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Mini Review

Roles of IL-5-producing group 2 innate lymphoid cells in eosinophil regulation

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Group 2 innate lymphoid cells (ILC2s) mediate rapid immune responses against microbial infection by secreting large amounts of T helper type 2 (Th2) cytokines. Exposure to environmental stimuli including parasites, viruses, bacteria and protease allergens, damages epithelial cells, resulting in the secretion of thymic stromal lymphopoietin (TSLP), interleukin (IL)-25 and IL-33. These cytokines are potent inducers of Th2 cytokines from ILC2s. ILC2-produced Th2 cytokines result in the recruitment of eosinophils, mast cells and basophils to inflammatory sites, thus initiating type 2 innate immunity. Immunological information from the innate immunity is then received by Th2 cells, leading to pathogen-specific antibody production and persistent eosinophil activation. Among Th2 cytokines, IL-5 acts particularly on eosinophil regulation. In cooperation with Th2 cells, IL-5-producing ILC2s regulate eosinophil biology in the steady state and innate immunity.

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Discoveries of group 2 innate lymphoid cell

Innate lymphoid cell (ILC) is a newly identified and characterized lymphocyte population that has been described as having a role in mediating acute innate immune reactions. Distinct types of T helper (Th) cells secrete characteristic cytokines to regulate adaptive immunity. Th type 2 (Th2) cells produce Th2 cytokines including interleukin (IL)-4, IL-5 and IL-13 and play roles in antigen-specific antibody production and eosinophil regulation. According to cytokine expression profile of ILCs, they are currently divided into three groups and given names analogous to Th

Table 1 Groups of ILCs and their unique features

Groups	Group 1 ILC	Group 2 ILC	Group 3 ILC
Analogous to	Th1	Th2	Th17
Members	NK cell, ILC1s	ILC2s (NH cell, Nuocyte, Ih2)	LTi cell, ILC3s
Characteristic Cytokines	IFN γ	IL-4, IL-5, IL-9, IL-13	IL-17A, IL-22
Key TFs for development	T-bet	GATA3, ROR α	ROR γ t
Main Functions or Responses involved in	Anti-viral immunity Anti-bacterial immunity Anti-tumor immunity	Anti-parasitic immunity Allergies	Formation of lymphoid organs Anti-bacterial immunity Inflammatory bowel diseases

GATA, GATA-binding protein; IFN, interferon; Ih2, innate type 2 helper; LTi, lymphoid tissue inducer; NH, natural helper; NK, natural killer; ROR, retinoic acid receptor-related orphan receptor; TF, transcription factor

cell subsets[1] (Table 1). Among them, group 2 ILCs (ILC2s) such as natural helper cells and nuocytes are characterized by the production of IL-4, IL-5, IL-9 and IL-13.

Recent advances in our understanding of ILC2s began with several seminal investigations in 2010[2-4]. It had been long believed that the major producers of Th2 cytokines were CD4$^+$ Th2 cells. Prior to 2010, however, several reports suggested the presence of a Th2 cytokine-producing non-B/non-T lymphocyte population in wild type and recombination activating gene (Rag)-deficient mice that had been administered IL-25 or infected with parasites[5-7]. Since 2010, intensive research aimed at characterization, identifying their effector functions and elucidating the hematopoietic development of this lymphocyte population has been conducted[8-11]. This lymphocyte population is now termed ILC2.

IL-5 is the predominant cytokine that regulates eosinophils

Numerous studies have revealed that eosinophil regulation is largely dependent on IL-5[12-14]. IL-5 is produced by many types of cells such as CD4$^+$ Th2 cells, mast cells, eosinophils, basophils and ILC2s. IL-5 is a homodimeric glycoprotein that binds the IL-5 receptor (IL-5R) complex that consists of an IL-5Rα chain, specific for IL-5, and a common β chain. The recently determined crystal structure of IL-5 in complex with IL-5Rα revealed that the IL-5 dimer associates with IL-5R α in a wrench-like structure[15,16]. This IL-5/IL-5R binding rapidly induces tyrosine phosphorylation of several proteins including Janus kinase 1(JAK1), JAK2, signal transducer and activator of transcription 5 (STAT5), phosphoinositide 3-kinse (PI3K) and mitogen-activated protein kinases (MAPKs)[17-20]. Phosphorylation of these molecules is evident in eosinophils[19, 21] and plays critical roles in eosinophil recruitment[22, 23], degranulation[24] and survival[25].

Mice deficient for IL-5 or IL-5Rα display severe defects in eosinophil development and activation[26, 27]. Under allergic conditions or helminth infection, IL-5 is specifically responsible for differentiation and proliferation of eosinophil progenitors in the bone marrow[28, 29], recruiting eosinophils in concert with eotaxin[30-32] and prolonging eosinophil survival in local inflammatory sites[33]. These studies have established that IL-5 significantly determines eosinophil regulation.

Eosinophils are involved in host defense, host homeostasis and disease

Eosinophils are a multitalented leukocyte that possesses opposing roles in health and various diseases[34-36]. Certainly, eosinophils play a protective role against invading pathogens including viruses, bacteria and, especially, parasites. Activation of eosinophils leads to the production of granule proteins, including major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil peroxidase, each of which is toxic to invading microorganisms. In addition to secreting cytotoxic molecules, eosinophils are equipped with a unique weapon against bacteria. IL-5 signaling induces eosinophils to release mitochondrial DNA bound to MBP and ECP to trap and kill bacteria in the gastrointestinal tract[37]. Eosinophils provide defenses against not only exogenous pathogens, but also endogenous abnormal cells, tumors. Priming by Th2 cytokines induces eosinophil influx into tumor-growing sites[38, 39] and IL-5 is potent to enhance antitumor activity of eosinophils[40].

Eosinophils also support adaptive immunity by modulating cytokine production from Th2 cells[41] and presenting antigens to Th2 cells. Antigen-presenting eosinophils migrate into lymph nodes[42-44] where they perform as antigen presenting cells[45-48]. Interestingly, eosinophils are involved in the maintenance of immunoglobulin production. In the bone marrow, eosinophils were shown to produce IL-6 and a proliferation-inducing ligand (APRIL), which have been demonstrated to maintain IgG1 production by plasma cells[49]. Our unpublished data also indicate a role for eosinophils in T cell-independent IgA production in the intestine.

Beyond their many roles in innate and adaptive immunity, homeostatic roles for eosinophils have been suggested in mammary gland development[50], pregnancy[51], and epithelial barrier function[52], although precise mechanisms remain obscure. Thus, eosinophils contribute to homeostasis in our bodies in a variety of ways.

In contrast, inappropriate and prolonged activation of eosinophils is strongly associated with allergic diseases such as asthma. Asthma is characterized by airway type 2 inflammation including eosinophilia and elevated production of Th2 cytokines, airway hyperresponsiveness (AHR), enhanced mucus secretion and airway remodeling. Two kinds of eosinophil-deficient mice, PHIL[53] and ΔdbI-GATA[54], were developed and have been examined to elucidate the contribution of eosinophils in asthma. PHIL mice demonstrated that eosinophils are involved in AHR and mucus secretion[53]. Conversely, ΔdbI-GATA mice exhibited an involvement of eosinophils in airway remodeling but not in AHR and mucus secretion[55]. Although there are some conflicting findings from the two eosinophil-deficient mice, these studies clearly showed crucial roles of eosinophils in asthma development. Eosinophils are also associated with gastrointestinal diseases such as food allergy, allergic colitis, eosinophil esophagitis and inflammatory bowel diseases[56]. In order to manipulate these eosinophil-associated diseases, we must understand the precise mechanisms underlying eosinophil regulation.

Function and characterization of ILC2

ILC2s produce large amounts of IL-5, IL-9 and IL-13, and play pivotal roles in various kinds of immune reactions such as allergic lung inflammation[57], parasitic infection[3, 4, 58], antiviral immunity[59, 60] and obesity[61]. In these reactions, one important role for ILC2s is to recruit and activate effector cells such as eosinophils. ILC2 effector functions are regulated by various cell surface cytokine receptors.

Although ILC2s lack surface lineage markers expressed by the known immune cell populations including T cells, B cells, NK cells, dendritic cells, macrophages, granulocytes and erythrocytes, they do express phenotypic markers including c-kit, Sca-1, Thy1, CD25 (IL-2Rα), IL-7Rα, TSLPR, IL-17BR (IL-25R) and ST2 (a component of IL-33R)[8, 11]. During their hematopoietic development in the bone marrow, ILC2s arise from a common lymphoid progenitor where their development is dependent upon transcription factors, such as inhibitor of DNA binding 2 (Id2)[4, 62], retinoic acid receptor-related orphan receptor-α (RORα)[63] and GATA-binding protein 3 (GATA3)[64, 65]. Using reporter systems targeting IL-5 or IL-13, ILC2s were revealed to localize to many different organs and tissues in the steady state, such as lung, mesenteric lymph nodes, skin, peritoneal cavity,

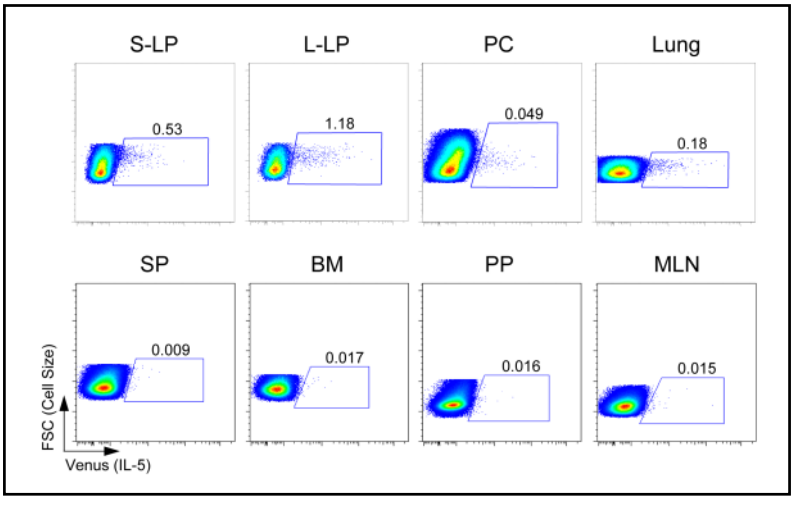

Fig.1 Analysis for IL-5-producing ILC2s in different organs and tissues

Lymphoid cells in IL-5/Venus knock-in (KI) reporter mice[66] were analyzed by flow cytometry. Panels show percentages of gated Venus$^+$ (IL-5-producing) cells with Venus expression and cell size (FSC) in the lamina propria of small intestine (S-LP), large intestine (L-LP), peritoneal cavity (PC), lung, spleen (SP), bone marrow (BM), Peyer's patch (PP) and mesenteric lymph node (MLN). Higher frequencies of IL-5-producing cells are present in the S-LP, L-LP, PC and lung in the steady state.

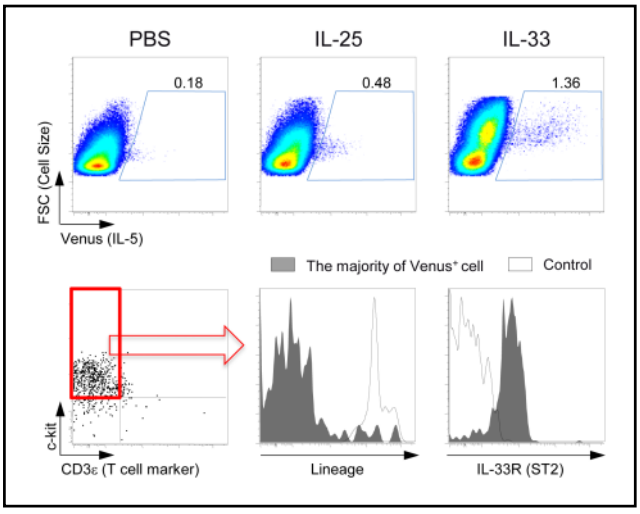

Fig.2 Expansion of lung IL-5-producing ILC2s in response to IL-25 and IL-33

IL-5/Venus KI mice were treated with PBS, recombinant IL-25 or IL-33 for three consecutive days. Upper panels show percentages of gated Venus+ cells. Lower left panel shows c-kit and CD3ε expression on Venus+ cells and the majority of these cells (squared in red) are not positive for lineage markers (lower middle) and express IL-33R (lower right), that is, ILC2s.

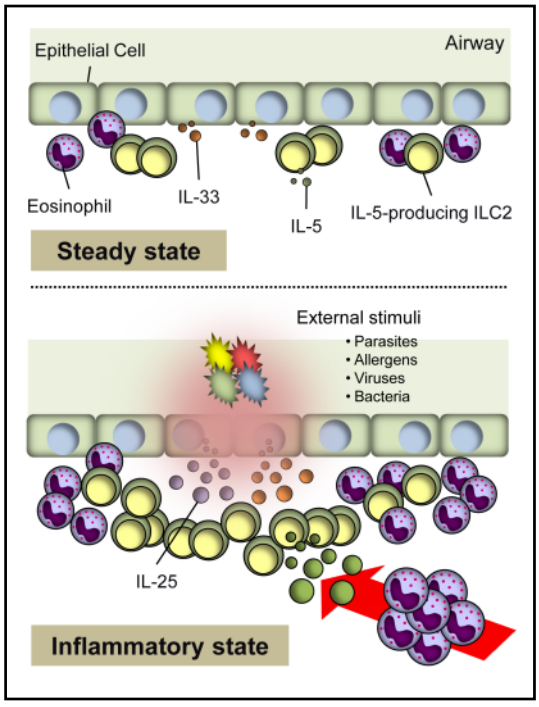

Fig.3 Schematic of lung eosinophil accumulation in the steady state and during inflammation

Basal eosinophil accumulation in the lung is carried out by IL-5-producing ILC2s. ILC2s are thought to be stimulated by IL-33 released spontaneously by epithelial cells. In inflammatory contexts, exogenous pathogenic stimuli induce damage to epithelial cells, leading to secretion of cytokines such as IL-25 and IL-33. Upon stimulation, ILC2s produce a large amount of IL-5 and mediate eosinophilia.

intestine and adipose tissues[2, 3, 61, 66](Fig.1). These findings suggest a role for ILC2s in supporting the homeostatic roles of eosinophils throughout a living body in the steady state.

Cytokines that regulate ILC2 effector functions

External inflammatory stimuli due to invading bacteria, viruses and parasites induce damage to epithelial barriers and result in the release of thymic stromal lymphopoietin (TSLP), IL-25 and IL-33. As indicated by the expression pattern of cytokine receptors on ILC2s, these cytokines stimulate neighboring ILC2s near epithelial cells, leading to the immediate secretion of large quantities of Th2 cytokines (Fig.2). This, in turn, recruits and activates effector cells to expel invading pathogens (Fig.3).

Responsiveness to these cytokines, however, seems to be varied according to the location of the ILC2s. In the lung, IL-33 mediates type 2 inflammation more efficiently than IL-25[66, 67], whereas in the skin TSLP induces ILC2-mediated inflammation independently of IL-33[68]. Moreover, IL-25 was demonstrated to be critical for promoting IL-13 secretion from ILC2 in oxazolone-induced colitis[69]. Precise roles for each of these cytokines as yet remain unclear. Exploring each cytokine's impact on ILC2s in different tissues and organs will inform the development of appropriate therapies for asthma and atopic dermatitis, for example, where the etiologic cytokines appear to be different.

IL-5-producing ILC2s regulate eosinophils in the steady state

A number of studies have now established roles for ILC2s in eosinophil regulation in cases of parasitic infection[3, 4, 58] and allergic reactions[10, 11, 70]. In order to respond immediately to pathogens, eosinophils must be recruited to mucosal surfaces prior to infection. This is likely facilitated by ILC2s as they produce certain levels of Th2 cytokines in the absence of apparent pathogenic stimuli. We investigated the roles of ILC2s in the steady state and revealed that they were important to maintain basal levels of eosinophils in the lung[66]. This likely contributes to eosinophil tumor surveillance[40, 66]. Consistent with our results, IL-5-producing ILC2s have been reported to control circadian

cycling and basal tissue accumulation of eosinophils, and this is regulated through food intake[71]. In the study, the neuropeptide, vasoactive intestinal peptide (VIP), was suggested to be a key molecule for IL-5 production through its receptor, VIP receptor type 2 (VPAC2), on ILC2s.

The regulation of Th2 cytokine production by ILC2s in the steady state still remains largely unknown. IL-33 may play such a role, as living cells are able to secrete IL-33 without necrosis induced by infection or tissue damage[72]. In addition, IL-33 signaling blockade in unprimed mice leads to a significant reduction of eosinophils in the intestine (our unpublished data). These observations suggest a role for IL-33 in inducing the constitutive production of IL-5 from ILC2s, leading to eosinophil recruitment (Fig.3).

Concluding remarks

Research utilizing animal models of human diseases will assist in the characterization of ILC2s in humans[73] and accelerate translational research. Asthma is one of the best-characterized allergic disorders associated with ILC2s and eosinophils, and it may be a candidate for therapies that specifically target ILC2s. Several studies have examined the effects of blockade of IL-25 or IL-33 signaling on asthma development. Anti-IL-25 monoclonal antibodies (mAbs)[74, 75], polyclonal anti-IL-33 antibodies[76] and anti-ST2 mAb[77] all successfully reduced asthmatic symptoms in animal models of asthma. In addition, the specific functions of IL-5 in eosinophil regulation prompted us to employ IL-5 as a therapeutic target specifically for asthma treatment. In clinical trials, targeting IL-5 or IL5Rα has been shown to reduce peripheral and sputum eosinophils, as well as symptomatic exacerbations in severe asthmatic patients with eosinophilia[78]. These results provide a promising foundation for further studying ILC2 as a therapeutic target. Although human clinical studies are warranted, further studies of murine ILC2s will be helpful for better understanding human ILC2s and developing next-generation treatments for allergic diseases.

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Conflict of interests

The authors have no conflicting financial interests.

References

1) Spits H, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, Koyasu S, Locksley RM, McKenzie AN, Mebius RE, Powrie F, Vivier E: Innate lymphoid cells --a proposal for uniform nomenclature. Nat Rev Immunol. 2013; 13: 145-149.
2) Price AE, Liang HE, Sullivan BM, Reinhardt RL, Eisley CJ, Erle DJ, Locksley RM: Systemically dispersed innate IL-13-expressing cells in type 2 immunity. Proc Natl Acad Sci U S A. 2010; 107: 11489-11494.
3) Neill DR, Wong SH, Bellosi A, Flynn RJ, Daly M, Langford TK, Bucks C, Kane CM, Fallon PG, Pannell R, Jolin HE, McKenzie AN: Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. Nature. 2010; 464: 1367-1370.
4) Moro K, Yamada T, Tanabe M, Takeuchi T, Ikawa T, Kawamoto H, Furusawa J, Ohtani M, Fujii H, Koyasu S: Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. Nature. 2010; 463: 540-544.
5) Fort MM, Cheung J, Yen D, Li J, Zurawski SM, Lo S, Menon S, Clifford T, Hunte B, Lesley R, Muchamuel T, Hurst SD, Zurawski G, Leach MW, Gorman DM, Rennick DM: IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies in vivo. Immunity. 2001; 15: 985-995.
6) Hurst SD, Muchamuel T, Gorman DM, Gilbert JM, Clifford T, Kwan S, Menon S, Seymour B, Jackson C, Kung TT, Brieland JK, Zurawski SM, Chapman RW, Zurawski G, Coffman RL: New IL-17 family members promote Th1 or Th2 responses in the lung: in vivo function of the novel cytokine IL-25. J Immunol. 2002; 169: 443-453.
7) Fallon PG, Ballantyne SJ, Mangan NE, Barlow JL, Dasvarma A, Hewett DR, McIlgorm A, Jolin HE, McKenzie AN: Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. J Exp Med. 2006; 203: 1105-1116.
8) Licona-Limon P, Kim LK, Palm NW, Flavell RA: TH2, allergy and group 2 innate lymphoid cells. Nat Immunol. 2013; 14: 536-542.
9) Koyasu S, Moro K: Th2-type innate immune responses mediated by natural helper cells. Ann N Y Acad Sci. 2013; 1283: 43-49.
10) Kim BS, Wojno ED, Artis D: Innate lymphoid cells and

allergic inflammation. Curr Opin Immunol. 2013; 25: 738-744.
11) Pishdadian A, Varasteh AR, Sankian M: Type 2 innate lymphoid cells: friends or foes-role in airway allergic inflammation and asthma. J Allergy (Cairo). 2012; 2012: 130937.
12) Kouro T, Takatsu K: IL-5- and eosinophil-mediated inflammation: from discovery to therapy. Int Immunol. 2009; 21: 1303-1309.
13) Takatsu K, Nakajima H: IL-5 and eosinophilia. Curr Opin Immunol. 2008; 20: 288-294.
14) Takatsu K: Interleukin-5 and IL-5 receptor in health and diseases. Proc Jpn Acad Ser B Phys Biol Sci. 2011; 87: 463-485.
15) Kusano S, Kukimoto-Niino M, Hino N, Ohsawa N, Ikutani M, Takaki S, Sakamoto K, Hara-Yokoyama M, Shirouzu M, Takatsu K, Yokoyama S: Structural basis of interleukin-5 dimer recognition by its alpha receptor. Protein Sci. 2012; 21: 850-864.
16) Patino E, Kotzsch A, Saremba S, Nickel J, Schmitz W, Sebald W, Mueller TD: Structure analysis of the IL-5 ligand-receptor complex reveals a wrench-like architecture for IL-5Ralpha. Structure. 2011; 19: 1864-1875.
17) Ogata N, Kouro T, Yamada A, Koike M, Hanai N, Ishikawa T, Takatsu K: JAK2 and JAK1 constitutively associate with an interleukin-5 (IL-5) receptor alpha and betac subunit, respectively, and are activated upon IL-5 stimulation. Blood. 1998; 91: 2264-2271.
18) Kouro T, Kikuchi Y, Kanazawa H, Hirokawa K, Harada N, Shiiba M, Wakao H, Takaki S, Takatsu K: Critical proline residues of the cytoplasmic domain of the IL-5 receptor alpha chain and its function in IL-5-mediated activation of JAK kinase and STAT5. Int Immunol. 1996; 8: 237-245.
19) Pazdrak K, Schreiber D, Forsythe P, Justement L, Alam R: The intracellular signal transduction mechanism of interleukin 5 in eosinophils: the involvement of lyn tyrosine kinase and the Ras-Raf-1-MEK-microtubule-associated protein kinase pathway. J Exp Med. 1995; 181: 1827-1834.
20) Sato S, Katagiri T, Takaki S, Kikuchi Y, Hitoshi Y, Yonehara S, Tsukada S, Kitamura D, Watanabe T, Witte O, Takatsu K: IL-5 receptor-mediated tyrosine phosphorylation of SH2/SH3-containing proteins and activation of Bruton's tyrosine and Janus 2 kinases. J Exp Med. 1994; 180: 2101-2111.
21) Coffer PJ, Schweizer RC, Dubois GR, Maikoe T, Lammers JW, Koenderman L: Analysis of signal transduction pathways in human eosinophils activated by chemoattractants and the T-helper 2-derived cytokines interleukin-4 and interleukin-5. Blood. 1998; 91: 2547-2557.
22) Sano M, Leff AR, Myou S, Boetticher E, Meliton AY, Learoyd J, Lambertino AT, Munoz NM, Zhu X: Regulation of interleukin-5-induced beta2-integrin adhesion of human eosinophils by phosphoinositide 3-kinase. Am J Respir Cell Mol Biol. 2005; 33: 65-70.
23) Kagami S, Nakajima H, Kumano K, Suzuki K, Suto A, Imada K, Davey HW, Saito Y, Takatsu K, Leonard WJ, Iwamoto I: Both stat5a and stat5b are required for antigen-induced eosinophil and T-cell recruitment into the tissue. Blood. 2000; 95: 1370-1377.
24) Pazdrak K, Olszewska-Pazdrak B, Stafford S, Garofalo RP, Alam R: Lyn, Jak2, and Raf-1 kinases are critical for the antiapoptotic effect of interleukin 5, whereas only Raf-1 kinase is essential for eosinophil activation and degranulation. J Exp Med. 1998; 188: 421-429.
25) Pazdrak K, Adachi T, Alam R: Src homology 2 protein tyrosine phosphatase (SHPTP2)/Src homology 2 phosphatase 2 (SHP2) tyrosine phosphatase is a positive regulator of the interleukin 5 receptor signal transduction pathways leading to the prolongation of eosinophil survival. J Exp Med. 1997; 186: 561-568.
26) Yoshida T, Ikuta K, Sugaya H, Maki K, Takagi M, Kanazawa H, Sunaga S, Kinashi T, Yoshimura K, Miyazaki J, Takaki S, Takatsu K: Defective B-1 cell development and impaired immunity against Angiostrongylus cantonensis in IL-5R alpha-deficient mice. Immunity. 1996; 4: 483-494.
27) Kopf M, Brombacher F, Hodgkin PD, Ramsay AJ, Milbourne EA, Dai WJ, Ovington KS, Behm CA, Kohler G, Young IG, Matthaei KI: IL-5-deficient mice have a developmental defect in CD5+ B-1 cells and lack eosinophilia but have normal antibody and cytotoxic T cell responses. Immunity. 1996; 4: 15-24.
28) Yamaguchi Y, Suda T, Suda J, Eguchi M, Miura Y, Harada N, Tominaga A, Takatsu K. Purified interleukin 5 supports the terminal differentiation and proliferation of murine eosinophilic precursors. J Exp Med. 1988; 167: 43-56.
29) Iwasaki H, Mizuno S, Mayfield R, Shigematsu H, Arinobu Y, Seed B, Gurish MF, Takatsu K, Akashi K:

Identification of eosinophil lineage-committed progenitors in the murine bone marrow. J Exp Med. 2005; 201: 1891-1897.
30) Pope SM, Brandt EB, Mishra A, Hogan SP, Zimmermann N, Matthaei KI, Foster PS, Rothenberg ME: IL-13 induces eosinophil recruitment into the lung by an IL-5- and eotaxin-dependent mechanism. J Allergy Clin Immunol. 2001; 108: 594-601.
31) Mattes J, Foster PS: Regulation of eosinophil migration and Th2 cell function by IL-5 and eotaxin. Curr Drug Targets Inflamm Allergy. 2003; 2: 169-174.
32) Yang M, Hogan SP, Mahalingam S, Pope SM, Zimmermann N, Fulkerson P, Dent LA, Young IG, Matthaei KI, Rothenberg ME, Foster PS: Eotaxin-2 and IL-5 cooperate in the lung to regulate IL-13 production and airway eosinophilia and hyperreactivity. J Allergy Clin Immunol. 2003; 112: 935-943.
33) Simon HU: Molecules involved in the regulation of eosinophil apoptosis. Chem Immunol Allergy. 2006; 91: 49-58.
34) Hogan SP, Rosenberg HF, Moqbel R, Phipps S, Foster PS, Lacy P, Kay AB, Rothenberg ME: Eosinophils: biological properties and role in health and disease. Clin Exp Allergy. 2008; 38: 709-750.
35) Kita H: Eosinophils: multifaceted biological properties and roles in health and disease. Immunol Rev. 2011; 242: 161-177.
36) Rothenberg ME, Hogan SP: The eosinophil. Annu Rev Immunol. 2006; 24: 147-174.
37) Yousefi S, Gold JA, Andina N, Lee JJ, Kelly AM, Kozlowski E, Schmid I, Straumann A, Reichenbach J, Gleich GJ, Simon HU: Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense. Nat Med. 2008; 14: 949-953.
38) Tepper RI, Coffman RL, Leder P: An eosinophil-dependent mechanism for the antitumor effect of interleukin-4. Science. 1992; 257: 548-551.
39) Tepper RI, Pattengale PK, Leder P: Murine interleukin-4 displays potent anti-tumor activity in vivo. Cell. 1989; 57: 503-512.
40) Simson L, Ellyard JI, Dent LA, Matthaei KI, Rothenberg ME, Foster PS, Smyth MJ, Parish CR: Regulation of carcinogenesis by IL-5 and CCL11: a potential role for eosinophils in tumor immune surveillance. J Immunol. 2007; 178: 4222-4229.
41) Mattes J, Yang M, Mahalingam S, Kuehr J, Webb DC, Simson L, Hogan SP, Koskinen A, McKenzie AN, Dent LA, Rothenberg ME, Matthaei KI, Young IG, Foster PS: Intrinsic defect in T cell production of interleukin (IL)-13 in the absence of both IL-5 and eotaxin precludes the development of eosinophilia and airways hyperreactivity in experimental asthma. J Exp Med. 2002; 195: 1433-1444.
42) Shi HZ, Humbles A, Gerard C, Jin Z, Weller PF: Lymph node trafficking and antigen presentation by endobronchial eosinophils. J Clin Invest. 2000; 105: 945-953.
43) van Rijt LS, Vos N, Hijdra D, de Vries VC, Hoogsteden HC, Lambrecht BN: Airway eosinophils accumulate in the mediastinal lymph nodes but lack antigen-presenting potential for naive T cells. J Immunol. 2003; 171: 3372-3378.
44) Duez C, Dakhama A, Tomkinson A, Marquillies P, Balhorn A, Tonnel AB, Bratton DL, Gelfand EW: Migration and accumulation of eosinophils toward regional lymph nodes after airway allergen challenge. J Allergy Clin Immunol. 2004; 114: 820-825.
45) Del Pozo V, De Andres B, Martin E, Cardaba B, Fernandez JC, Gallardo S, Tramon P, Leyva-Cobian F, Palomino P, Lahoz C: Eosinophil as antigen-presenting cell: activation of T cell clones and T cell hybridoma by eosinophils after antigen processing. Eur J Immunol. 1992; 22: 1919-1925.
46) Padigel UM, Lee JJ, Nolan TJ, Schad GA, Abraham D: Eosinophils can function as antigen-presenting cells to induce primary and secondary immune responses to Strongyloides stercoralis. Infect Immun. 2006; 74: 3232-3238.
47) Shi HZ, Xiao CQ, Li CQ, Mo XY, Yang QL, Leng J, Chen YQ: Endobronchial eosinophils preferentially stimulate T helper cell type 2 responses. Allergy. 2004; 59: 428-435.
48) MacKenzie JR, Mattes J, Dent LA, Foster PS: Eosinophils promote allergic disease of the lung by regulating CD4(+) Th2 lymphocyte function. J Immunol. 2001; 167: 3146-3155.
49) Chu VT, Frohlich A, Steinhauser G, Scheel T, Roch T, Fillatreau S, Lee JJ, Lohning M, Berek C: Eosinophils are required for the maintenance of plasma cells in the bone marrow. Nat Immunol. 2011; 12: 151-159.
50) Gouon-Evans V, Rothenberg ME, Pollard JW: Postnatal mammary gland development requires macrophages and eosinophils. Development. 2000; 127: 2269-

2282.
51) Robertson SA, Mau VJ, Hudson SN, Tremellen KP: Cytokine-leukocyte networks and the establishment of pregnancy. Am J Reprod Immunol. 1997; 37: 438-442.
52) Furuta GT, Nieuwenhuis EE, Karhausen J, Gleich G, Blumberg RS, Lee JJ, Ackerman SJ: Eosinophils alter colonic epithelial barrier function: role for major basic protein. Am J Physiol Gastrointest Liver Physiol. 2005; 289: G890-G897.
53) Lee JJ, Dimina D, Macias MP, Ochkur SI, McGarry MP, O'Neill KR, Protheroe C, Pero R, Nguyen T, Cormier SA, Lenkiewicz E, Colbert D, Rinaldi L, Ackerman SJ, Irvin CG, Lee NA: Defining a link with asthma in mice congenitally deficient in eosinophils. Science. 2004; 305: 1773-1776.
54) Yu C, Cantor AB, Yang H, Browne C, Wells RA, Fujiwara Y, Orkin SH: Targeted deletion of a high-affinity GATA-binding site in the GATA-1 promoter leads to selective loss of the eosinophil lineage in vivo. J Exp Med. 2002; 195: 1387-1395.
55) Humbles AA, Lloyd CM, McMillan SJ, Friend DS, Xanthou G, McKenna EE, Ghiran S, Gerard NP, Yu C, Orkin SH, Gerard C: A critical role for eosinophils in allergic airways remodeling. Science. 2004; 305: 1776-1779.
56) Rothenberg ME: Eosinophilic gastrointestinal disorders (EGID). J Allergy Clin Immunol. 2004; 113: 11-28; quiz9.
57) Bartemes KR, Iijima K, Kobayashi T, Kephart GM, McKenzie AN, Kita H: IL-33-responsive lineage- CD25+ CD44(hi) lymphoid cells mediate innate type 2 immunity and allergic inflammation in the lungs. J Immunol. 2012; 188: 1503-1513.
58) Yasuda K, Muto T, Kawagoe T, Matsumoto M, Sasaki Y, Matsushita K, Taki Y, Futatsugi-Yumikura S, Tsutsui H, Ishii KJ, Yoshimoto T, Akira S, Nakanishi K: Contribution of IL-33-activated type II innate lymphoid cells to pulmonary eosinophilia in intestinal nematode-infected mice. Proc Natl Acad Sci U S A. 2012; 109: 3451-3456.
59) Chang YJ, Kim HY, Albacker LA, Baumgarth N, McKenzie AN, Smith DE, Dekruyff RH, Umetsu DT: Innate lymphoid cells mediate influenza-induced airway hyper-reactivity independently of adaptive immunity. Nat Immunol. 2011; 12: 631-638.
60) Monticelli LA, Sonnenberg GF, Abt MC, Alenghat T, Ziegler CG, Doering TA, Angelosanto JM, Laidlaw BJ, Yang CY, Sathaliyawala T, Kubota M, Turner D, Diamond JM, Goldrath AW, Farber DL, Collman RG, Wherry EJ, Artis D: Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus. Nat Immunol. 2011; 12: 1045-1054.
61) Molofsky AB, Nussbaum JC, Liang HE, Van Dyken SJ, Cheng LE, Mohapatra A, Chawla A, Locksley RM: Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. J Exp Med. 2013; 210: 535-549.
62) Yokota Y, Mansouri A, Mori S, Sugawara S, Adachi S, Nishikawa S, Gruss P: Development of peripheral lymphoid organs and natural killer cells depends on the helix-loop-helix inhibitor Id2. Nature. 1999; 397: 702-706.
63) Wong SH, Walker JA, Jolin HE, Drynan LF, Hams E, Camelo A, Barlow JL, Neill DR, Panova V, Koch U, Radtke F, Hardman CS, Hwang YY, Fallon PG, McKenzie AN: Transcription factor RORalpha is critical for nuocyte development. Nat Immunol. 2012; 13: 229-236.
64) Hoyler T, Klose CS, Souabni A, Turqueti-Neves A, Pfeifer D, Rawlins EL, Voehringer D, Busslinger M, Diefenbach A: The transcription factor GATA-3 controls cell fate and maintenance of type 2 innate lymphoid cells. Immunity. 2012; 37: 634-648.
65) Mjosberg J, Bernink J, Golebski K, Karrich JJ, Peters CP, Blom B, te Velde AA, Fokkens WJ, van Drunen CM, Spits H: The transcription factor GATA3 is essential for the function of human type 2 innate lymphoid cells. Immunity. 2012; 37: 649-659.
66) Ikutani M, Yanagibashi T, Ogasawara M, Tsuneyama K, Yamamoto S, Hattori Y, Kouro T, Itakura A, Nagai Y, Takaki S, Takatsu K: Identification of innate IL-5-producing cells and their role in lung eosinophil regulation and antitumor immunity. J Immunol. 2012; 188: 703-713.
67) Barlow JL, Peel S, Fox J, Panova V, Hardman CS, Camelo A, Bucks C, Wu X, Kane CM, Neill DR, Flynn RJ, Sayers I, Hall IP, McKenzie AN: IL-33 is more potent than IL-25 in provoking IL-13-producing nuocytes (type 2 innate lymphoid cells) and airway contraction. J Allergy Clin Immunol. 2013; 132: 933-941.
68) Kim BS, Siracusa MC, Saenz SA, Noti M, Monticelli LA, Sonnenberg GF, Hepworth MR, Van Voorhees AS, Comeau MR, Artis D: TSLP elicits IL-33-independent

innate lymphoid cell responses to promote skin inflammation. Sci Transl Med. 2013; 5: 170ra16.
69) Camelo A, Barlow JL, Drynan LF, Neill DR, Ballantyne SJ, Wong SH, Pannell R, Gao W, Wrigley K, Sprenkle J, McKenzie AN: Blocking IL-25 signalling protects against gut inflammation in a type-2 model of colitis by suppressing nuocyte and NKT derived IL-13. J Gastroenterol. 2012; 47: 1198-1211.
70) Chang YJ, DeKruyff RH, Umetsu DT: The role of type 2 innate lymphoid cells in asthma. J Leukoc Biol. 2013; 94: 933-940.
71) Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, Molofsky AB, Thornton EE, Krummel MF, Chawla A, Liang HE, Locksley RM: Type 2 innate lymphoid cells control eosinophil homeostasis. Nature. 2013; 502: 245-248.
72) Kakkar R, Hei H, Dobner S, Lee RT: Interleukin 33 as a mechanically responsive cytokine secreted by living cells. J Biol Chem. 2012; 287: 6941-6948.
73) Mjosberg JM, Trifari S, Crellin NK, Peters CP, van Drunen CM, Piet B, Fokkens WJ, Cupedo T, Spits H: Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. Nat Immunol. 2011; 12: 1055-1062.
74) Siegle JS, Hansbro N, Dong C, Angkasekwinai P, Foster PS, Kumar RK: Blocking induction of T helper type 2 responses prevents development of disease in a model of childhood asthma. Clin Exp Immunol. 2011; 165: 19-28.
75) Ballantyne SJ, Barlow JL, Jolin HE, Nath P, Williams AS, Chung KF, Sturton G, Wong SH, McKenzie AN: Blocking IL-25 prevents airway hyperresponsiveness in allergic asthma. J Allergy Clin Immunol. 2007; 120: 1324-1331.
76) Liu X, Li M, Wu Y, Zhou Y, Zeng L, Huang T: Anti-IL-33 antibody treatment inhibits airway inflammation in a murine model of allergic asthma. Biochem Biophys Res Commun. 2009; 386: 181-185.
77) Ramaprakash H, Shibata T, Duffy KE, Ismailoglu UB, Bredernitz RM, Moreira AP, Coelho AL, Das AM, Fursov N, Chupp GL, Hogaboam CM: Targeting ST2L potentiates CpG-mediated therapeutic effects in a chronic fungal asthma model. Am J Pathol. 2011; 179: 104-115.
78) Garcia G, Taille C, Laveneziana P, Bourdin A, Chanez P, Humbert M: Anti-interleukin-5 therapy in severe asthma. Eur Respir Rev. 2013; 22: 251-257.