# CYTOKINES AND BEYOND: REGULATION OF INNATE IMMUNE RESPONSES DURING HELMINTH INFECTION

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## Abstract

Parasitic helminth infection elicits a type 2 cytokine-mediated inflammatory response. During type 2 inflammation, damaged or stimulated epithelial cells exposed to helminths and their products produce alarmins and cytokines including IL-25, IL-33, and thymic stromal lymphopoietin. These factors promote innate immune cell activation that supports the polarization of CD4$^+$ T helper type 2 (Th2) cells. Activated innate and Th2 cells produce the cytokines IL-4, −5, −9, and −13 that perpetuate immune activation and act back on the epithelium to drive goblet cell hyperplasia and increased epithelial cell turnover. Together, these events drive worm expulsion and wound healing processes. While the role of Th2 cells in this context has been heavily studied, recent work has revealed that epithelial cell-derived cytokines are drivers of key innate immune responses that are critical for type 2 anti-helminth responses. Cutting-edge studies have begun to fully assess how other factors and pathways, including lipid mediators, chemokines, Fc receptor signaling, danger-associated molecular pattern molecules, and direct cell-cell interactions, also participate in shaping innate cell-mediated type 2 inflammation. In this review, we discuss how these pathways intersect and synergize with pathways controlled by epithelial cell-derived cytokines to coordinate innate immune responses that drive helminth-induced type 2 inflammation.

## Keywords

innate immune cell; helminth; epithelial cell-derived cytokine; eicosanoid; Notch

## INTRODUCTION

Cytokines direct the mammalian immune response to an array of pathogens, including viruses, single-celled prokaryotes and eukaryotes, and multicellular eukaryotic organisms [1-4]. A diversity of mammalian cytokines has evolved, with specific groups of cytokines mediating distinct host immune responses to different pathogen types [1-4]. Infection with large, multicellular parasitic helminths that reside in and on host tissues elicits a unique type

2 cytokine response [3,5-7]. Type 2 cytokines such as IL-4, −5, −9, and −13 are produced by innate immune cells and polarized CD4$^+$ T helper type 2 (Th2) cells to coordinate epithelial cell responses including goblet cell hyperplasia, increased mucin production, enhanced smooth muscle contractility, and increased epithelial cell turnover [5-8]. Together, these activities drive worm expulsion and wound healing responses that control worm-induced tissue damage [3,5-9] (Fig. 1).

Recent studies have demonstrated the importance of innate immune cells in promoting helminth-induced type 2 inflammation [3,5-11]. Group 2 innate lymphoid cells (ILC2s), basophils, dendritic cells (DCs), alternatively activated macrophages (AAMacs), eosinophils, and mast cells are rich sources of type 2 and other cytokines that promote effector responses and tissue repair [3,5-11]. Intensive study has revealed that the epithelial cell-derived cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) activate type 2 innate immune responses [3,6-8,11-13] (Fig. 1). However, gaps remain in our understanding of how cytokines intersect with other host and pathogen-derived molecules to control these key innate immune responses.

The effect of IL-4, −9 and −13 on innate cells, particularly AAMacs, has recently been extensively reviewed [6,7,9,14-17]. Thus, this review will discuss how epithelial cell-derived cytokines, lipids, chemokines, antibodies, danger-associated molecular patterns (DAMPs), and cell-cell interactions control innate immune responses during type 2 inflammation (Table 1). While we will focus on studies conducted in murine models of helminth infection, we will also refer to the literature on innate immune activities during type 2 allergic inflammation in mice. Finally, we will highlight emerging evidence that shows that effects of epithelial cell-derived cytokines synergize with the activities of other mediators to orchestrate helminth-induced innate immune responses.

## CYTOKINE PATHWAYS THAT REGULATE INNATE IMMUNE RESPONSES DURING HELMINTH INFECTION

### Epithelial Cell-derived Cytokines and Alarmins

Epithelial cells are one of the first cell types exposed to intestinal helminths [3,6-8,11-13]. Thus, cytokines including IL-25, IL-33, and TSLP that are released from stimulated, injured, or dying epithelial cells are critical for the induction of innate immune responses that drive the type 2 inflammatory process [3,6-8,11-13]. In the intestine, IL-25 is largely produced by tuft cells, rare chemosensory cells that become prominent during helminth infection [18-20]. Single cell RNA sequencing analysis of small intestinal epithelial cells showed that a subset of CD45-expressing tuft cells may also be a major TSLP source [21], establishing tuft cells as central cytokine producers in the inflamed epithelium [18-21]. IL-33, on the other hand, is produced in response to damage by a range of epithelial cell types during helminth infection [8,13,22,23]. Whether a specific epithelial cell lineage has a higher propensity to produce IL-33 is unclear and the subject of ongoing studies. Notably, mast cells [24,25], inflammatory DCs [23], basophils, and eosinophils [13,26] may also produce IL-25, IL-33, and TSLP, but the significance of hematopoietic sources of these cytokines during helminth infection is not fully understood.

Epithelial damage appears to be a key event that leads to the release of IL-25, IL-33, and TSLP [3,6-8,11-13]; however, the pathways that control the transcription, production, and secretion of these cytokines during helminth infection are not fully described. A recent study demonstrated that the intestinal metabolite succinate can promote IL-25 release from tuft cells that activates ILC2s during infection with *Nippostrongylus brasiliensis* and *Heligmosomoides polygyrus*, parasites used as models of hookworm infection in mice [27]. Some allergens have enzymes that can proteolytically activate IL-33 [28] or induce TSLP secretion [29], and helminth-derived proteases may play a similar role in the induction of epithelial cell-derived cytokine responses during worm infection [8,30-32]. However, how changes in diet, microbiota-derived intestinal metabolites [6,27,33,34], or helminth proteases [8,30-32] regulate innate immune responses during helminth-induced type 2 inflammation is not fully elucidated.

IL-25, IL-33, and TSLP can mediate the recruitment, expansion, activation, and/or cytokine producing capacity of innate cells that express their cognate receptors [3,6-8,11-13]. The effects of these cytokines on different innate immune cell types are infection- and tissue-dependent, suggesting that these cytokines play non-redundant roles in helminth species-specific immune responses (in-depth coverage of this topic can be found in [3,6-8,11-13]). However, despite intensive study, questions remain regarding how epithelial cell-derived cytokines control innate immune responses in the complex tissue microenvironment. For example, the exact role of IL-33 in granulocyte activation during helminth infection remains to be elucidated. IL-33 deficient mice had more *Mcpt8* (a basophil-specific protease) and more mast cells during *N. brasiliensis* infection compared to wild type controls [35], suggesting that IL-33 does not promote basophil or mast cell population expansion, or that compensatory mast cell hyperplasia and basophilia occurs in response to IL-33 deficiency. Similarly, despite eosinophil expression of the IL-33 receptor [13,36], impaired eosinophil accumulation in IL-33 deficient mice [35] may be due to a decrease in IL-5, eotaxin, or IL-13 produced by IL-33-activated ILC2s rather than a direct IL-33 effect on eosinophils [37,38]. Importantly, the type 2 inflammatory roles and functions of epithelial- and immune cell-derived alarmins and cytokines outside of IL-25, IL-33, and TSLP, including the tumor necrosis factor family member TL1A [39,40] and endogenous DAMPs [3,8], are not clear. In this vein, a number of studies have revealed tissue- and cell-specific effects of IL-1 family members such as IL-18 during type 2 inflammation [8,41,42], but these findings remain to be fully investigated, specifically during helminth infection. Employing reporter and transgenic mouse strains for *in vivo* studies in helminth infection will increase our understanding of the novel effects and functional redundancies of various epithelial cell-derived cytokines on innate immune cells.

### Chemokines and Chemokine Receptors

Chemokines are cytokines that ligate their cognate receptors to promote cell migration and positioning between and within tissues [43]. Various *in vitro* and *in vivo* models show that migration of cells can be controlled by soluble mediators that orchestrate transient and temporal cell movement or by immobilized factors that facilitate directed movement and spatial positioning of cells [43]. Type 2 inflammation-associated innate immune cells express a variety of chemokine receptors in the steady-state and during type 2 inflammation

[43-45], suggesting that chemokines coordinate innate immune cell movements that control type 2 inflammatory responses. In support of this idea, human epidemiological data and murine studies have shown that levels of eotaxin, CCL17, CCL22, CCL5 (RANTES), and CCL24 are increased during helminth infection [46,47]. CCR3, a receptor for eotaxin and a number of other chemokines, has a role in the recruitment of eosinophils during helminth infection [47]. In addition, mast cells are responsive to CCL3 and CXCL2 produced by DCs during exposure to *Fasciola hepatica* fluke antigen [48]. While ILC2s and basophils express some of the important chemokine receptors associated with type 2 inflammation (reviewed in [44,45]), how chemokines control the migration of these cells into tissues and their spatial positioning in the tissue site during helminth infection has not been fully explored.

### Growth Factors/Survival Cytokines

Growth factors and survival cytokines such as IL-2, −3, −5, −7 and granulocyte-macrophage colony-stimulating factor (GM-CSF) promote the survival, differentiation, and activation of innate immune cells during helminth infection [3,5,6,49-51]. IL-3, IL-5, and GM-CSF are secreted by activated T cells, mast cells, macrophages, and ILC2s and drive increases in numbers of granulocytes [37,38,49,50,52-55]. IL-3 is a potent promoter of basophil and mast cell responses, mediating the mobilization, survival, and activation of IL-4-producing basophils [50,52,55-58], and eliciting mast cell development and responses during helminth infection [55]. Conversely, GM-CSF and IL-5 play important roles in eosinophil biology, with GM-CSF promoting the *in vitro* survival of eosinophils [54], and IL-5 acting as a key eosinophil survival factor both *in vitro* and *in vivo* [59]. Notably, the importance of GM-CSF and IL-5, and of eosinophils in general, during helminth infection remains unclear and may be dependent on the species of parasite [60]. For example, GM-CSF was not critical for protection against *N. brasiliensis*, but mice lacking the common β chain (and thus signaling by both GM-CSF and IL-5) were less resistant [61], suggesting that IL-5 promotes type 2 inflammation in this context. However, eosinophils are not required for primary resistance to infection [60] so the relevant cellular targets of IL-5 in *N. brasiliensis* infection and during infection with other species remain unclear.

IL-2 and IL-7 act predominantly on cells of the lymphoid lineage, in particular ILC2s, and in doing so act as critical mediators of ILC2-dependent type 2 inflammation [5,51,62-68]. IL-2 derived from T cells promotes the survival and expansion of IL-13-producing ILC2s and Th2 cells in the protective response against *N. brasiliensis* [63,69], though IL-2 is not required for ILC2 function in *H. polygyrus* infection [70]. Likewise, stromal cell-derived IL-7 delivers a potent anti-apoptotic, proliferative survival signal to ILC progenitors and mature ILC2s, directing ILC development, ILC2 lineage determination, and lymphoid organogenesis, though how IL-7 affects other aspects of ILC2 functionality *in vivo* is less clear [5,51,62,63,65-68].

### NON-CYTOKINE PATHWAYS THAT REGULATE INNATE IMMUNE RESPONSES DURING HELMINTH INFECTION

**Bioactive Lipid Mediators**—Bioactive lipid mediators such as the eicosanoid prostaglandins (PGs) and leukotrienes (LTs) are released under type 2 and other inflammatory conditions [71-75]. They play numerous crucial roles in the promotion,

suppression, and regulation of type 2 inflammation [71-76]. Eicosanoids are synthesized by cyclic oxidation of polyunsaturated fatty acids such as arachidonic acids and linoleic acids in the diet or released from membrane phospholipids [71-73]. These lipids are produced by mast cells, macrophages, and other cell types in response to epithelial cell-derived cytokines, damage signals, and crosslinking of Fc receptors [71-78] (Fig. 2). ILC2s [79-83], eosinophils [84,85], basophils [85,86], and mast cells [86,87] express eicosanoid receptors and respond to their cognate ligands (Fig. 2). While we understand more about how eicosanoids function during allergic inflammation, their roles during helminth infection have recently been explored. New studies show that LTs promote anti-helminth ILC2 functions during *H. polygyrus* infection, and during *N. brasiliensis* infection, LTs activated ILC2s in an NFAT-dependent manner [88] and promoted eosinophil accumulation [84]. In addition, $PGE_2$ licensed DCs to induce Th2 polarization in mice in response to egg antigen from *Schistosoma mansoni*, a trematode parasite that can infect both mice and humans [89]. Numerous studies have focused on how $PGD_2$ and its receptor CRTH2 (chemoattractant receptor homologous molecule expressed on Th2 cells) can promote production of type 2 cytokines and accumulation of eosinophils, ILC2s, basophils, mast cells, and Th2 cells during type 2 inflammation [67,74,75,79,81,85,90-93]. Only one study has investigated the role of the $PGD_2$-CRTH2 pathway during helminth infection, showing that ILC2 accumulation in the lung was impaired in CRTH2 deficient mice in a model of chronic type 2 pulmonary inflammation induced by *N. brasiliensis* infection [81]. Further studies will be needed to assess how eicosanoids control innate immune responses in the intestine during helminth infection, particularly as regards the potential suppressive or pro-resolving properties of the eicosanoid family [71,73,76] (Fig. 2).

Finally, how lipids other than eicosanoids, including steroids and sphingolipids, regulate innate immune responses during helminth infection is largely unexplored. One study has shown a role for sex hormones in DC and Th2 responses that control sex-specific differences in resistance to *Trichuris muris*, a whipworm parasite of mice [94]. Regarding sphingolipids, sugar-containing glycolipids, a recent study showed that sphingosine 1 phosphate-mediated chemotaxis controlled redistribution of inflammatory ILC2s during *N. brasiliensis* infection [95]. However, there is much work to be done to determine how sex hormones, naturally occurring corticosteroids such as cortisol, other steroid lipids, and various glycolipids impact innate immune function in helminth infection.

**Direct Cellular Interactions**—While many signals that control type 2 inflammation are released into the tissue microenvironment, others involve direct cell-cell interactions that modulate target cell gene expression and function [3,7,96]. For instance, the interaction that occurs between antigen presenting cells and naïve T cells drives the acquisition of critical type 2 inflammatory effector functions in CD4^{+} T cells that culminates in Th2 polarization [97-102]. During helminth-induced type 2 inflammation, this interaction is critically dependent on classical DCs that express MHC II and provision of co-stimulation through interactions between CD40 and OX40L and their receptors [97-102]. This topic has been reviewed extensively in [98,99] and thus our discussion will focus on other cell-cell interactions of note.

Innate immune cells such as eosinophils, basophils, and ILC2s express MHC II and costimulatory molecules [63,65,103-108]. While these molecules are classically thought of as important for the activation and differentiation of T cells, innate cell function can also be modulated via these pathways [3,5-7], particularly for ILC2s [5,67]. Engagement of MHC II and CD80 and CD86 on ILC2s can elicit cytokine production and proliferation and facilitate T cell interactions [63,109], though the full significance of MHC II expression on ILC2s is unclear. Interactions between ICOS and ICOSL also facilitate ILC2 survival and cytokine production [106]. Basophils express MHC II, and some early studies suggested that these cells can present antigen to T cells [103-105]. More recent work using new tools to dissect basophil biology has shown that antigen presentation in the lymph node is likely not a critical function of basophils *in vivo* [100-102,110-112], though an interesting recent study has shown that basophils can acquire peptide-MHC II complexes from DCs through trogocytosis that allows them to present antigen [113]. Basophil MHC II expression could facilitate interactions between basophils and Th2 cells in the tissue that serve to amplify Th2 cell cytokine production. In addition to the ongoing inquiry related to the role of MHC II expression on granulocytes, how expression of various co-stimulatory molecules by basophils, mast cells, and eosinophils affects their function is not yet clear.

Other direct cellular interactions that occur in the context of the Notch signaling pathway and integrin pathways are important in the regulation of type 2 innate immune cells. In Notch signaling, interaction of a Notch receptor-bearing cell with a ligand-bearing cell leads to release and nuclear translocation of the Notch intracellular domain, where it forms a transcriptional activating complex with the transcription factor recombining binding protein suppressor of hairless (RBPJ) that binds DNA, resulting in changes in target gene expression [96]. Notch signaling drives development of mast cells and ILC2s [114-116], the differentiation of KLRG1^{+} inflammatory ILC2s [117], cytokine production by bone marrow-derived basophils *in vitro* [118], and localization of mast cells within the intestine during helminth infection [119] (Fig. 3). Notch signaling in CD4^{+}T cells controls polarization to the Th2 fate [96,115,120,121], but the full significance of Notch signaling in innate cells remains to be fully described (Fig. 3). Integrin expression is key for the appropriate localization and accumulation of innate immune cells during helminth infection, with impaired mast cell recruitment and worm clearance observed during infection with the nematode *Trichinella spiralis* in β7 integrin-deficient mice [122]. Basophils upregulate integrins during *N. brasiliensis* infection in mice, suggesting that these molecules play a role in regulating an array of innate immune cells [123], but the full scope of integrin-mediated pathways that orchestrate innate immune responses during infection with various helminth species also requires further inquiry.

**Antibodies and Fc Receptors—**A hallmark of the immune response to parasite infection is immunoglobulin (Ig) E binding to Fc receptors on the surface of mast cells and basophils, leading to degranulation and secretion of inflammatory mediators [58,124,125]. This interaction, which bridges antigen specific and innate immunity, is mediated largely by the high affinity IgE receptor (FcεRI) that is constitutively expressed on mast cells and basophils [58,111,124-126]. Class-switched IgE signals through a complex network including FcεRI, the low affinity IgE receptor CD23, the IgE and FcεRI binding protein

galectin-3, complement receptors, and integrins [126]. IgG binding to the inhibitory Fc receptor FcγRII-B or activating Fc receptors FcγRI, FcγRII-A, FcγRIII, or FcγRIV also impacts the function of innate immune cells in inflammation [127], and Fcγ receptors play a role in trapping of *H. polygyrus* larvae during secondary infection [128]. FcεR-and FcγR-dependent pathways may intersect, synergizing to facilitate worm expulsion during murine infection with the roundworm *Strongyloides venezuelensis* [129]. However, further studies are needed to dissect the complex interplay between Ig types and their respective activating or inhibitory Fc receptors on innate cells during helminth infection.

**Neurotrophic Factors**—A burst of interest in neuroimmunology has led to a number of recent studies that show that interactions between the nervous system and innate immune cells control type 2 inflammation. ILC2s localize close to neurons in the intestine and accumulate and produce type 2 cytokines in response to the neuropeptide neuromedin U (NMU), promoting worm clearance in *N. brasiliensis* infection [130,131] and allergic lung inflammation [132]. Further, ILC2s in the lung respond to other neurotrophic factors produced by pulmonary neuroendocrine cells during allergy [133]. A very recent study has shown that ILC2s that expressed the β2-adrenergic receptor were inhibited following receptor agonism, and β2-adrenergic receptor deficient mice had increased resistance to *N. brasiliensis* and *H. polygyrus* infections, suggesting that sympathetic nervous system signals can dampen ILC2 responses [134]. Earlier work showed that other type 2 innate cells also have connections to neurons, similar to ILC2s. Mast cells and eosinophils become activated and home to tissues in response to NMU [135,136]. Further, mast cells produce factors that stimulate neurons directly, including serotonin, histamine, and neurotrophin 4 that induces smooth muscle innervation [137]. While the study of the crosstalk between the nervous system and the immune system during helminth infection is still in early days, the nervous system clearly plays an important role in directing innate immune functions that support the type 2 inflammatory response.

**DAMPs and Other Alarmins**—Tissue damage caused by helminth migration, feeding, or secreted proteases drives the release of a wide array of alarmins including high mobility group box 1 protein, matrix metalloproteinases, S100 family proteins, uric acid crystals, and extracellular adenosine derivatives that are strong activators of anti-helminth and wound healing responses (reviewed in [6,8,138]). For example, extracellular purine-nucleoside adenosine released by damaged tissue is a potent regulator of type 2 inflammation [139,140]. Mice lacking the $A_{2B}$ adenosine receptor had impaired Th2 cell development, tissue eosinophilia, AAMac formation, ILC2 activation, and *H. polygyrus* and *N. brasiliensis* expulsion *in vivo* [140]. Notably however, *in vitro* ligation of different adenosine receptors had differential effects on ILC2 cytokine production [139], suggesting that the effects of adenosine on innate immune cells may be complex. Likewise, mast cells respond to danger-associated extracellular ATP via the P2X7 receptor to drive downstream ILC2 activation and worm expulsion [25]. While roles for other DAMPs have been described in the context of allergic inflammation [8], less is known about these alarmins during helminth infection, and the mechanisms by which these molecules activate or suppress antihelminth type 2 inflammatory responses are still unclear.

## CROSSTALK BETWEEN EPITHELIAL CELL-DERIVED CYTOKINES AND OTHER INNATE IMMUNE CELL REGULATORS

**Biochemical Synergy**—*In vitro* approaches and *in vivo* studies of helminth infection in single-gene knockout or transgenic mice have allowed us to understand many mechanisms that control innate immune responses during type 2 inflammation [3,5-11] (Fig. 1). However, these approaches can lead to oversimplification of the complex *in vivo* environment, in which scores of biochemical factors are produced concurrently or in tightly regulated spatial and temporal circuits. Excitingly, recent studies have addressed how various novel host, pathogen, and microbiota-derived factors synergize to orchestrate type 2 inflammation [6,7]. In this final section, we will focus on recent work that explores the intersections between epithelial cell-derived cytokine pathways and other mediators of innate immune cells that coordinate type 2 immune responses. It is important to note that some of these studies have been conducted in the context of allergic inflammation, and it remains to be seen whether similar results will be observed in helminth infection.

**A Web of Regulation**—There is significant evidence for crosstalk between epithelial cell-derived cytokine pathways and type 2 innate immune functions that depend on soluble mediators, including chemokines and bioactive lipids [6-8,141]. For instance, epithelial cell-derived cytokines can act back on epithelial cells to induce release of chemotactic factors during *N. brasiliensis* infection]. TSLP exposure promoted chemokine production and release from basophils during *T. muris* infection [143], and IL-33 elicited chemokine release from numerous innate immune cell types in the context of allergic inflammation [141]. Similarly, *in vitro* studies demonstrated that IL-33 and TSLP can induce release of $PGD_2$ from mast cells [78,144], and $PGE_2$ can conversely induce IL-33 production from DCs and macrophages [145]. Together, these studies suggest that epithelial cell-derived cytokines promote downstream accumulation of other biochemical species, and vice versa. In addition, exposure to PGs and LTs can potentiate IL-33-mediated activation of ILC2s during *N. brasiliensis* infection [88,146], suggesting that proper exposure to different signals in the correct order can lead to optimal type 2 inflammatory responses (Fig. 2).

Signals downstream of antibodies binding to Fc receptors can also intersect with pathways mediated via epithelial cell-derived cytokines during type 2 inflammation [58,124,125]. FcεR and FcγR signaling activated the production of epithelial-derived cytokines in various myeloid cell types *in vitro* and during type 2 allergic inflammation in the lung [24,147,148]. Interestingly, epithelial-derived cytokines can also prime specific Fc receptor-dependent effector functions in innate immune cells. For example, IL-25 increased IgE-mediated degranulation of allergic human basophils without affecting the release of IL-4, IL-8 and IL-13 [149]. In atopic dermatitis, signaling via FcγRI increased expression of the TSLP receptor on monocyte-derived DCs [150]. These data show that intersection of Fc receptor and epithelial cell-derived cytokine pathways may be important in bridging innate and adaptive responses in type 2 inflammation.

Type 2 innate immune cells must also integrate the signals received from epithelial cell-derived cytokines and from direct interactions with other cell types, with exposure to epithelial cell-derived cytokines often facilitating these cell-cell interactions [6,7,96,115].

TSLP induced expression of OX40L on human and mouse DCs, facilitating their capacity to prime Th2 cells *in vitro* and during allergic sensitization [151,152]. IL-33 could also drive activation of DCs and ILC2s during allergy, highlighted by upregulation of OX40L and CD40 [153,154]. Likewise, IL-33 may upregulate MHC II on bone marrow-derived mast cells *in vitro* [155], though the functional significance of this remains to be determined. Similarly, IL-25 and IL-33 regulated the expression of OX40L in lung ILC2s, which promoted downstream activation of the Th2 response during helminth infection [107]. Finally, cell-cell interactions can also prime a cell to receive signals delivered via cytokine receptors. For example, exposure of ILC2s to Notch signals in combination with IL-25 enhanced their functional plasticity during allergic airway inflammation, allowing them to produce the effector cytokines IL-5 and IL-13 as well as IL-17 [117] (Fig. 3).

## DISCUSSION AND FUTURE DIRECTIONS

Exciting ongoing research continues to reveal new aspects of innate immune cell regulation and function during helminth-induced type 2 inflammation [3,5-11]. We now understand many effects of epithelial cell-derived cytokines, lipids, Fc receptor signaling, and direct cell-cell interactions on innate immune responses during type 2 inflammation [3,6-8,11-13]. Notably, we are beginning to unravel how networks of these factors synergize spatially and temporally during helminth infection to promote innate immune-dependent type 2 inflammation, worm expulsion, and wound-healing responses. However, significant work remains to be done in this area. Some of the studies discussed here have been conducted *in vitro* or in the context of allergic disease, and these findings should be tested *in vivo* during helminth infection. Systems immunology approaches and mouse models that allow for cell lineage-specific and inducible deletion of players in innate immune regulatory networks *in vivo* during infection will be needed to better understand how innate immune cell activities are controlled in the tissue. In addition, studying how epithelial cell-derived cytokine and other pathways integrate intracellularly on the molecular level, through the use of common signaling molecules, pathways, or transcription factors, will require cutting-edge *in vivo* biochemical tools that could leverage optogenetic approaches and live imaging. Thinking more broadly, more studies are needed to dissect how epithelial cell-derived cytokine responses integrate signals from microbiota- and diet-derived factors to shape innate immune responses in health and inflammation [6,33,34]. Finally, we understand little about how the diversity of soluble biochemical factors present in the human intestine during helminth infection can modulate innate immune-dependent type 2 inflammatory responses. Studies that address this gap and bridge work in murine models and in helminth-infected human patients will inform the development of critical new strategies to manage, treat, or prevent helminth infection in humans.

## ACKNOWLEDGEMENTS

## Abbreviations:

| | |
|---|---|
| **AAMac:** | alternatively activated macrophage |
| **CRTH2:** | chemoattractant receptor homologous molecule expressed on Th2 cells |
| **DAMP:** | danger-associated molecular pattern |
| **DC:** | dendritic cell |
| **GM-CSF:** | granulocyte-macrophage colony-stimulating factor |
| **ILC2:** | group 2 innate lymphoid cell |
| **Ig:** | immunoglobulin |
| **LT:** | leukotriene |
| **NMU:** | neuromedin U |
| **PG:** | prostaglandin |
| **RBPJ:** | recombining binding protein suppressor of hairless |
| **Th2:** | $CD4^+$ T helper type 2 |
| **TSLP:** | thymic stromal lymphopoietin |

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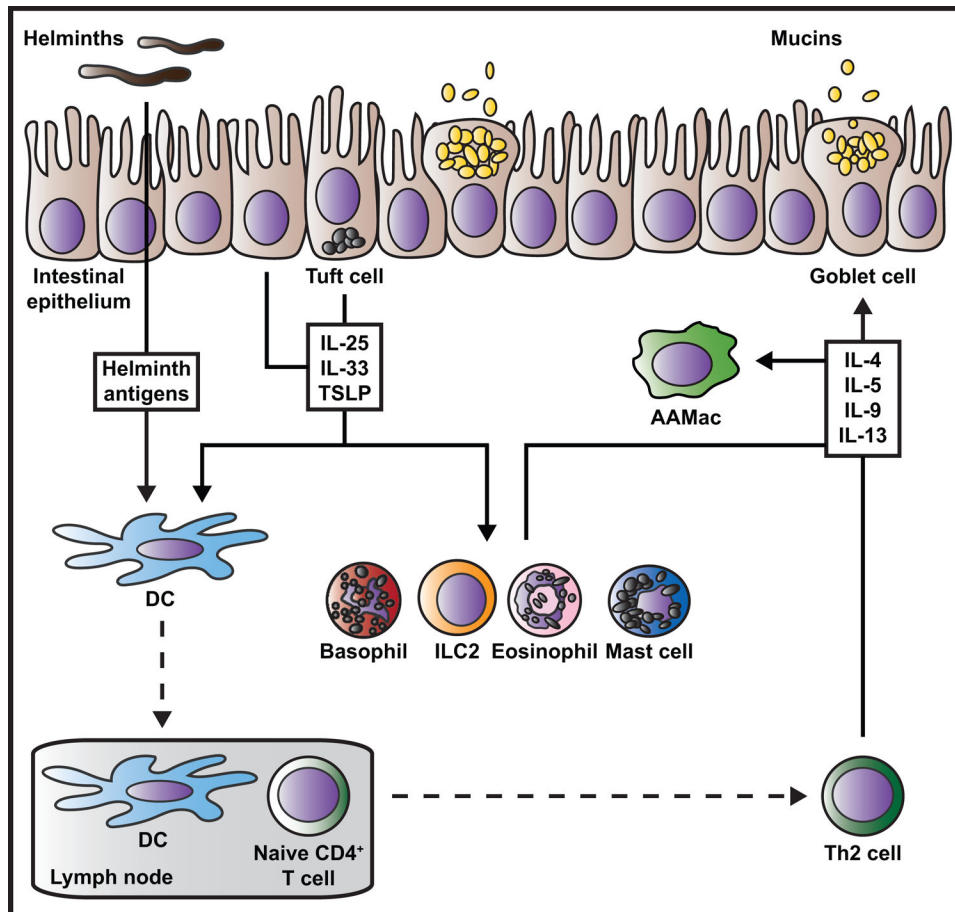
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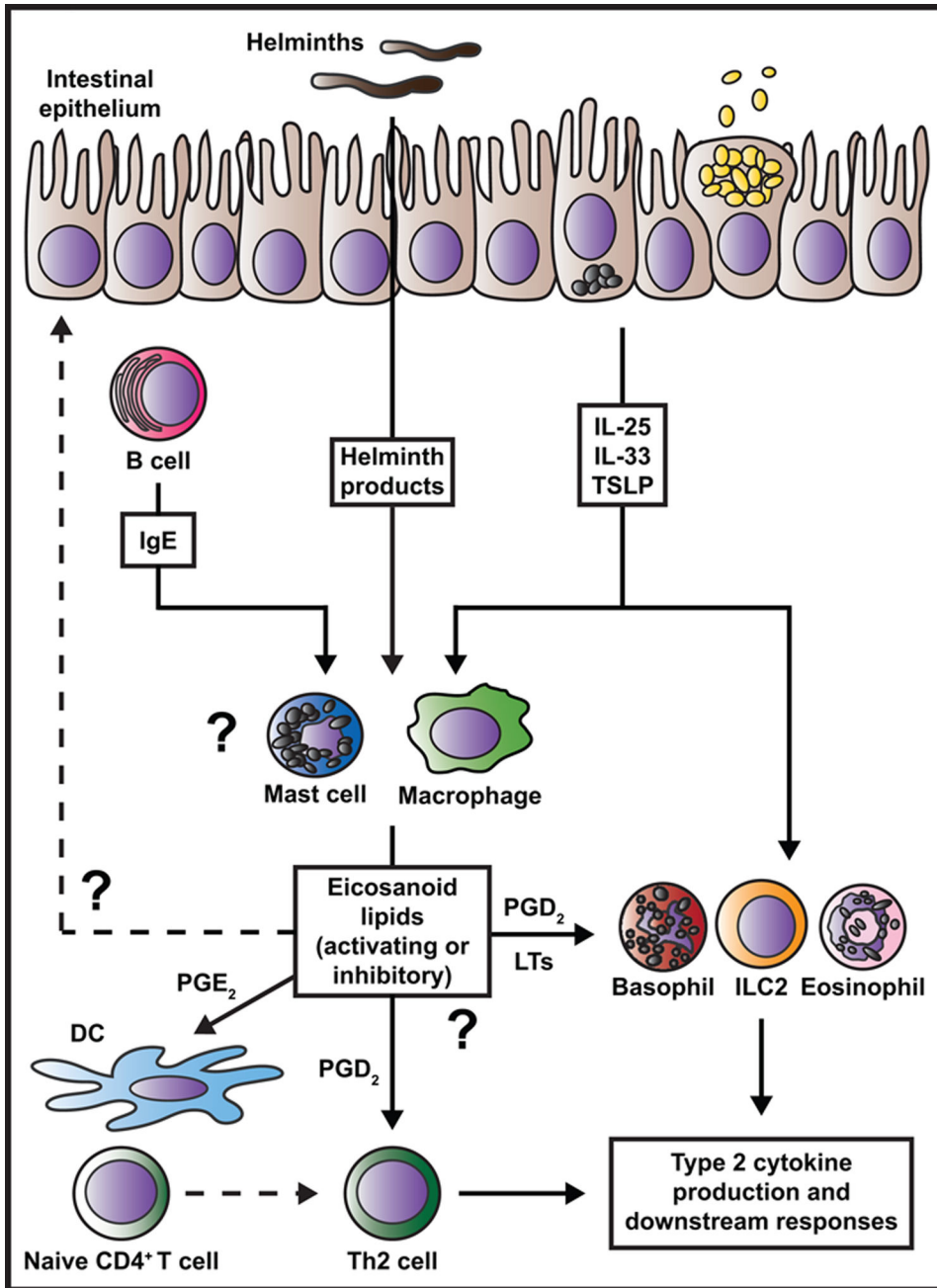
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**Figure 1. Current paradigm for the regulation of type 2 inflammation during helminth infection.**
Damaged, stimulated, or dying intestinal epithelial cells produce cytokines and alarmins
such as IL-25, IL-33, and TSLP in response to helminth parasite infection. Tuft cells are a
rich source of IL-25. Epithelial cell-derived cytokines act on a variety of innate immune
cells including basophils, ILC2s, eosinophils, and mast cells, delivering potent activation,
proliferation, recruitment, and/or survival signals. Epithelial cell-derived cytokines also act
on DCs that take up and process helminth antigens, grooming these cells to travel to the
draining lymph nodes where they present antigen to naïve CD4$^+$ T cells and promote Th2
polarization. In the tissue site, activated innate immune cells and recruited Th2 cells produce
large amounts of the type 2 cytokines IL-4, −5, −9, and −13. Different cell types
differentially produce these cytokines (not depicted here). Type 2 cytokines amplify innate
and adaptive immune cell activation and contribute to wound repair (not depicted here), with
IL-4 serving as a key activator of AAMac polarization. IL-4 and IL-13 act back on the
damaged epithelium and non-hematopoietic cells to cause goblet cell hyperplasia, tuft cell
mobilization, increased intestinal permeability and contractility, and increased epithelial cell
turnover that promote worm expulsion.

**Figure 2. Proposed model for eicosanoid regulation of innate immune responses during helminth-induced type 2 inflammation.**

IgE crosslinking of FcεRI, helminth products, or epithelial cell-derived cytokines elicit production or release of eicosanoids including PGs and LTs from mast cells and macrophages during helminth infection. PGE$_2$ can act on DCs to promote their ability to polarize naïve CD4$^+$ T cells to the Th2 fate. PGD$_2$ and LT species activate various innate immune cells and Th2 cells to produce type 2 cytokines and induce accumulation of these cells in tissues. These eicosanoid-mediated effects occur simultaneously or in sequence with events precipitated by epithelial cell-derived cytokines, driving synergistic and highly coordinated spatial and temporal regulation of innate immune cell activities. Open questions
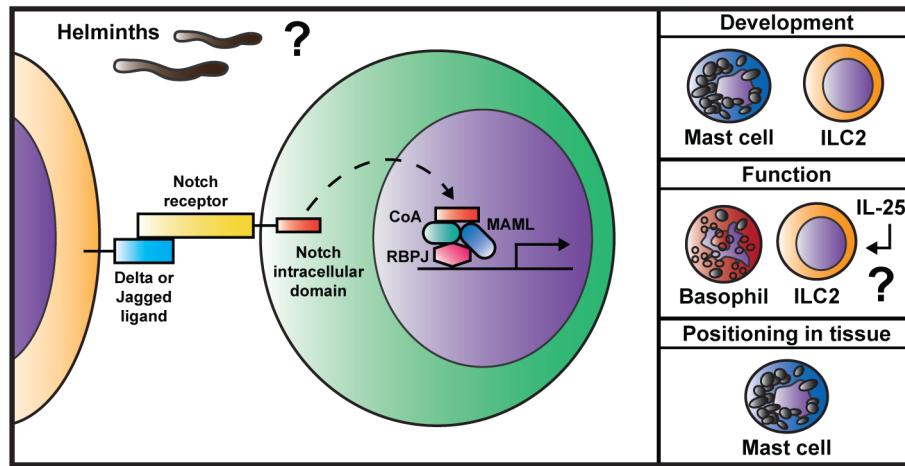
remain regarding 1) whether eicosanoids act on the epithelium to promote or suppress anti-helminth effector responses, 2) how different eicosanoid family members promote, suppress, or resolve innate immune cell effector functions, and 3) the identity of key eicosanoid-producing cell types in the intestine.

**Figure 3. Notch signaling affects innate immune cell responses during type 2 inflammation.**
Notch signaling occurs when a ligand-bearing cell interacts with a cell expressing a Notch receptor. This leads to cleavage of the Notch intracellular domain in the receiving cells and translocation to the nucleus. In the nucleus, the Notch intracellular domain forms a transcriptional activating complex along with Mastermind-like protein (MAML), various co-activators (CoA), and the transcription factor RBPJ. The complex binds to DNA and regulates expression of target genes. Notch signaling can regulate the development of innate immune cells (mast cells and ILC2s), their differentiation and function (basophils and ILC2s), and their positioning in tissues (mast cells). How Notch signaling intersects with epithelial cell-derived cytokine-mediated pathways and specifically how innate immune cell-intrinsic Notch affects type 2 inflammation *in vivo* during helminth infection remains unclear.

**Table 1:**

**Regulators of innate immune cell responses during type 2 inflammation.**

Factors discussed in the text (list not exhaustive) that regulate basophil, mast cell, ILC2, DC, or eosinophil functions during type 2 inflammation. Cellular targets and supporting references cited in the text are highlighted, with possible cellular sources indicated.

| Factor | Function during type 2 inflammation | Known or proposed direct cellular targets and supporting references | Cellular sources (secreted factors only) |
|---|---|---|---|
| Adenosine | Promotes IL-33 production | Unclear *in vivo* [140] | Damaged tissue stromal cells? |
| β7 integrin | Promotes cell accumulation in the small intestine | Mast cells [122] | NA |
| CCR3 ligands (ie. eotaxin) | Elicits cell migration | Mast cells, eosinophils [47,48] | DCs, macrophages |
| GM-CSF | Supports cell survival (effect *in vivo* remains unclear) | Eosinophils [61] | Activated T cells, mast cells, macrophages, ILC2s |
| IgG | Promotes anti-parasite effector responses | Mast cells [129] | B cells |
| IgE | Elicits degranulation and promotes type 2 cytokine production | Basophils, mast cells [58,124-126 (reviews)] | B cells |
| IL-2 | Supports cell proliferation and survival | ILC2s [63,69,70] | T cells, ILCs |
| IL-3 | Promotes cell differentiation, survival, and activation | Basophils, mast cells [55-57; 50,52,58 (reviews)] | T cells |
| IL-5 | Promotes cell accumulation in tissues, survival, and type 2 cytokine production | Eosinophils [61; 59,60 (reviews)] | Th2 cells, eosinophils, mast cells |
| IL-7 | Supports cell differentiation and survival | ILC2s [62,63,65,66,68; 51,67 (reviews)] | Stromal cells |
| IL-18 | Suppresses cell survival and type 2 cytokine production | Mast cells [41; 42 (review)] | Macrophages, DCs, epithelial cells (active or precursor forms) |
| IL-25 | Promotes cell accumulation in tissues, activation, and type 2 cytokine production and potentiates degranulation | Basophils, ILC2s, eosinophils [18-21,27,36,79,107,109,117,149; 8 (review)] | Tuft cells, granulocytes |
| IL-33 | Promotes cell accumulation in tissues, activation, survival, and type 2 cytokine and prostaglandin production or release | Basophils, mast cells, ILC2s, DCs, eosinophils [22,23,25,35-38,54,78,79,88,107,144,146,148,153-155; 8,13,141 (reviews)] | Epithelial and myeloid cells |
| Leukotrienes (LTs) | Promote cell accumulation in tissues and type 2 cytokine production | ILC2s, eosinophils [80,82,84,88,146; 86,87 (reviews)] | Mast cells, basophils, eosinophils |
| MHC II interactions | Support cell proliferation, enable interactions with T cells, and promote type 2 cytokine production | Basophils (?), ILC2s, DCs [63,103-105,109; 98,99 (reviews)] | NA |
| NMU | Promotes cell accumulation in tissues, activation, and type 2 cytokine production | Mast cells, ILC2s, eosinophils [130-132,135,136] | Neurons |

| Factor | Function during type 2 inflammation | Known or proposed direct cellular targets and supporting references | Cellular sources (secreted factors only) |
|---|---|---|---|
| Notch signaling | Controls cell differentiation and tissue localization and promotes type 2 cytokine production | Basophils, mast cells, ILC2s [114-119] | NA |
| PGD$_2$ | Promotes cell accumulation in tissues, activation, chemotaxis, and type 2 cytokine production | Basophils, mast cells, ILC2s, eosinophils [74,79,81,85,90,91,93; 67,75,92 (reviews)] | Mast cells |
| PGE$_2$ | Supports Th2 polarizing capacity and promotes IL-33 production | DCs [89,145,153,154] | Mast cells |
| Sphingosine 1 phosphate | Promotes chemotaxis | ILC2s [95] | Platelets, erythrocytes, endothelium, hepatocytes |
| TL1A | Promotes cell accumulation in tissues, activation, survival, and type 2 cytokine production | ILC2s [39,40] | T cells, myeloid, epithelial, and endothelial cells |
| TSLP | Supports Th2 polarizing capacity and promotes type 2 cytokine, chemokine, and prostaglandin production or release | Basophils, mast cells, ILC2s, DCs [26,31,143,144,150-152; 12 (review)] | Epithelial and myeloid cells |