Basophils and Eosinophils in Nematode Infections

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Introduction

Helminths remain one of the most prolific pathogens in the world. Following infection, helminths interact with various epithelial cell surfaces, including skin, lung, and gut. Recent works have shown that epithelial cells produce a series of cytokines such as TSLP, IL-33, and IL-25 that lead to the induction of innate and acquired type 2 immune responses, which we named Type 2 epithelial cytokines. Although basophils and eosinophils are relatively rare granulocytes under normal conditions (0.5% and 5% in peripheral blood, respectively), both are found with increased frequency in type 2 immunity, including allergy and helminth infections. Recent reports showed that basophils and eosinophils not only express effector functions in type 2 immune reactions, but also manipulate the response toward helminths. Furthermore, basophils and eosinophils play non-redundant roles in distinct responses against various nematodes, providing the potential to intervene at different stages of nematode infection. These findings would be helpful to establish vaccination or therapeutic drugs against nematode infections.

Keywords: helminth, nematode, allergy, basophil, eosinophil, Th2, type 2 immunity, Type 2 epithelial cytokines

INTRODUCTION

Basophils and eosinophils, first described by Paul Ehrlich in 1879, are granulocytes (1, 2). Basophils and eosinophils are relatively rare when compared to other leukocytes. Basophils and eosinophils predominantly exist at most 0.5% and 5%, respectively, in peripheral blood under normal conditions, and have short half-lives when compared to lymphocytes. Intriguingly, basophils and eosinophils are evolutionally conserved in many animal species, suggesting their crucial and beneficial roles in vivo.

Basophils share some features with tissue-resident mast cells, which are abundant in peripheral tissues and long-lived cells. Basophils and mast cells are characterized by the expression of basophilic granules, surface expression of FcεRI, a high affinity IgE receptor, and release of chemical mediators (i.e., histamine) in response to cross-linking of surface IgE binding to FcεRI by antigens. Eosinophils have eosinophilic granules that contain eosinophil peroxidase (EPO), major basic protein, ribonulease cationic protein and eosinophil-derived neurotoxin, which are associated with allergic disorders and protection against parasites. In addition, Interleukin-5 receptor subunit-α on eosinophils define their unique biology in response to IL-5 produced by ILC2 and memory Th2 cells. Despite rarities of basophils and eosinophils in homeostatic conditions, basophils and eosinophils are found with increased their frequencies in peripheral tissues and play nonredundant roles in type 2 immune responses such as allergic inflammation and helminth infections. In the past 15 years, several works using deficient mice and specific-Cre mice.

Open Access

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Microbial Immunology, a section of the journal Frontiers in Immunology

Received: 15 July 2020
Accepted: 23 October 2020
Published: 27 November 2020

Citation:
Obata-Ninomiya K, Domeier P and Ziegler SF (2020) Basophils and Eosinophils in Nematode Infections. Front. Immunol. 11:583824, doi: 10.3389/fimmu.2020.583824
for basophils or eosinophils characterized the indispensable roles of basophils and eosinophils in pathophysiology. In this review, we summarize the latest research on the pivotal and nonredundant roles of basophils and eosinophils in nematode infection. This review would be helpful to establish vaccination or therapeutic drugs against nematode infections.

DEVELOPMENT OF BASOPHILS AND EOSINOPHILS

Granulocytes develop from pluripotent CD34+ granulocyte progenitor (GP) cells in bone marrow through granulocyte/monoocyte progenitors (GMPs). GMPs derive the eosinophil lineage-committed progenitors (EoPs), and pre-basophil and mast cell progenitors (pre-BMPs and BMCPs) in bone marrow and the basophil/mast cell progenitors (BMCps) in spleen. The pre-BMPs and BMCPs give rise to the mast cell progenitors (MCPs) and the basophil progenitors (BaPs) (3, 4). Controversially, Mukai et al. mentioned that BMCPs developed into mast cells, and not into basophils (5). The differentiation of basophils is regulated by Signal transducer and activator of transcription 5 (STAT5), the transcription factor distal promoter-derived Runx-related transcription factor 1 (Runx1), Interferon Regulatory factor 8 (IRF8), GATA binding protein 1 (GATA-1), GATA-2, and CCAAT/Enhancer Binding Protein α (C/EBPα) (5–10). STAT5 signaling is required for the differentiation of pre-BMPs into both basophils and mast cells through induction of GATA2, C/EBPα, and Microphthalmia-Associated Transcription Factor (MITF) that is important for differentiation of mast cells. Runx1-deficient mice exhibit a reduction of BaPs and basophils. Expression of IRF8 in GPs that seemingly develop from GMP to give rise to pre-BMP and BMCPs, is important for development of basophils upstream of GATA-2. The differentiation of eosinophils is regulated by GATA binding protein 1 (GATA-1), PU.1, and the CCAAT-enhancing binding protein (c/EBP) family of transcription factors. GATA-1 and PU.1 synergistically promote transcription of major basic protein (MBP). The absence of both MBP and EPO resulted in near complete loss of eosinophils in vivo (11).

GATA-1 reprograms immature myeloid cells to develop three different hematopoietic progenitor lineages: erythroid cells, megakaryocytes and granulocytes. GATA-1 is essential for maturation of erythroid and megakaryocyte precursors and positive autoregulation of GATA-1 expression is mediated by high affinity palindromic GATA-binding sites in the GATA-1 promoter (12, 13). Deletion of these GATA-binding sites in mice (called ΔdblGATA mice) results in a complete ablation of mature eosinophils (14). ΔdblGATA mice exhibit normal platelet development, and red blood cell production is only subtly impaired, but GATA-1 null mice have an embryonic lethal phenotype, with profound anemia and defective megakaryocyte development. As a result of these findings, ΔdblGATA mice were used as model of “eosinophil-deficient” mice, but later studies have defined additional roles for GATA-1 in the development of basophils and mast cells (15). GATA-1 expression is involved in the development and activity of megakaryocyte/erythrocye progenitors, basophil/mast cell progenitors, basophil progenitors, mast cell progenitors and eosinophil progenitors but not granulocyte/monocyte progenitors (16–19). More recent studies have shown that ΔdblGATA mice exhibit additional defects in the generation of basophil precursor cells (BaP) and mature basophils (3, 20). Furthermore, basophils that do develop in ΔdblGATA mice have impaired IL-4 production and CD63 expression after cross-linking of antigen-specific IgE. Knockdown of GATA-1 in basophils in vitro resulted in defective basophil development, reduced degranulation and lower production of IL-4 in response to antigen stimulation. These suggested that defects in basophils of ΔdblGATA mice are due to decreased expression of GATA-1. In contrast to basophils, mast cell development in ΔdblGATA mice is not overtly impacted (21, 22). Similar to this, GATA-1-deletion does not affect development of mast cells in vivo and in vitro (23, 24). Collectively, ΔdblGATA mice showed developmental and functional impairments in basophils and eosinophils. In addition, the transcription factor GATA-1 controls both basophils and eosinophils.

BASOPHILS

Basophilia in Parasite Infection

Although basophils make up a small proportion (<0.5%) of leukocytes in the blood, they accumulate in peripheral tissues during type 2 inflammation. Infiltration of basophils is observed in local lesions after helminth infection, and allergic skin diseases, implying that they may play important roles in supporting the inflammation (25, 26). Similar to allergic diseases, basophils accumulate in skin lesions of humans and mice after infestation with ectoparasites (27–29). However, unlike mice, blood basophilia rarely occurs in humans following nematode infections (30).

CD4+ T cell-derived IL-3 is critical for the survival and proliferation of basophils during a nematode infection (31). IL-3 activates basophils to produce IL-4 through IL-3Rα and FcRγ chain complex (32). Thymic stromal lymphopoietin (TSLP) induced by helminth infection, supports basophil proliferation and promotes induction of Th2 cytokine responses in Trichinella infection (33). During Heligmosomoides polygyrus (Hp) infection, IL-3, IgG1, and IgE selectively promote basophil expansion (34). IgE signaling promotes IL-3Rα chain expression on basophils (35). The factors that drive basophil expansion downstream of the IgE/FcɛRI axis are still unknown. In mast cells, IgE induces survival via binding to FcɛRI on mast cells by signaling through Bcl-1, a Bcl-2 family protein. However, the IgE/FcɛRI/Bcl-1 axis apparently is not operative in human basophils (36, 37).

Basophils and Type 2 Epithelial Cytokines

TSLP, IL-33, and IL-25 are predominantly produced from barrier epithelial cells to initiate type 2 immune responses, including eosinophilia. Thus, they are referred to as Type 2 epithelial cytokines.
Basophils express receptors for TSLP and IL-33 (38). TSLP activates basophils to produce IL-4, resulted in establishment of Th2 cell-dependent immunity (38). IL-33 activates basophils and mast cells to enhance the degranulation and production of cytokines such as IL-4, IL-6, and IL-13 (39). IL-33-mediated mast cells to enhance the degranulation and production of Th2 cell-dependent immunity (38). IL-33 activates basophils and activates basophils to produce IL-4, resulted in establishment of basophil activation has been discussed in atopic dermatitis (40).

The role of basophils in TSLP-dependent inflammation has been studied well, using topical vitamin D3 analog (MC903)-induced model of atopic dermatitis. Basophil-specific IL-4-deficient mice (IL-4 3 UTR mice) exhibit impaired ear swelling, reduced levels of antigen-specific serum IgE and diminished production of type 2 cytokines in lymph nodes after topical MC903 treatment (21). In addition, TSLP-stimulated basophils enhance ILC2 responses through production of IL-4, resulting in skin inflammation (45). However, basophil-specific TSLPR-deficiency by bone marrow chimera does not confer protection from cutaneous inflammation or limit serum IgE titers after topical MC903 treatment (46). Furthermore, Basophil-specific TSLPR-deficiency in Mcpt8creTslprfl/fl mice, did not impair the severity of the airway inflammation, generation of Th2 cells or levels of serum IgE when compared to control mice after intranasal challenges of antigen with MC903, suggesting that this type 2 inflammatory response was mediated by TSLPR on DC and CD4+ T cells, but not basophils and ILC2 cells (47).

**Basophils and Th2 Differentiation in Helminth Infection**

Basophils promote Th2 cell differentiation through IL-4 production during Trichinella spiraris (Ts), Heligmosomoides polygyrus (Hp) and Litomosoides sigmodontis Filaria infections (33, 48, 49). Giacomin et al. showed that deficiency of TSLPR, but not IL-3R, impaired basophilia in draining lymph nodes during Ts infection, which is associated with reduction of Th2 cells. Also, Th2 cell-mediated immune responses are important for expulsion of Hp parasites during re-infection (50).

Naïve CD4+ T cells require the interaction with peptide-loaded MHC class II (MHC-II) complexes on antigen presenting cells (APCs) to differentiate into Th2 cells, so Th2-differentiation could be primed by basophils. Pioneering work by Hida et al. showed that basophils produce IL-4 to support APCs, and promote Th2 cell differentiation (51). This finding was supported by follow-up studies from other research groups (52, 53). Later, three independent groups observed that basophils express MHC-II and secrete IL-4 to induce the differentiation of naïve CD4+ T cells to Th2 cells. Furthermore, depletion of basophils by anti-FcεRIα antibody (clone MAR-1) diminished Th2 cell differentiation in vivo. These findings suggest that basophils are professional APCs that express peptide-loaded MHC-II, induce Th2 differentiation in a cysteine protease papain-administration model, IgE and antigen-induced model and Trichuris muris (Tm) in primary infection (54–56).

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Basophils are important for the expulsion of Tm from the cecum in primary infection. In the Tm model of helminth infection, Webb LM et al. showed that basophil localization to the caecum, but not the spleen, is regulated by Notch expression (63). Thus, Notch signaling in basophils is critical to induction of type 2 immune responses, including Th2 cell generation, RELM-β expression in cecum and resulting Tm clearance.

Recently, it has been reported that basophils can inhibit the type 2 immune responses via increase of expression of neuromedin B (NMB) receptors in ILC2 cells in primary infection of Nb, suggesting that basophils are not always inducer or enhancer of Type 2 immune responses (64).

**Basophils and M2-Type Macrophages in Helminth Infection**

M2-type macrophages play key roles in regulating allergy and confer protective roles against helminths (50, 65–67). M2-type macrophages also protect against fatal lung damage in primary Nb infection (68).

Basophil depletion by Thy1.2 or CD200R3 antibody correlates with increased worm burden after re-infection with Nippostrongylus brasiliensis (Nb) (69–71) (Figure 1 and Table 1), and this protection is mediated by basophil-derived type 2 cytokines (72). During Nb infection, cross-linking of Nb antigen-specific IgE promotes basophil activation and IL-4 production. Basophil-derived IL-4 promotes M2-type macrophage differentiation, and the production of anti-parasitic enzyme Arginase-1 to protect against.
secondary Nb infection in the skin (73). Similar to this, Depletion of macrophages expressing Relma that is a marker of M2-type macrophages increased worm burden in the lungs and gut (68). Conversely, basophil-deiciency did not affect the protection against a secondary subcutaneous inoculation of *Strongyloides venezuelensis* (Sv) or *Strongyloides ratti* (Sr), which originally penetrate skin to infect the hosts by a mechanism that is similar to Nb (74–76) (Table 2).

### TABLE 1 | The experimental models of nematode infections.

| Helminth                  | Infection stage | Natural Route of infection | Route of Experimental inoculation | Characteristics of Infection                                                                 | Model for infection in human (infection route) |
|---------------------------|----------------|---------------------------|----------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------|
| *Nippostrongylus brasiliensis* | L3 larvae      | Skin penetration          | i.d., s.c.                        | Naturally penetrate the skin and migrate to the lungs. Parasites then migrate to the gut to lay eggs. Short-lived infection. | Ascaris lumbricoides (Oral ingestion), Hookworms; Necator americanus (Oral ingestion), Ancylostoma duodenale (Oral ingestion or skin penetration), Strongyloides stercolaris (Skin penetration) |
| *Strongyloides venezuelensis* | L3 larvae      | Skin penetration          | s.c.                             | Chronic infection from ingestion of larvae                                                    | Trichinella spiralis (Oral ingestion)         |
| *Strongyloides ratti*      | L3 larvae      | Oral ingestion            | p.o.                             | Food-borne (infective juvenile), zoonotic parasite                                            | Trichuris trichiura (Oral ingestion)          |
| *Heligmosomoides polygyrus* | L3 larvae      | Oral ingestion            | p.o.                             | Ingestion of infectious eggs that hatch in the ocum and colon                                  | Human filarial diseases; Brugia malayi, Brugia timori, Wuchereria bancrofti, Onchocerca volvulus, Loa loba |
| *Trichinella spiralis*     | L1 larvae      | Oral ingestion            | p.o.                             | Adult worms inhabit the pleural cavity                                                        |                                               |
| *Trichuris muris*          | Eggs           | Oral ingestion            | p.o.                             | Chronic infection                                                                            |                                               |
| *Litomosoides sigmodontis* | L3 larvae      | mite                      | s.c., mite                        |                                               |                                               |
| *Brugia pahangi*           | L3 larvae      | mosquito                  | s.c.                             |                                               |                                               |
M2-type macrophages also provide protection against secondary infection of *Heligmosomoides polygyrus* (Hp), but M2-type macrophage differentiation during Hp infection is induced by IL-4 from CD4+ T cells in small intestine (50). However, the expression of FcR, IL-4 and IL-13 on basophils is required for Th2 cell priming, downstream M2-type macrophage differentiation and Hp worm clearance (48). Taken together, after surface-bound IgE is cross-linked by helminth-derived antigens, basophils produce IL-4 and IL-13 to induce M2-type macrophage differentiation, resulting in expulsion of Nb and Hp from the skin and small intestine.

Non-basophils can also produce type 2 cytokines to induce M2-type macrophages in protection against Nb re-infection in the lungs (67, 82). As described by Chen et al. neutrophils in Nb-infected mice upregulated IL-13 transcripts in secondary infection, suggesting that neutrophils could promote M2-type macrophage activation in the lungs to clear Nb parasites (67). Conversely, another study showed that ILC2 and Th2 cells, but not neutrophils, could potentially induce M2-type macrophage activation to kill Nb at the lung during secondary infection (82).

**Basophil-Derived Proteases**

Basophil-derived proteases, including serine protease mouse mast cell protease-8 (mMCP-8), and tryptase mMCP-11, play an important role in promoting skin inflammation (83, 84). The mMCP-11 increases vascular permeability, allowing for increased migration of basophils, eosinophils, macrophages and neutrophils. Intriguingly, mMCP-11-deficiency ameliorates IgE-mediated chronic allergic inflammation in the skin. Furthermore, intradermal administration of mMCP-8, induces the production of Cxcl1, Ccl2, and Ccl24, which recruit neutrophils, monocytes, and eosinophils into the lesion. Similar to atopic dermatitis, Nb re-infection is characterized by increased numbers of neutrophils, macrophages, eosinophils and basophils in the skin lesion and high titer of IgE in the serum. However, the role of these proteases in anti-helminth immunity is not yet known.

Basophils are involved in resistance against both *Strongyloides venezuelensis* (Sv) and *Strongyloides ratti* (Sr) in primary infection (75, 76). The contributions of basophils in induction and expansion of Th2 cells are negligible, although those parasites are expelled by type 2 immune responses from small intestine. It might be possible that basophil-specific molecules such as mMCP-8 and mMCP-11 are associated with the protection against these nematodes.

**EOSINOPHIL**

Eosinophils make up about 5% of leukocytes in peripheral blood, and have a short half-life in circulation. However, the number of circulating eosinophils are increased in patients with allergic diseases and helminth infections. Eosinophil granules contain major basic protein, eosinophil cationic protein, eosinophilic peroxidase and eosinophil-derived neurotoxin.

Approximately, 7–10% of the total protein content of human eosinophils consists of galectin-10, while mice do not contain a functional galectin-10 gene (85, 86). Upon Eosinophil activation, secreted galectin-10 protein forms aggregates, called Charcot-Leyden crystals, at sites of inflammation. Charcot-Leyden crystals were first described as extracellular bipyramidal crystals in the airways of patients with asthma in 1853 by Charcot, and this observation was confirmed by Leyden in 1872. However, the link between Charcot-Leyden crystals and eosinophilic airway disease and/or mucus production was largely forgotten for over 100 years. Recent work from Persson et al. showed that intratracheal administration of galectin-10 promoted the infiltration of neutrophils and monocytes, and Th2 cell priming (87).

GM-CSF, IL-3, and IL-5 accelerate the growth, maturation, survival, and activation of eosinophils. GM-CSF-deficient mice exhibit impaired recruitment of eosinophils to airways in a model of allergic airway. IL-5 deficiency is correlated with a 2- to 3-fold reduction in B-1 cells and eosinophils as compared control mice. However, the eosinophils that did develop in IL-5-deficient mice were morphologically similar to eosinophils in

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**TABLE 2** | The role of basophils and eosinophils in nematode infections.

| Helminth                  | The role of Basophils                                                                 | The role of eosinophils                                                                 | Reference |
|---------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------|
| *Nippostrongylus brasiliensis* | Basophils protect from re-infection in the skin.                                    | - CXCR6*ST2*+ Th2 cells facilitate eosinophilia in the lungs to reduce the fecundity in the lungs in re-infection. | (73)      |
| *Strongyloides venezuelensis* | Basophil-depletion in Mcpt8DTR mice revealed minor contribution of basophils in primary infection and minor or no roles in secondary infection. | - The duration of Sv was increased in ΔdblGATA mice in primary infection (unpublished data) | (77)      |
| *Strongyloides ratti*    | - The number of intestinal nematodes and faecal eggs is elevated in Mcpt8-Cre mice. | - IL-5 deficiency increased the number of intestinal worms and faecal eggs.          | (75)      |
| *Heligmosomoides polygyrus* | Mcpt8-Cre mice have a high number of eggs in feces during re-infection.             | - The fecundity of Hp was increased in ΔdblGATA and PHIL mice during re-infection.   | (79)      |
| *Trichinella spiralis*   | - Th2 immune response is reduced in Bas-TRECK mice.                                 | - Eosinophils increased the survival of muscle larvae                                | (76)      |
| *Trichuris muris*        | - Basophil depletion via MAR-1 treatment increases the number of Th2 cells and impairs Tm expulsion. | - Eosinophil depletion by anti-IL-5 Ab treatment does not change worm expulsion.    | (78)      |

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control mice, but IL-5–deficient mice failed to develop blood and tissue eosinophilia in response to helminth infection (88). IL-5 transgenic (IL-5tg) mice overexpressing IL-5 in homeostatic condition have elevated numbers of circulating eosinophils, neutrophils, lymphocytes and monocytes (89).

Eosinophils and Type 2 Epithelial Cytokines

Type 2 epithelial cytokines activate ILC2 and Th2 cells to produce IL-5 and IL-13, leading to eosinophil infiltration in allergic inflammation and helminth infection (77, 90, 91).

It has been reported that eosinophils express own receptors for Type 2 epithelial cytokines. Human eosinophils express functional TSLP receptor components: TSLPR and IL-7Rα. TSLP up-regulates the expression of adhesion molecule CD18 and intercellular adhesion molecule-1, while down-regulating L-selectin, resulting in increased migration by eosinophils to promote tissue eosinophilia (92). TSLP also induces eosinophil degranulation and the release of eosinophil extracellular traps to capture extracellular bacteria (93). Although TSLP supports the survival of various leukocytes including T cells and non-hematopoietic cells, the role of TSLP in maintaining eosinophil survival is controversial (94–96). Two studies examined the role of TSLP in survival of eosinophils; one reported that enhanced survival of eosinophils, the other did not report a notable change in eosinophil survival (97, 98). These results suggest that eosinophils are involved in pathogen defense when TSLP production is triggered by environmental factors. Furthermore, Tuft cells located in mucosal epithelial layer predominantly produce IL-25 to activate ILC2 cells (99). Tuft cells monitor the microbial metabolite succinate to initiate type 2 inflammation including tuft cell and goblet cell hyperplasia, and eosinophilia (100).

Eosinophil in the Skin in Helminth Infections

Eosinophilia in the skin occurs during re-infection with Nippostrongylus brasiliensis (Nb), while ΔdblGATA mice lacking eosinophils are susceptible to re-infection of Nb. Thus, eosinophils are believed to play an important role in providing protection during Nb re-infection (101, 102). As we mentioned above, since ΔdblGATA mice display numerical and functional aberrancy in basophils, adoptive transfer of wild-type basophils into ΔdblGATA mice confers the protective immunity against Nb in the skin in re-infection (20). Antibody-mediated depletion of eosinophils, with a combination of anti-IL-5 and anti-Siglec-F antibodies does not change the duration of primary Nb infection, but eosinophils are required to stall parasite maturation in the lung during re-infection with Nb (77, 108). Adoptive transfer of CXCR6+ST2+ memory Th2 cells from Nb-sensitized mice conferred resistance to Nb in the lungs of recipient mice. IL-5 is also required to induce major basic protein (MBP) secretion by eosinophils (77). Adoptive transfer of eosinophils, but not MBP-depleted eosinophils, into the lungs inhibited Nb maturation. MBP expression in eosinophils is also required for eosinophils to kill Strongyloides stercoralis (Ss) parasites in implanted cell-impermeable diffusion chambers (109). Collectively, these findings suggest that eosinophils protect from Nb re-infection in the lungs but not skin, and that MBP produced by eosinophils is required for protection against Nb and Ss.

IL-5 transgenic (IL-5tg) mice overexpressing IL-5 in homeostatic condition have elevated numbers of circulating eosinophils, neutrophils, lymphocytes and monocytes (89). Since IL-5tg mice exhibit a pronounced elevation of eosinophils, they are classically used to model chronic eosinophilia in mice. IL-5tg are highly responsive to several helminth infections, including Nb and Ss (109, 110). Adoptive transfer of eosinophils from IL-5tg mice conferred the protection against Nb. These imply that high levels of IL-5 confer the capacity to protect from Nb infection to eosinophils (111). In the same context, Yasuda et al. demonstrated that Ss infection prior to Nb infection caused mice to acquire a highly responsive “trained” phenotype. This trained phenotype was associated with a reduction in the number of Nb larvae in the lungs as a result of an enhanced accumulation of ILC2 cells that produced IL-5 and IL-13 to promote pulmonary eosinophilia (107).

BASOPHILS, EOSINOPHILS, AND ANTIBODY PRODUCTION DURING HELMINTH INFECTION

B cells are required for protection from various infections of nematodes including Strongyloides venezuelensis, Nippostrongylus brasiliensis (Nb), Trichurus muris and Heligmosomoides polygyrus (48, 73, 74, 112), and both basophils and eosinophils are crucial for the production and maintenance of parasite-specific antibodies during Trichinella spiraris infection (49, 80). Early evidence suggests that basophils, CD4+ T cells and B cells provide interconnecting roles in the response to parasitic infection,
but the mechanisms that coordinate these cells remain poorly understood.

Activated basophils express CD40 ligand and secrete IL-4 and IL-13, which are required for IgE class-switching and production during parasitic infection. However, this basophils activation is predominantly mediated by FcεRI cross-linking, suggesting that the capacity for basophils to activate B cell class-switch recombination occurs after the initial priming of parasite-specific B cells. Alternatively, after co-culture with basophils, CD4+ T cells exhibit an augmented capacity to induce IgE class-switching in B cells, so basophils could also prime IgE responses through a CD4+ T cell intermediate. After class-switching, basophils support the survival of plasma cells and memory B cells through the production of IL-4 and IL-6 in the spleen and bone marrow, and eosinophils support the survival of plasma cells in the bone marrow through the secretion of IL-6 and APRIL.

IgE production relies on IL-4 production by follicular helper cells (Tfh) and CD40 ligand and secretes IL-4 and IL-13, which are required for IgE class-switching and production during parasitic infection. However, this basophils activation is predominantly mediated by FcεRI cross-linking, suggesting that the capacity for basophils to activate B cell class-switch recombination occurs after the initial priming of parasite-specific B cells. Alternatively, after co-culture with basophils, CD4+ T cells exhibit an augmented capacity to induce IgE class-switching in B cells, so basophils could also prime IgE responses through a CD4+ T cell intermediate. After class-switching, basophils support the survival of plasma cells and memory B cells through the production of IL-4 and IL-6 in the spleen and bone marrow, and eosinophils support the survival of plasma cells in the bone marrow through the secretion of IL-6 and APRIL.

Collectively, basophils and eosinophils have the potential to contribute to the generation of IgE specific for helminth and helminth-derived antigens, and in turn, these antibodies coat FcεRI on basophils to arm them for rapid activation during re-infection of the helminth.

**VACCINATION AGAINST HELMINTH**

*Litomosoides sigmodontis* (Ls) is a filarial nematode parasite that is used as a model of filarial diseases. The parasites are inoculated or transmitted through the skin barrier by mites, and they inhabit the pleural cavity after developing into adult worms. When irradiated parasites are injected into mice as a method of vaccination, protective immunity against Ls larvae is induced in a basophil-dependent manner, but basophils are dispensable as effector cells against live Ls (128). Vaccination of mice with *Heligmosomoides polygyrus* (Hp)-excretory secretory products confers the resistance against Hp larvae, but protective immunity depends on neutrophils, but not eosinophils, basophils or mast cells. However, basophils (but not eosinophils) do contribute to the
worn expulsed during secondary re-infection with Hp (48, 79, 129). Killing trapped parasites in the small intestine is partially dependent on eosinophils.

The adjuvant effects of TNF-α have been well documented. Mast cells produced TNF-α to orchestrate the recruitment of T cells and dendritic cells into draining lymph nodes in Escherichia coli or Klebsiella pneumoniae infections (130). Other studies showed that TNF-α and synthetic granules mimicking granules of mast cells can be used for vaccination (131). Recently, Piliponsky AM et al. published that basophil-derived TNF-α enhanced survival in a sepsis in mice (132). Together with this, it could be possible to use basophils as one of the primary targets for vaccination as the adjuvant function.

CONCLUSION

Here, we summarized the roles of basophils and eosinophils in nematode infections. We also showed that granulocytes are stringently controlled by type 2 epithelial cytokines, and control type 2 immune responses by promoting Th2 cell differentiation and antibody production. Recent findings demonstrate that basophils and eosinophils are key players in protective immune responses against helminths. Although basophils and eosinophils are not primarily associated with directly killing nematodes during primary infection, these cells hinder parasite burden during reinfection by enacting the rapid deployment of type 2 immune responses. In response to nematode parasite re-infection, basophils are armed with IgE specific for nematodes or their products and accumulate in the peripheral tissues. After antigen stimulation, basophils secrete IL-4 to induce M2-type macrophages, and proteases to rapidly recruit monocytes, neutrophils, and eosinophils to the infection site. In response to IL-5, eosinophils are activated to a “trained” phenotype and produce major basic protein (MBP) to kill nematodes. On the other hand, eosinophils can also support nematode survival and tissue repair during the resolving phase. Further studies are necessary to fully characterize how basophils and eosinophils coordinate their cell-specific responses to expel nematodes. However, therapeutic targeting of basophils and eosinophils or their products could be crucial for developing novel therapeutic interventions against nematode infections.

AUTHOR CONTRIBUTIONS

KO-N, PPD and SFZ wrote the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

Support for this work was provided by NIH grants AI068731, AI125378, AI124220, and HL098067 to SFZ.

ACKNOWLEDGMENTS

We thank Y. Kurashima, K. Miyake, H. Tsutsui, and M. Iki for helpful discussion.

REFERENCES

1. Karasuyama H, Mukai K, Obata K, Tsujimura Y, Wada T. Nonredundant roles of basophils in immunity. Annu Rev Immunol (2011) 29:45–69. doi: 10.1146/annurev-immunol-031210-101257
2. Blanchard C, Rothenberg ME. Biology of the eosinophil. Adv Immunol (2009) 101:81–121. doi: 10.1016/S0065-2776(08)01003-1
3. Arinobu Y, Iwasaki H, Gurish MF, Mizuno S, Shigematsu H, Ozawa H, et al. Developmental checkpoints of the basophil/mast cell lineages in adult murine hematopoiesis. Proc Natl Acad Sci U S A (2005) 102(50):18105–10. doi: 10.1073/pnas.0509148102
4. Qi X, Hong J, Chaves L, Zhuang Y, Chen Y, Wang D, et al. Antagonistic regulation by the transcription factors C/EBPalpha and MITF specify basophil and mast cell fates. J Immunol (2013) 39(1):97–110. doi: 10.1016/j.imuni.2013.06.012
5. Mukai K, BenBarak MJ, Tachibana M, Nishida K, Karasuyama H, Taniuchi I, et al. Critical role of P1-Runx1 in mouse basophil development. Blood (2012) 120(1):76–85. doi: 10.1182/blood-2011-12-399113
6. Ohmori K, Luo Y, Jia Y, Nishida J, Wang Z, Bunting KD, et al. IL-3 induces basophil expansion in vivo by directing granulocytemonocyte progenitors to differentiate into basophil lineage-restricted progenitors in the bone marrow and by increasing the number of basophil/mast cell progenitors in the spleen. J Immunol (2009) 182(5):2835–41. doi: 10.4049/jimmunol.08002870
7. Kitamura Y, Morii E, Ippo T, Ito A. Effect of MITF on mast cell differentiation. Mol Immunol (2002) 38(16-18):1173–6. doi: 10.1016/s0161-5890(02)00098-5
8. Takemoto CM, Lee YN, Jegga AG, Zablocki D, Brandal S, Shahlaee A, et al. Mast cell transcriptional networks. Blood Cells Mol Dis (2008) 41(1):82–90. doi: 10.1016/j bcm.2008.02.005
9. Iwasaki H, Mizuno S, Arinobu Y, Ozawa H, Mori Y, Shigematsu H, et al. The order of expression of transcription factors directs hierarchical specification of hematopoietic lineages. Genes Dev (2006) 20(21):3010–21. doi: 10.1101/gad.1493506
10. Sasaki H, Kurotaki D, Osato N, Sato H, Sasaki I, Koizumi S, et al. Transcription factor IRF8 plays a critical role in the development of murine basophils and mast cells. Blood (2015) 125(2):358–69. doi: 10.1182/blood-2014-02-557983
11. Doyle AD, Jacobsen EA, Ochikur SI, McGarry MP, Shim KG, Nguyen DT, et al. Expression of the secondary granule proteins major basic protein 1 (MBP-1) and eosinophil peroxidase (EPX) is required for eosinophilopoiesis in mice. Blood (2013) 122(5):781–90. doi: 10.1182/blood-2013-01-473405
12. Kobayashi M, Nishikawa K, Yamamoto M. Hematopoietic regulatory domain of gata1 gene is positively regulated by GATA1 protein in zebrafish embryos. Development (2001) 128(12):2341–50.
13. Tsai SF, Strauss E, Orkin SH. Functional analysis and in vivo footprinting implicate the erythroid transcription factor GATA-1 as a positive regulator of its own promoter. Genes Dev (1991) 5(6):919–31. doi: 10.1101/gad.5.6.919
14. Yu C, Cantor AB, Yang H, Browne C, Wells RA, Fujiwara Y, et al. 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(11):1387–95. doi: 10.1084/jem.20020656
15. Migliaccio AR, Rana RA, Sanchez M, Lorenzini R, Centurione L, Bianchi L, et al. GATA-1 as a regulator of mast cell differentiation revealed by the phenotype of the GATA-1low mouse mutant. J Exp Med (2003) 197(3):281–96. doi: 10.1084/jem.20021149
16. Akashi K, Traver D, Miyamoto T, Weissman IL. A clonogenic common myeloid progenitor that gives rise to all myeloid lineages. Nature (2000) 404(6774):193–7. doi: 10.1038/35004599
17. Drissen R, Buza-Vidas N, Woll P, Thonguea S, Gambardella A, Giustacchini A, et al. Distinct myeloid progenitor-differentiation pathways identified through single-cell RNA sequencing. *Nat Immunol* (2016) 17(6):666–76. doi:10.1038/ni.3412

18. Harigae H, Takahashi S, Suwabe N, Ohtsu H, Gu L, Yang Z, et al. Differential roles of GATA-1 and GATA-2 in growth and differentiation of mast cells. *Genes Cells* (1998) 3(1):39–50. doi:10.1046/j.1354-4406.1998.00166.x

19. Zon LI, Yamaguchi Y, Yee K, Albee EA, Kimura A, Bennett JC, et al. Expression of mRNA for the GATA-binding proteins in human eosinophils and basophils: potential role in gene transcription. *Blood* (1993) 81(12):3234–41. doi:10.1182/blood.V81.12.3234

20. Nei Y, Obata-Ninomiya K, Tsutsui H, Ishiwata K, Miyasaka M, Matsumoto K, et al. GATA-1 regulates the generation and function of basophils. *Proc Natl Acad Sci U S A* (2013) 110(46):18620–5. doi:10.1073/pnas.1311668110

21. Hussain M, Bercord L, Walsh KP, Penna Rodriguez M, Mueller C, Kim BS, et al. Basophil-derived IL-4 promotes epicutaneous antigen sensitization concomitant with the development of food allergy. *J Allergy Clin Immunol* (2018) 141(1):223–34 e5. doi:10.1016/j.jaci.2017.02.035

22. Sharma S, Tomar S, Dharne M, Ganesan V, Smith A, Yang Y, et al. Deletion of DeltadblGata motif leads to increased predisposition and severity of IgE-mediated food-induced anaphylaxis response. *PLoS One* (2014) 19(8):e0219357. doi:10.1371/journal.pone.0219357

23. Ohmeda K, Moriguchi T, Ishijima Y, Satoh H, Philipsen S, et al. Basophil transcription factor GATA1 is dispensable for mast cell differentiation in adult mice. *Mol Cell Biol* (2014) 34(10):1812–26. doi:10.1128/MCB.01524-13

24. Sasaki H, Kurotaki D, Tamura T. Regulation of basophil and mast cell development by transcription factors. *Allergol Int* (2016) 65(2):127–34. doi:10.1016/j.alit.2016.01.006

25. Obata K, Mukai K, Tsujimura Y, Ishiwata K, Kawano Y, Minegishi Y, et al. Thymic stromal lymphopoietin-dependent basophils promote Th2 immunity through single-cell RNA sequencing. *Allergy* (2013) 68(1):87. doi:10.1111/j.1398-9995.2012.03412

26. Herbst T, Esser J, Prati M, Kulagin M, Stettler R, Zaiss MM, et al. Antibodies and IL-3 support helminth-induced basophil expansion. *Proc Natl Acad Sci U S A* (2012) 109(37):14954–9. doi:10.1073/pnas.1117588109

27. Hill DA, Siracusa MC, Abt MC, Kim BS, Kobuley D, Kubo M, et al. Commensal bacteria-derived signals regulate basophil hematopoiesis and allergic inflammation. *Nat Med* (2012) 18(4):538–46. doi:10.1038/nm.2657

28. Nakahigashi K, Otsuka A, Tomari K, Miyachi Y, Kabashima K. Evaluation of IL-33 required for IL-3-induced IL-4 production in basophils. *J Immunol* (2008) 201(6):791–800. doi:10.4049/jimmunol.0700377

29. Xiang Z, Moller C, Nilsson G. IgE-receptor activation induces survival and BFI-1 expression in human mast cells but not basophils. *Allergy* (2006) 61(9):1040–6. doi:10.1111/j.1398-9995.2006.01024.x

30. Ziegler SF, Ardis D. Sensing the outside world: TSLP regulates barrier immunity. *Nat Immunol* (2010) 11(4):289–93. doi:10.1038/ni.1852

31. Kondo Y, Yoshimoto T, Yasuda K, Futatsugi-Yumikura S, Morimoto M, Hayashi N, et al. Administration of IL-33 induces airway hyperresponsiveness and goblet cell hyperplasia in the lungs in the absence of adaptive immune system. *Immunol* (2008) 20(6):791–800. doi:10.1016/j.imimm.2007.09.007

32. Herbst T, Esser J, Stettler R, Zaiss MM, et al. Basophil-derived IL-4 promotes epicutaneous antigen sensitization concomitant with the development of food allergy. *J Allergy Clin Immunol* (2018) 141(1):223–34 e5. doi:10.1016/j.jaci.2017.02.035

33. Sharma S, Tomar S, Dharne M, Ganesan V, Smith A, Yang Y, et al. Deletion of DeltadblGata motif leads to increased predisposition and severity of IgE-mediated food-induced anaphylaxis response. *PLoS One* (2014) 19(8):e0219357. doi:10.1371/journal.pone.0219357

34. Ohmeda K, Moriguchi T, Ishijima Y, Satoh H, Philipsen S, et al. Basophil transcription factor GATA1 is dispensable for mast cell differentiation in adult mice. *Mol Cell Biol* (2014) 34(10):1812–26. doi:10.1128/MCB.01524-13

35. Sasaki H, Kurotaki D, Tamura T. Regulation of basophil and mast cell development by transcription factors. *Allergol Int* (2016) 65(2):127–34. doi:10.1016/j.alit.2016.01.006

36. Obata K, Mukai K, Tsujimura Y, Ishiwata K, Kawano Y, Minegishi Y, et al. Basophils are essential initiators of a novel type of chronic allergic inflammation. *Blood* (2007) 110(3):913–20. doi:10.1182/blood-2007-01-068718

37. Ito Y, Satoh T, Takayama K, Miyagishi C, Walls AF, Yokozeki H. Basophil recruitment and activation in inflammatory skin diseases. *Allergy* (2011) 66(8):1107–13. doi:10.1111/j.1398-9995.2011.02570.x

38. Wada T, Ishiwata K, Koseki H, Ishikura T, Ugaqjin T, Ohnuma N, et al. Selective ablation of basophils in mice reveals their nonredundant role in acquired immunity against ticks. *J Clin Invest* (2010) 120(4):2867–75. doi:10.1172/JCI42680

39. Nakahigashi K, Otsuka A, Tomari K, Miyachi Y, Kabashima K. Evaluation of basophil infiltration into the skin lesions of tick bites. *Case Rep Dermatol* (2013) 5(1):48. doi:10.1016/j.crder.2013.06.001

40. Ohta T, Yoshikawa S, Tabakawa Y, Yamaji K, Ishiwata K, Shirata H, et al. Skin CD4(+) Memory T Cells Play an Essential Role in Acquired Anti-Tick Immunity through Interleukin-3-Mediated Basophil Recruitment to Tick-Feeding Sites. *Front Immunol* (2017) 8:1348. doi:10.3389/fimmu.2017.01348

41. Mitre E, Nutman TB. Lack of basophila in human parasitic infections. Am J Trop Med Hyg (2003) 69(1):87–91. doi:10.4269/ajtmh.2003.69.87

42. Shen T, Kim S, Do J, Wang L, Lantz C, Urban JF, et al. T cell-derived IL-3 plays key role in parasite infection-induced basophil production but is dispensable for in vivo basophil survival. *Int Immunol* (2008) 20(9):1201–9. doi:10.1038/immunolimdx0677

43. Hida S, Yamassaki S, Sakamoto Y, Takamoto M, Obata K, Takai T, et al. Fc receptor-gamma-chain, a constitutive component of the IL-3 receptor, is required for IL-3-induced IL-4 production in basophils. *Nat Immunol* (2009) 10(2):214–22. doi:10.1038/ni.1686

44. Giacomin PR, Siracusa MC, Walsh KP, Gencris RK, Kubo M, Comeau MR, et al. Thymic stromal lymphopoietin-dependent basophils promote Th2 cytokine responses following intestinal helminth infection. *J Immunol* (2012) 189(9):4371–8. doi:10.4049/jimmunol.1200691

45. Herbst T, Esser J, Prati M, Kulagin M, Stettler R, Zaiss MM, et al. Antibodies and IL-3 support helminth-induced basophil expansion. *Proc Natl Acad Sci U S A* (2012) 109(37):14954–9. doi:10.1073/pnas.1117588109

46. Hill DA, Siracusa MC, Abt MC, Kim BS, Kobuley D, Kubo M, et al. Commensal bacteria-derived signals regulate basophil hematopoiesis and allergic inflammation. *Nat Med* (2012) 18(4):538–46. doi:10.1038/nm.2657
Ohnmacht C, Voehringer D. Basophils protect against reinfection with helminths.

Inclan-Rico JM, Ponessa JJ, Valero-M Adjali J, Yamanishi Y, Karasuyama H. Treg-mediated suppression of the Th2 response in helminth infection.

Hammad H, Plantinga M, Deswarte K, Pouliot P, Willart MA, Kool M, et al. MHC class II-dependent basophil-CD4+ T cell interactions prime a long-lived effector macrophage phenotype that mediates accelerated larval expulsion.

Tsutsui H, Yamanishi Y, Ohtsuka H, Sato S, Yoshikawa S, Karasuyama H. RELMα-expressing macrophages protect against fatal lung damage and helminth expulsion.

Obata-Ninomiya et al. Basophils and Eosinophils in Nematode Infections

Basophils orchestrate chronic allergic dermatitis and protective immunity against intestinal helminths. J Exp Med (2013) 210(12):2583–95. doi: 10.1084/jem.20130761

Matsumoto M, Sasaki Y, Yasuda K, Takai T, Muramatsu M, Yoshimoto T, et al. IgG and IgE collaboratively accelerate expulsion of Strongyloides venezuelensis in a primary infection. Infect Immun (2013) 81(7):2518–27. doi: 10.1128/IAI.00285-13

Mukai K, Karasuyama H, Kabashima K, Kubo M, Galli SJ. Differences in the Importance of Mast Cells, Basophils, IgE, and IgG versus That of CD4+ T Cells and ILC2 Cells in Primary and Secondary Immunity to Strongyloides venezuelensis. Infect Immun (2017) 85(5):e00553–17. doi: 10.1128/IAI.00553-17

Reitz M, Brunn ML, Voehringer D, Breloer M. Basophils are dispensable for the establishment of protective adaptive immunity against primary and challenge infection with the intestinal helminth parasite Strongyloides ratti. PLoS Negl Trop Dis (2018) 12(11):e0066992. doi: 10.1371/journal.pntd.0066992

Obata-Ninomiya et al. The skin is an important bulwark of acquired immunity against intestinal nematode infection.

Tang XZ, Jung JB, Allen CDC. A case of mistaken identity: The MAR-1 antibody to mouse FcepsilonRIalpha cross-reacts with FcgammaRI and FcgammaRIV.

FcgammaRIV antibody to mouse FcepsilonRIalpha cross-reacts with FcgammaRI and FcgammaRIV.

Allen CDC. The Basoph8 Mice Enable an Unbiased Detection and a Conditional Gene Disruption of Basophils.

Perrigoue JG, Saenz SA, Siracusa MC, Allenspach EJ, Taylor BC, Giacomin PR, et al. MHC class II-dependent basophil-CD4+ T cell interactions promote self T(H)2 cytokine-dependent immunotolerance. Nat Immunol (2009) 10(7):769–705. doi: 10.1038/ni.1740

Sokol CL, Chu NQ, Yu S, Nish SA, Lauffer TM, Medzhitov R. Basophils function as antigen-presenting cells for an antigen-induced T helper type 2 response. Nat Immunol (2009) 10(7):713–20. doi: 10.1038/ni.1738

Yoshimoto T, Yasuda K, Tanaka H, Nakahira M, Imay I, Fujimori Y, et al. Basophils contribute to T(H)2 IgE responses in vivo via IL-4 production and presentation of peptide-MHC class II complexes to CD4+ T cells. Nat Immunol (2009) 10(7):706–12. doi: 10.1038/ni.1737

Lang Z, Jung JB, Allen CDC. A case of mistaken identity: The MAR-1 antibody to mouse FcepsilonRIalpha cross-reacts with FcgammaRI and FcgammaRIV.

The Basoph8 Mice Enable an Unbiased Detection and a Conditional Gene Disruption of Basophils.

Basophils orchestrate chronic allergic dermatitis and protective immunity against intestinal helminths. J Exp Med (2013) 210(12):2583–95. doi: 10.1084/jem.20130761

Matsumoto M, Sasaki Y, Yasuda K, Takai T, Muramatsu M, Yoshimoto T, et al. IgG and IgE collaboratively accelerate expulsion of Strongyloides venezuelensis in a primary infection. Infect Immun (2013) 81(7):2518–27. doi: 10.1128/IAI.00285-13

Mukai K, Karasuyama H, Kabashima K, Kubo M, Galli SJ. Differences in the Importance of Mast Cells, Basophils, IgE, and IgG versus That of CD4+ T Cells and ILC2 Cells in Primary and Secondary Immunity to Strongyloides venezuelensis. Infect Immun (2017) 85(5):e00553–17. doi: 10.1128/IAI.00553-17

Reitz M, Brunn ML, Voehringer D, Breloer M. Basophils are dispensable for the establishment of protective adaptive immunity against primary and challenge infection with the intestinal helminth parasite Strongyloides ratti. PLoS Negl Trop Dis (2018) 12(11):e0066992. doi: 10.1371/journal.pntd.0066992

Obata-Ninomiya et al. The skin is an important bulwark of acquired immunity against intestinal nematode infection.

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Allen CDC. The Basoph8 Mice Enable an Unbiased Detection and a Conditional Gene Disruption of Basophils.

Perrigoue JG, Saenz SA, Siracusa MC, Allenspach EJ, Taylor BC, Giacomin PR, et al. MHC class II-dependent basophil-CD4+ T cell interactions promote self T(H)2 cytokine-dependent immunotolerance. Nat Immunol (2009) 10(7):769–705. doi: 10.1038/ni.1740

Sokol CL, Chu NQ, Yu S, Nish SA, Lauffer TM, Medzhitov R. Basophils function as antigen-presenting cells for an antigen-induced T helper type 2 response. Nat Immunol (2009) 10(7):713–20. doi: 10.1038/ni.1738

Yoshimoto T, Yasuda K, Tanaka H, Nakahira M, Imay I, Fujimori Y, et al. Basophils contribute to T(H)2 IgE responses in vivo via IL-4 production and presentation of peptide-MHC class II complexes to CD4+ T cells. Nat Immunol (2009) 10(7):706–12. doi: 10.1038/ni.1737

Tang XZ, Jung JB, Allen CDC. A case of mistaken identity: The MAR-1 antibody to mouse FcepsilonRIalpha cross-reacts with FcgammaRI and FcgammaRIV.

The Basoph8 Mice Enable an Unbiased Detection and a Conditional Gene Disruption of Basophils.

Basophils orchestrate chronic allergic dermatitis and protective immunity against intestinal helminths. J Exp Med (2013) 210(12):2583–95. doi: 10.1084/jem.20130761

Matsumoto M, Sasaki Y, Yasuda K, Takai T, Muramatsu M, Yoshimoto T, et al. IgG and IgE collaboratively accelerate expulsion of Strongyloides venezuelensis in a primary infection. Infect Immun (2013) 81(7):2518–27. doi: 10.1128/IAI.00285-13

Mukai K, Karasuyama H, Kabashima K, Kubo M, Galli SJ. Differences in the Importance of Mast Cells, Basophils, IgE, and IgG versus That of CD4+ T Cells and ILC2 Cells in Primary and Secondary Immunity to Strongyloides venezuelensis. Infect Immun (2017) 85(5):e00553–17. doi: 10.1128/IAI.00553-17

Reitz M, Brunn ML, Voehringer D, Breloer M. Basophils are dispensable for the establishment of protective adaptive immunity against primary and challenge infection with the intestinal helminth parasite Strongyloides ratti. PLoS Negl Trop Dis (2018) 12(11):e0066992. doi: 10.1371/journal.pntd.0066992

Obata-Ninomiya et al. The skin is an important bulwark of acquired immunity against intestinal nematode infection.

Tang XZ, Jung JB, Allen CDC. A case of mistaken identity: The MAR-1 antibody to mouse FcepsilonRIalpha cross-reacts with FcgammaRI and FcgammaRIV.

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Allen CDC. The Basoph8 Mice Enable an Unbiased Detection and a Conditional Gene Disruption of Basophils.

Perrigoue JG, Saenz SA, Siracusa MC, Allenspach EJ, Taylor BC, Giacomin PR, et al. MHC class II-dependent basophil-CD4+ T cell interactions promote self T(H)2 cytokine-dependent immunotolerance. Nat Immunol (2009) 10(7):769–705. doi: 10.1038/ni.1740

Sokol CL, Chu NQ, Yu S, Nish SA, Lauffer TM, Medzhitov R. Basophils function as antigen-presenting cells for an antigen-induced T helper type 2 response. Nat Immunol (2009) 10(7):713–20. doi: 10.1038/ni.1738

Yoshimoto T, Yasuda K, Tanaka H, Nakahira M, Imay I, Fujimori Y, et al. Basophils contribute to T(H)2 IgE responses in vivo via IL-4 production and presentation of peptide-MHC class II complexes to CD4+ T cells. Nat Immunol (2009) 10(7):706–12. doi: 10.1038/ni.1737

Tang XZ, Jung JB, Allen CDC. A case of mistaken identity: The MAR-1 antibody to mouse FcepsilonRIalpha cross-reacts with FcgammaRI and FcgammaRIV.

The Basoph8 Mice Enable an Unbiased Detection and a Conditional Gene Disruption of Basophils.
lack eosinophilia but have normal antibody and cytotoxic T cell responses. *Immunity* (1996) 4(1):15–24, doi: 10.1016/s1074-7613(00)80294-0

97. Dant LA, Strath M, Mellor AL, Sanderson CJ. Eosinophils in transgenic mice expressing interleukin 5. *J Exp Med* (1990) 172(5):1425–31, doi: 10.1084/jem.172.5.1425

98. Yasuda K, Muto T, Kawagoe T, Matsumoto M, Sasaki Y, Matsushita K, et al. 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(9):3451–6, doi: 10.1073/pnas.12042109

99. Endo Y, Hirahara K, Inuma T, Shinoda K, Tumes DJ, Asou HK, et al. The interleukin-33-p38 kinase axis confers memory T helper 2 cell pathogenicity in the airway. *Immunity* (2015) 42(2):294–308, doi: 10.1016/j.immuni.2015.01.016

100. Noh JY, Shin JU, Park CO, Lee N, Jin S, Kim SH, et al. Thymic stromal lymphopoietin receptor (TSLPR) expression on eosinophils and enhance TSLP-stimulated degranulation. *Eur J Immunol* (2015) 19(3):781–91, doi: 10.1002/eji.201409015

101. Roechman Y, Leonard WI. The role of thymic stromal lymphopoietin in CD8+ T cell homeostasis. *Immunol* (2008) 181(11):7699–705, doi: 10.4049/immunol.181.11.7699

102. Kuan EL, Ziegler SF. A tumor-myalid cell axis, mediated via the cytokines IL-1alpha and TSLP, promotes the progression of breast cancer. *Nat Immunol* (2018) 19(4):366–74, doi: 10.1038/s41590-018-0066-6

103. Wang Q, Du J, Zhu J, Yang X, Zhou B. Thymic stromal lymphopoietin (TSLP) induces chemotactic and prosurvival effects in eosinophils: implications in allergic inflammation. *Am J Respir Cell Mol Biol* (2010) 43(3):305–15, doi: 10.1165/rcmb.2009-0180OC

104. Morshed M, Yousefi M, Moeini A, Jafari AM. TSLP: the key regulator of Th2 cell differentiation and airway eosinophilia. *Int Arch Allergy Immunol* (2012) 155(3):183–91, doi: 10.1159/000323777

105. Blackwell NM, Else KJ. B cells and antibodies are required for resistance to the parasitic gastrointestinal nematode Trichuris muris. *Immunity* (2001) 69(6):3860–8, doi: 10.1016/s1074-7613(00)80294-0

106. Gauchat JF, Henchoz S, Mazzie G, Aubry JP, Brunner T, Blasey H, et al. Induction of human IgE synthesis in B cells by mast cells and basophils. *J Allergy Clin Immunol* (2012) 109(9):3451–9, doi: 10.1067/mc.2012.9720

107. Shin EH, Osada Y, Chai JY, Matsumoto N, Takatsu K, Kojima S. Protective roles of eosinophils in Nippostrongylus brasiliensis infection. *Int Arch Allergy Immunol* (1997) 114(Suppl 1):1–45, doi: 10.1159/00023777

108. Denzel A, Maus UA, Rodriguez Gomez M, Moll C, Niedermeier M, Winter DUSP10 constrains innate IL-33-mediated cytokine production in ST2(hi) memory-type pathogenic Th2 cells. *Nat Commun* (2018) 9(1):4231, doi: 10.1038/s41467-018-06468-8

109. Yasuda K, Adachi T, Koida A, Nakainshi K. Nematode-Infected Mice Acquire Resistance to Subsequent Infection With Unrelated Nematode by Inducing Highly Responsive Group 2 Innate Lymphoid Cells in the Lung. *Front Immunol* (2018) 9:2130, doi: 10.3389/immunol.2018.02132

110. Voehringer D, Reese DA, Huang X, Shinkai K, Locksley RM. Type 2 immunity is controlled by IL-4/IL-13 expression in hematopoietic non-eosinophilic cells of the innate immune system. *J Exp Med* (2006) 203(6):1435–46, doi: 10.1084/jem.20052544

111. O’Connell AE, Hes JA, Santiago GA, Nolan TJ, Lok JB, Lee JJ, et al. Major basic protein from eosinophils and myeloperoxidase from neutrophils are required for protective immunity to Strongyloides stercoralis in mice. *Infect Immun* (2011) 79(7):2770–8, doi: 10.1128/IAI.00931-10

112. Herbert DR, Lee JJ, Lee NA, Nolan TJ, Schad GA, Abraham D. Role of IL-5 in innate and adaptive immunity to larval Strongyloides stercoralis in mice. *J Immunol* (2000) 165(8):5454–51, doi: 10.4049/jimmunol.165.8.5454

113. Morawetz RA, Garbuzenko E, Rubin A, Reich R, Pickholz D, Gillery P, et al. Human eosinophils regulate human lung- and skin-derived Th2 cells via dendritic cells. *Eur J Immunol* (2011) 41(6):1651–61, doi: 10.1002/eji.184.5.1651

114. Punnonen J, Yssel H, de Vries JE. The relative contribution of IL-4 and IL-13 to human IgE synthesis induced by activated CD4+ or CD8+ T cells. *J Allergy Clin Immunol* (1997) 100(6 Pt 1):792–801, doi: 10.1016/s1074-7613(00)80294-0

115. Fish SC, Donaldson DD, Goldman SJ, Williams CM, Kasaian MT. IgE generation and mast cell effector function in mice deficient in IL-4 and IL-13. *Immunity* (2005) 174(2):7176–24, doi: 10.4049/jimmunol.174.12.7176

116. Morawetz RA, Garbuzenko E, Rubin A, Reich R, Pickholz D, Gillery P, et al. Purified human peripheral blood basophils release interleukin-13 and preformed IgE. *J Exp Med* (1996) 184(5):1651–61, doi: 10.1084/jem.184.5.1651

117. Nondorf M, Else KJ. B cells and antibodies are required for resistance to the parasitic gastrointestinal nematode Trichuris muris. *Immunity* (2001) 69(6):3860–8, doi: 10.1016/s1074-7613(00)80294-0

118. Mitchell M, Lopez-Otin C, Schumacker A, Searle P, Li Y, Guo L, et al. The extracellular domain of IL-33 mediates Th2 cell differentiation. *J Immunol* (2019) 203(7):3553–65, doi: 10.4049/jimmunol.1900111

119. Rodriguez Gomez M, Talke Y, Goebel N, Hermann F, Reich B, Mack M. Basophils support the survival of plasma cells in mice. *J Immunol* (2015) 185(12):7180–5, doi: 10.4049/jimmunol.1800112

120. Chu VT, Fröhlich A, Steinhausner G, Scheel T, Roch T, Fillatreau S, et al. Eosinophils are required for the maintenance of plasma cells in the bone marrow. *Nat Immunol* (2011) 12(2):151–9, doi: 10.1038/ni.1981

121. Harada Y, Tanaka S, Motomura Y, Harada Y, Ohno S, Ohno S, et al. The 3’ enhancer CNS2 is a critical regulator of interleukin-4-mediated humoral immunity in follicular helper T cells. *Immunity* (2012) 36(2):188–200, doi: 10.1016/j.immuni.2012.02.002

122. Crotty S. T follicular helper cell differentiation, function, and roles in disease. *Immunity* (2014) 41(4):529–42, doi: 10.1016/j.immuni.2014.10.004

123. Ueno H, Banchereau J, Vinuesa CG. Pathophysiology of T follicular helper cells in humans and mice. *Nat Immunol* (2015) 16(2):142–52, doi: 10.1038/ni.3054

124. Gowthaman U, Chen JS, Zhang B, Flynn WF, Lu Y, Song W, et al. Identification of a T follicular helper cell subset that drives anaphylactic IgE. *Science* (2019) 365(6456):eaaw6433, doi: 10.1126/science.aaw6433

125. Shan M, Carrillo J, Yeste A, Gutzeit C, Segura-Garzon D, Walland AG, et al. Secreted IgD Amplifies Humoral T Helper 2 Cell Responses by Binding Basophils via Galectin-9 and CD44. *Immunity* (2018) 49(4):709–24, doi: 10.1016/j.immuni.2018.08.013
127. Clement RL, Daccache J, Mohammed MT, Diallo A, Blazar BR, Kuchroo VK, et al. Follicular regulatory T cells control humoral and allergic immunity by restraining early B cell responses. Nat Immunol (2019) 20(10):1360–71. doi: 10.1038/s41590-019-0472-4

128. Torrero MN, Morris CP, Mitre BK, Hubner MP, Fox EM, Karasuyama H, et al. Basophils help establish protective immunity induced by irradiated larval vaccination for filariasis. Vaccine (2013) 31(36):3675–82. doi: 10.1016/j.vaccine.2013.06.010

129. Hewitson JP, Filbey KJ, Esser-von Bieren J, Camberis M, Schwartz C, Murray J, et al. Concerted activity of IgG1 antibodies and IL-4/IL-25-dependent effector cells trap helminth larvae in the tissues following vaccination with defined secreted antigens, providing sterile immunity to challenge infection. PLoS Pathog (2015) 11(3):e1004676. doi: 10.1371/journal.ppat.1004676

130. Kurashima Y, Kiyono H. New era for mucosal mast cells: their roles in inflammation, allergic immune responses and adjuvant development. Exp Mol Med (2014) 46:e83. doi: 10.1038/emm.2014.7

131. St John AL, Chan CY, Staats HF, Leong KW, Abraham SN. Synthetic mast-cell granules as adjuvants to promote and polarize immunity in lymph nodes. Nat Mater (2012) 11(3):250–7. doi: 10.1038/nmat3222

132. Piliponsky AM, Shubin NJ, Lahiri AK, Traong P, Clauson M, Niino K, et al. Basophil-derived tumor necrosis factor can enhance survival in a sepsis model in mice. Nat Immunol (2019) 20(2):129–40. doi: 10.1038/s41590-018-0288-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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