known that type 2 cytokines including interleukin-4 (IL-4), IL-5 and IL-13 from activated T helper type 2 (Th2) cells are crucial for the emergence of allergic outcomes, such as release of IgE, mucus production, smooth muscle cell contraction and recruitment of eosinophils, basophils and mast cells.¹ Recently, evidence is accumulating that group 2 innate lymphoid cells (ILC2s) are a major source of type 2 cytokines and have become one of the key effector immune cells in driving allergic inflammation.^{2–4}

Summary

Group 2 innate lymphoid cells (ILC2s) are an important component of the innate immune system that execute important effector functions at barrier surfaces, such as lung and skin. Like T helper type 2 cells, ILC2s are able to release high amounts of type 2 cytokines that are essential in inducing allergic inflammation and eliminating helminth infections. The past few years have contributed to our better understanding of the interactions between ILC2s and other cells of the immune system via soluble factors or in a cell–cell contact manner. Myeloid cells, including mononuclear leukocytes and polymorphonuclear leukocytes, are excellent sensors of tissue damage and infection and can influence ILC2 responses in the process of allergic inflammation. In this review, we summarize recent insights on how myeloid cell subsets regulate ILC2 activation with focus on soluble factors in the context of allergic inflammation.

Keywords: allergic inflammation; group 2 innate lymphoid cells; myeloid cell.

The ILC2s, which resemble Th2 cells, rely on the expression of transcription factor GATA binding protein 3 (GATA3) for their development and function. However, ILC2s lack antigen-specific receptor but respond quickly to epithelium-derived cytokines including IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) during allergic inflammation.⁵ Upon activation, ILC2s produce large amounts of type 2 cytokines IL-5, IL-13 and IL-9, and thereby contribute to allergic responses and clearance of helminth infections.⁶ On the other hand, ILC2s secrete amphiregulin, which promotes the restoration of damaged tissues.⁷ Of note, ILC2s are recognized as tissue-resident cells and act as ‘early sentinel’ cells that elicit type 2 immune responses in lung, intestine, skin and adipose tissue.⁸ Recently, numerous studies have demonstrated that

Abbreviations: DCs, dendritic cells; GATA3, GATA binding protein 3; G-CSF, granulocyte colony-stimulating factor; IFN, interferon; IL, interleukin; ILC2s, group 2 innate lymphoid cells; mDCs, myeloid DCs; MDSCs, myeloid-derived suppressor cells; M-MDSCs, monocytic MDSCs; MIF, migration inhibitory factor; MΦ, macrophage; pDCs, plasmacytoid DCs; PGD2, Prostaglandin D2; Pla2g5, group V phospholipase A2; PMN-MDSCs, polymorphonuclear MDSCs; Th2, T helper type 2; TSLP, thymic stromal lymphopoietin

ILC2 responses during allergic inflammation can be modulated by a variety of factors including cytokines, hormones, lipid mediators, neuropeptides, nutrients and cell surface molecules, as excellently reviewed elsewhere.^{6,9,10} Meanwhile, emerging data have indicated that ILC2s communicate with cells of the innate and adaptive immune systems and contribute to inflammatory processes in the context of allergic diseases.^{11,12} Although activated ILC2s are known to modulate the recruitment and function of myeloid cells, the regulation of ILC2 responses by myeloid cells is of great interest in enhancing our understanding of how mediators from myeloid cells influence type 2 immune responses during allergic inflammation.

In mammals, myeloid cell development arises in a step-wise fashion that begins in the yolk sac and ends in the bone marrow.¹³ During myelopoiesis, myeloid progenitors branch up into monocytic and granulocytic lineages generating mononuclear leukocytes including monocytes, macrophages (MΦ) and dendritic cells (DCs), as well as polymorphonuclear leukocytes including neutrophils, mast cells, basophils and eosinophils. They circulate through the blood and lymphatic system and rapidly migrate to sites of tissue damage and infection through a variety of chemokine receptors.¹³ Then, they use various pattern recognition receptors to recognize pathogen-associated molecular patterns in tissues, and thereby display innate immunity such as phagocytosis and production of effector molecules (i.e. cytokines or lipid mediators). On the other hand, like ILC2s, some myeloid cells are tissue-resident cells and respond quickly to microbial and other tissue-derived signals.^{14,15} Although ILC2-derived cytokines are critical in modulating the recruitment and activation of myeloid cells,¹¹ acute and chronic tissue inflammation is often accompanied by activation of local myeloid cells followed by crosstalk with ILC2s.^{8,12,16} This highlights the great importance of myeloid cells in regulating ILC2-driven allergic inflammation.

Understanding the complex social networking of immune cells with ILC2s in local tissues during health and disease would definitely contribute to finding critical checkpoints that can be used for developing therapeutic strategies. To this end, we highlight how various myeloid cells regulate ILC2-mediated type 2 immune responses, focusing on their roles in allergic diseases such as asthma and atopic dermatitis.

Mononuclear leukocytes and ILC2s

Monocytes/ MΦ

Monocytes develop from progenitors in the bone marrow and migrate into peripheral tissues such as lung via the bloodstream under homeostatic and inflammatory conditions.¹⁷ Recruitment of monocytes is important

for effective control and clearance of viral, bacterial, fungal and protozoal infections, but they are also involved in the pathogenesis of ILC2-mediated lung inflammation. One study showed that Ly6c-positive monocytes recruited to the lung can produce IL-33, a key ILC2 activator, which may contribute to the pathogenesis of house-dust-mite-induced airway inflammation.¹⁸

MΦ, which are phagocytes that can originate from monocytes, are critical effectors and regulators of inflammation. Currently, three major classes of lung MΦ have been recognized based on their ontogeny, mode of maintenance and location within the tissue.¹⁹ Two of these, 'primitive' interstitial MΦ and alveolar MΦ, originate from hematopoietic progenitors arising from the yolk sac and fetal liver, respectively. The third major population of 'definitive' interstitial MΦ comes from circulating monocytes and becomes the 'primitive' interstitial MΦ over time. Of note, MΦ also play an essential role in lung inflammation by regulating ILC2 responses. Alveolar MΦ can activate ILC2s by producing IL-33 in a model of influenza A virus-induced airway hyperreactivity,²⁰ whereas one study showed that resident alveolar MΦ suppressed allergic lung inflammation in house dust mite and ovalbumin murine models.²¹ This discrepancy may be the result of the use of different airway inflammation murine models. Further, in a mouse model of hookworm-mediated lung injury, Nieves *et al.* demonstrated that defective AMP-activated protein kinase activity in alveolar MΦ and conventional DCs impairs ILC2 responses through increased IL-12/23p40 production.²² Another study, in an *Alternaria*-induced pulmonary inflammation, found that macrophage-associated group V phospholipase A2 (Pla2g5) enhances lung ILC2 activation through the regulation of IL-33 induction and free fatty acid production.¹⁶ Still, one recent study showed that MΦ migration inhibitory factor (MIF) is required for ILC2 responses and MΦ polarization into M2 phenotype which is essential for the clearance of intestinal helminth parasites.²³ As MΦ can produce migration inhibitory factor, it may regulate ILC2 activation in allergic lung inflammation. Moreover, IL-5 and IL-13 produced by activated ILC2s can also promote the MΦ activation.²⁴ Hence, concerted actions of monocyte/MΦ and ILC2s may contribute to lung inflammation upon an allergen challenge.

Dendritic cells

Dendritic cells, the most potent professional antigen-presenting cells, act as key mediators at the interface of the innate and adaptive immune systems. Human DCs are a heterogeneous population of cells that can be divided into myeloid DCs (mDCs) and plasmacytoid DCs (pDCs).²⁵ The mDCs are thought to promote allergic inflammation

by eliciting type 2 immunity to inhaled allergens;²⁶ however, pDCs, the major source of type I interferon (IFN), exert a negative regulation in airway inflammation by dampening the Th2 responses.²⁷ Similar to MΦ, mouse bone marrow-derived DCs are found to produce IL-33 via Toll-like receptor/nuclear factor-κB signaling pathways, and CD11c⁺ DCs in ocular mucosal surface and the draining cervical lymph nodes can produce IL-33,²⁸ implying that DC-derived IL-33 may enhance ILC2 responses in allergic inflammation. One recent study showed that mDCs from blood in patients with allergic rhinitis promoted ILC2 proliferation and ILC2s secreting IL-13 and IL-9 through the IL-33/ST2 pathway, whereas activation of pDCs suppressed ILC2 activation via IL-6.²⁹ However, whether mDCs can affect ILC2 responses *in vivo* needs further investigation. Interestingly, studies have found that both type I and type II IFNs suppress ILC2 function, suggesting that IFN-secreting cells, including DCs, serve as important negative regulators of ILC2 responses.^{30,31} Indeed, several studies demonstrated that pDC-derived IFN negatively regulates ILC2 cells in murine asthma models.^{32–34} Furthermore, DCs are critical to activate Th2 responses during ongoing airway inflammation.³⁵ In a model of papain-induced lung inflammation, one study demonstrated that ILC2-derived IL-13 activates CD11b⁺ CD103⁻ lung DCs to produce the chemokine CCL17, promoting the recruitment of CCR4⁺ memory Th2 cells to the lung.³⁶ Taken together, DCs are key players in regulating ILC2s and Th2-driven allergic airway inflammation, and modulating DC activity may have great clinical implications in asthma treatment.

Polymorphonuclear leukocytes and ILC2s

Neutrophils

Neutrophils, a type of polymorphonuclear leukocyte, originate from bone marrow myeloid precursors. Notably, neutrophils are the first leukocytes that migrate to an inflammatory site, where they contribute to eliminating pathogens by multiple means, such as phagocytosis, degranulation and neutrophil extracellular traps.^{37,38} Although neutrophils are undoubtedly key players of acute infection, several lines of evidence show that they are also major effectors of allergic airway inflammation. Neutrophilic asthma is a typically non-Th2/type 2 asthma that is prevalent among individuals with steroid-resistant asthma.³⁹ Interestingly, Patel *et al.* recently demonstrated that the regulatory role of neutrophils on ILC2s may rationally account for the failure of neutrophil-targeting therapies for people with asthma.⁴⁰ In a mouse model of house-dust-mite-mediated allergic airway inflammation, they found that depletion of neutrophils resulted in a dramatic increase in systemic granulocyte colony-stimulating factor (G-CSF) concentrations, which are ordinarily

negatively controlled in the periphery by transmigrated lung neutrophils. G-CSF then functioned to augment allergen sensitization either by activating ILC2s or acting on bone marrow progenitors to drive monocytosis and finally caused the exacerbated Th2 inflammation, epithelial remodeling and airway resistance.⁴⁰ Intriguingly, a subpopulation of Lin⁻ GATA3⁺ ST2⁺ ILC2s, in the presence of IL-33 and leukotrienes, was found to produce IL-17 *in vitro* and in a mouse of model of IL-33 or papain-induced lung inflammation,⁴¹ which suggests that some ILC2s may promote the migration of neutrophils to the lung by producing IL-17. Moreover, a recent study showed that short-chain fatty acids derived from fermentation of dietary fibers by the gut microbiota modulated pulmonary ILC2s to secrete IL-17A, which is linked to enhanced neutrophil recruitment to the lung.⁴² It is noteworthy that IL-17 is typically not a signature cytokine for ILC2s, the source and role of IL-17-producing ILC2s during allergic inflammation requires further exploration. Additionally, type 2 immune-associated neutrophil infiltration also requires the mouse RNase A homologue, eosinophil-associated ribonuclease 11, which is secreted by alternatively activated macrophages downstream of IL-25-stimulated ILC2s.⁴³ ILC2-derived IL-5 can also directly initiate CXCR2⁺ neutrophils to produce IL-5 during traumatic injury.⁴⁴ Altogether, these studies highlight the complex regulatory role of neutrophils in asthma, at least in part by affecting ILC2 function or being regulated upon ILC2 activation.

Polymorphonuclear myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells with a potent ability to suppress T-cell responses under various pathological conditions, including cancer, inflammation, trauma and infection.⁴⁵ Based on morphology and specific cell-surface molecules, MDSCs can be classified into two subpopulations: polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (M-MDSCs).⁴⁶ Two studies have shown that ILC2-derived IL-13 can activate M-MDSCs in cancers,^{47,48} suggesting the importance of the ILC2–MDSC axis in pathological conditions. Meanwhile, given their remarkable immunosuppressive ability towards Th2 cells, the negative regulation of MDSCs in airway inflammation has been well demonstrated.^{49,50} Interestingly, Cao *et al.* recently found that PMN-MDSCs, but not M-MDSCs, effectively inhibited ILC2 function both *in vitro* and *in vivo*, which attenuated allergic airway inflammation.⁵¹ They further showed that cyclo-oxygenase-1, which is required for PMN-MDSCs to inhibit Th2 responses,⁴⁹ may mediate the suppressive effects of PMN-MDSCs on ILC2 activation. Therefore, enhancing PMN-MDSCs may be beneficial for treating ILC2-driven allergic asthma.

Mast cell

Mast cells, rich in cytoplasmic granules, originate from bone-marrow-derived hematopoietic progenitors that can traffic into all vascularized tissues where they complete their development. They, especially IgE-primed mast cells, regulate both the innate and the adaptive immune responses in inflammatory disorders including allergic inflammation.⁵² In particular, mast cells contribute to the outcome of lung inflammation through the secretion of mediators that act on other cell types, including ILC2s. For instance, mast cells can express IL-33 upon IgE stimulation.⁵³ Using models of skin anaphylaxis, one study showed that mast-cell-derived IL-33 can initiate neutrophilic inflammation by communicating with basophils.⁵⁴ Moreover, IL-33 can also potentiate IgE-mediated human mast cell responses by increasing both mast cell degranulation frequency and degranulation magnitude.⁵⁵ Interestingly, IL-33 produced by mast cells is crucial for the induction of IL-13-producing ILC2s and the clearance of helminth infections.⁵⁶ However, Morita *et al.* found that IL-33-stimulated mast-cell-derived IL-2 enhances expansion of numbers of regulatory T cells, thereby suppressing papain-induced allergic inflammation,⁵⁷ suggesting that mast cells may impair type 2 immune responses in the acute phase of allergic inflammation. Another study found that IL-9 increases IL-2 production by mast cells, which leads to expansion of CD25⁺ ILC2s and subsequent activation of Th9 cells, which promotes lung inflammation in cystic fibrosis.⁵⁸ Notably, IgE-primed mast-cell-derived prostaglandin D2 (PGD2) is an important and potent activator of human ILC2s,⁵⁹ whereas dermal ILC2-derived IL-13 may play a role in suppressing mast cell activation.⁶⁰ Taken together, the mast cell–ILC2 axis may display distinct actions in early and chronic allergic inflammation, and a better understanding of the role of mast cells in modulating human ILC2-driven allergic airway inflammation requires further investigation.

Basophil

Basophils are the least common type of granulocyte that mature in the bone marrow from myeloid stem cells and then enter the circulation. Similar to mast cells, basophils express high-affinity IgE receptors (FcεRI), and secrete histamine and Th2 cytokines after activation.^{61,62} However, basophils and mast cells are distinct cell lineages and basophils display important and non-redundant roles in protective immunity against parasitic infections, and in allergic or autoimmune pathologies.^{61–63} In particular, basophils are closely associated with allergic inflammation by participating in Th2 skewing by producing IL-4, IL-6 and IL-13.⁶⁴ Basophils derived from individuals with asthma, which express ST2 (IL-33 receptor α chain), can

produce IL-4 and IL-13 upon IL-33 stimulation.⁶⁵ Interestingly, Motomura *et al.* reported that basophil-derived IL-4 can enhance the expression of the chemokine CCL11, as well as IL-5, IL-9 and IL-13 in ILC2s, resulting in eosinophilic lung inflammation induced by protease allergens in mice.⁶⁶ In humans, the number of activated basophils is enhanced in the sputum of people with asthma and correlated with airway and blood eosinophils.⁶⁷ Two studies also showed that IL-33 or TSLP can induce basophils to produce IL-4, which enhanced ILC2 proliferation and their production of IL-5 and IL-13, and exacerbated the atopic dermatitis-like inflammation.^{68,69} These results highlight the importance of basophils in modulating ILC2 function during allergic inflammation. Apart from IL-4, basophils secrete a variety of effector molecules such as pro-inflammatory eicosanoids that contribute to allergic diseases.⁶¹ As studies have demonstrated that both murine and human ILC2s directly respond to leukotrienes,^{70–72} it is possible that other mediators produced by basophils may act together with IL-4 to regulate ILC2 function. Further, TSLP-elicited and IL-3-elicited basophils display distinct responsiveness and functional potential in response to IL-3, IL-18, or IL-33,⁷³ whereas how the distinct regulation of basophils impacts on ILC2 biology needs to be addressed.

Eosinophils

Eosinophils develop in the bone marrow and migrate to inflammatory foci driven by pro-inflammatory chemokines, such as eotaxin. It is well established that eosinophilia is one of the hallmarks in allergic diseases including asthma.⁷⁴ Lung ILC2-derived IL-5 plays a key role in the activation and recruitment of eosinophils to the airways.⁷⁵ In response to inflammatory stimuli, eosinophils degranulate and release active mediators, such as major basic protein or eosinophil peroxidase, which are critical for eliminating parasites.⁷⁶ Additionally, they also produce type 2 cytokines (such as IL-4 and IL-13),^{77,78} suggesting a role in promoting allergic inflammation.

Although the emergence of numerous eosinophils has become an important parameter of ILC2 activation, recent data showed that eosinophils can also influence ILC2 responses. Depletion of eosinophils in IL-33 or ovalbumin or house dust mite allergen-induced lung inflammation caused a significant reduction of total and activated pulmonary ILC2s,⁷⁹ suggesting a critical role for eosinophils in the maintenance of ILC2s. A recent study found that eosinophil extracellular traps can induce the lung epithelium to produce IL-33 and TSLP, and thereby activated ILC2 responses and increased airway hyperresponsiveness in mice,⁸⁰ suggesting a critical role of eosinophil extracellular traps in reinforcing the type 2 immune responses in severe asthma. In humans, the number of eosinophils with extracellular traps is

positively correlated with ILC2s in severe asthma.⁸⁰ Additionally, as eosinophils are a major source of IL-4, a activator for human ILC2, it is possible that IL-4-producing eosinophils can act on human ILC2s in eosinophil-associated inflammation.⁸¹ Together, these studies have shown that eosinophils and ILC2s engage in reciprocal regulation, and their crosstalk over inflammation remains to be analyzed.

Concluding remarks

The ILC2s are a prominent source of type 2 cytokines in both lymphoid and non-lymphoid organs, and play an essential role in the onset and/or maintenance of allergic inflammation, as well as in eliminating parasites. As ILC2s are tissue-resident cells, it is becoming increasingly evident that regulation of ILC2 responses during allergic inflammation involves a variety of soluble factors, immune cells and non-immune cells. Myeloid cells, with their properties of rapid activation and recruitment, are critical in tuning ILC2 proliferation and function by

releasing soluble mediators or possibly by a cell-cell contact manner in the process of allergic inflammation (Fig. 1). Meanwhile, emerging data also show that ILC2-derived cytokines can act on the migration and activation of myeloid cells, and thereby reinforce the type 2 immune responses in allergic diseases.^{11,12} Defining the complex interactions between myeloid cells and ILC2s during acute and chronic inflammation will greatly advance our understanding of the contributions of the myeloid cell-ILC2 networks in the pathogenesis of allergic diseases. Furthermore, ILC2s can be divided into conventional ILC2s and inflammatory ILC2s induced by IL-33 and IL-25, respectively.^{82,83} Recent studies have also found IL-10-producing ILC2s,⁸⁴ and IL-17-producing ILC2s^{41,85} in allergic airway inflammation. However, whether myeloid cells can affect ILC2 plasticity in health and disease remains to be investigated. Finally, although mouse models are very useful in addressing the relationships between myeloid cells and ILC2s, future investigations on the human myeloid cell-ILC2 regulatory axis may shed new light on critical checkpoints that can be manipulated for treating ILC2-

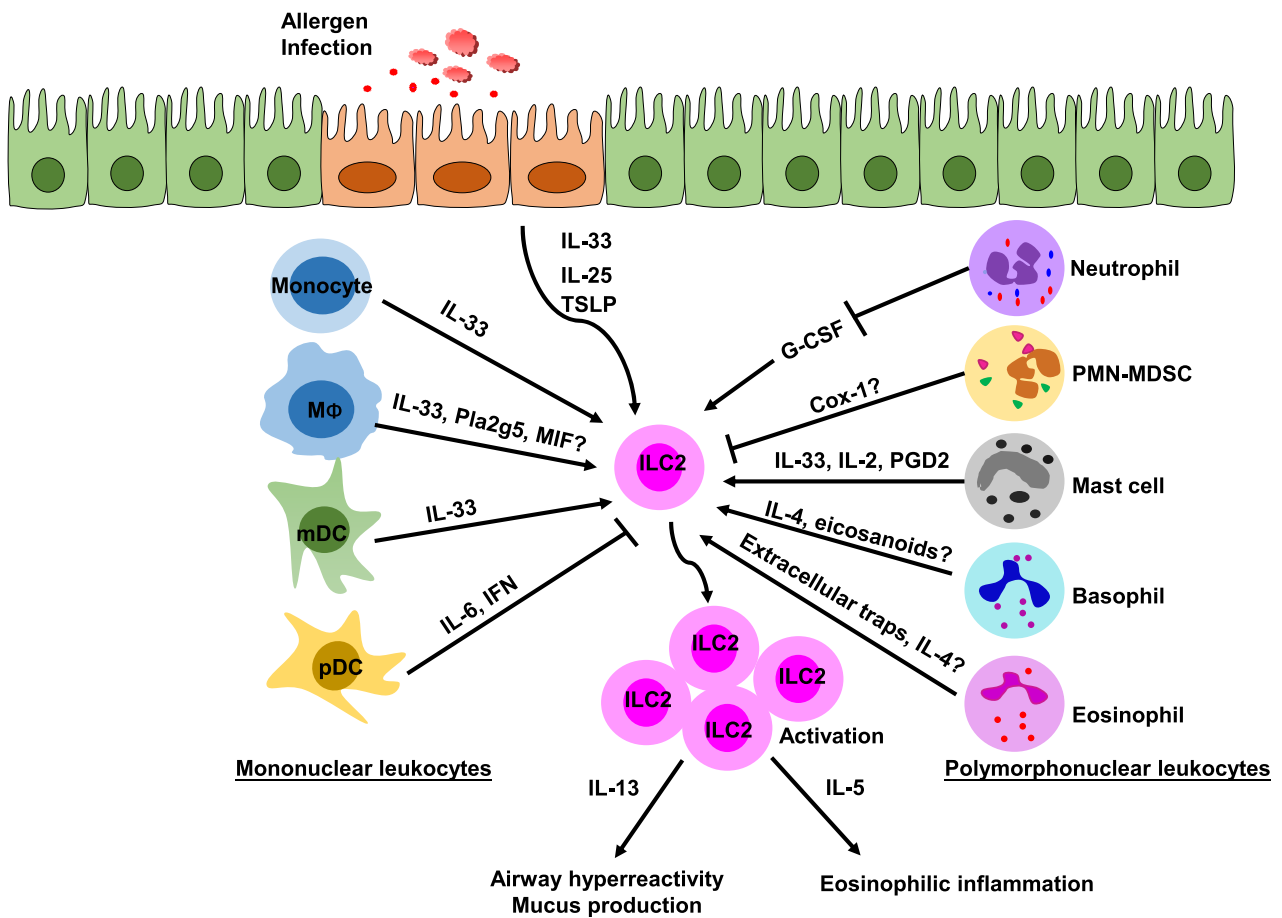


Figure 1. The effect of myeloid cells on the group 2 innate lymphoid cell (ILC2) responses. The role of mononuclear leukocytes (left) and polymorphonuclear leukocytes (right) in the regulation of ILC2s are shown, along with key molecules involved in each. MΦ, macrophage. '?' denotes that the regulation remains to be investigated.

driven allergic inflammation, as well as for improving immunity against helminths.

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Disclosures

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