REVIEW ARTICLE

Tissue-specific immunity in helminth infections

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A characteristic feature of host responses to helminth infections is the development of profound systemic and tissue-localised Type 2 immune responses that play critical roles in immunity, tissue repair and tolerance of the parasite at tissue sites. These same Type 2 responses are also seen in the tissue-associated immune-pathologies seen in asthma, atopic dermatitis and many forms of allergies. The recent identification of new subtypes of immune cells and cytokine pathways that influence both immune and non-immune cells and tissues creates the opportunity for reviewing helminth parasite–host responses in the context of tissue specific immunity. This review focuses on the new discoveries of the cells and cytokines involved in tissue specific immune responses to helminths and how these contribute to host immunity against helminth infection and allow the host to accommodate the presence of parasites when they cannot be eliminated.

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INTRODUCTION

The Type 2 immune response is the product of a special evolutionary relationship between a host and its parasites

Over millions of years, the selective evolutionary pressures of infectious agents, sex, lifespan and diet has shaped the immune system of many mammalian species[1]. For the challenges faced by each species the immune inflammatory responses need to be efficient in removing damaging pathogens, but they need to be tightly regulated to avoid immune pathology of vital tissues associated with feeding and reproduction[2,3]. In this review, we focus on how new knowledge of helminth induced immune responses can be applied to the tissue specific host immune responses that are provoked by the invading parasite and that are relevant to the acquisition of immunity and ongoing immune pathology[4]. The most common parasites of humans are soil-transmitted helminths (STH) including whipworms, roundworms, and hookworms. Reportedly, one billion people are infected worldwide, mainly in countries with tropical and subtropical climates where people are in regular contact with infective larvae in the environment[5]. Once they have established themselves in the host, adult STHs reside in the gastrointestinal tract, in intimate contact with the mucosal surfaces of the gut. Infection can often last for many years, with the presence of adult worms being well tolerated by the host immune cells at mucosal sites and there being very little effect on host microbiome, food uptake, reproduction and response to invading pathogens[5–7]. Irrespective of the STH species, a defining characteristic of parasitic infection is that they preferentially stimulate strong systemic and local type 2 immune responses. The potential benefit of these Type 2 responses to host immunity was first revealed in in vitro experiments demonstrating the parasiticidal properties of eosinophils and marking the lineage as one of the key Type 2 effector cell types that confer immunity against the parasite[8,9]. Further studies using murine models of helminth infections have led to the discovery of other novel immune cells such as type 2 innate lymphoid cells (ILC2s) that are an innate source of the cytokines IL-5 and IL-13 and play a role in expanding and activating eosinophils and inducing mucus secreting goblet cell hyperplasia[10–12]. Furthermore, recent experimental studies of chronic helminth infections have revealed the function of tuft cells in the gastric epithelium[13,14], and the importance of T regulatory cells (T_{REG})[15–17] and IL-10-producing B regulatory cells (B_{REG})[18] in anti-helminth immunity.

The host immune responses induced by helminth infection

The host Type 2 immune responses stimulated by invading helminths is thought to be regulated by a complex interplay between epithelial cells, eosinophils, basophils, mast cells, ILC2s, T helper type 2 cells (T_H2) and effector cytokines such as IL-3, IL-4, IL-5, IL-9, IL-13, and IgE antibodies[19]. Blood eosinophilia is a hallmark feature of parasitic infections, especially for parasites that migrate through multiple tissues[20]. Type 2 immune responses are thought to be necessary for parasite killing and clearance, and to prevent detrimental damage to the host[3], with mounting evidence that type 2 immune responses are also required for returning damaged tissues to normal physiological function. ILC2 activation is thought to be required in early life for generating anti-inflammatory M2 macrophages and contributing to homeostasis[21]. Additionally, type 2 immune responses have been shown to be involved in thermogenesis[22], and recently IL-13 has been identified as a driving factor for the skin dendritic cell subsets involved in inducing T_H2 development in the lymph node[23]. Investigations of parasite induced responses have also revealed how the release of the so called alarmin cytokines such as IL-25, IL-33, and Thymic Stromal Lymphopoietin (TSLP) from damaged tissues that can act alone or together with other cytokines (e.g. IL-2, IL-9), lipid mediators, hormones, and neurotransmitters to eliminate the parasite and resolve the damage caused by infection[19,24–31]. The cytokines IL-4, IL-13, IL-3, IL-5, and IL-9 are considered key to helminth induced type 2 immune responses, which together with

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CD4 T cells, ILC2s, eosinophils, basophils and mast cells form a conserved mechanism that leads to expulsion of helminth species often referred to as the "weep and sweep" response[32–34].

The potential for gut dwelling parasites to affect host physiology and behavior

The gut is well recognized in human physiology as an immune organ that is key to regulating the health of the whole body. This point is clearly observed with the higher incidence of skin diseases appearing in patients suffering from gut inflammatory conditions such as coeliac disease, Crohn's disease, and ulcerative colitis[35]. Also, there is emerging evidence for a gut-brain axis associated with the regulation of host metabolism, neurodevelopmental disorders, neuroinflammation, and stress levels[36–39]. Investigations of the molecules secreted by gut dwelling adult parasites have revealed they can bind host cell receptors and mediate functional host responses, including induction of T_{REG} cells, altering DC activity or blocking initiation of type 2 immune responses[40–44].

Experimental vs natural models for investigating tissue specific Type 2 immune responses to helminths

Several murine based parasite infection models have been used to explore how the helminth infected host responds immunologically to tissue migrating helminth parasites and how in situations of chronic infection the host is made tolerant, or becomes tolerant, to the presence of parasites in the body. The most commonly used parasites have included *Nippostrongylus brasiliensis* and *Heligmosomoides polygyrus*. *N. brasiliensis* follows the life cycle of skin penetration, tissue migration to the lung, gut colonization and egg reproduction before expulsion by the host[45] (Fig. 1). By contrast the strictly enteric *H. polygyrus* models chronic helminth infection by establishing itself in the small intestine and persisting for several months in the rodent host[45,46]. Similarly, *Strongyloides ratti* and *Strongyloides venezuelensis*, which transit through the lungs before reaching the gut, have been used to model the human parasite *Strongyloides stercoralis*. Although these parasites do not establish a chronic infection in mouse experimental models, they have given good insights into host-parasite interaction and revealed the cellular and cytokine effector mechanisms involved in parasite tolerance, immunity and

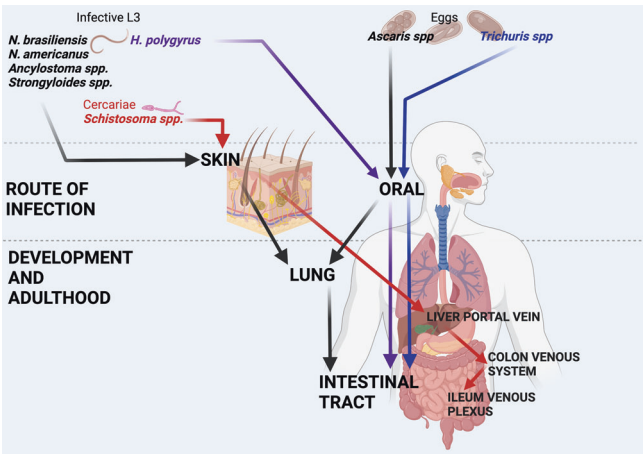

Fig. 1 Hookworm life cycle. Infective larvae (iL3) survive in warm humid environments. Upon contact with the human host, they penetrate the skin (1), migrate through the circulatory vasculature to the lung (2), where they molt, and are carried up by the trachea by the host muco-ciliary ladder and swallowed. Larvae are retained in the small intestine (3) where they develop to the adult stage, mate, and produce eggs. Eggs are released with the feces into the environment, they hatch, develop through three stages to the infective L3. This review will focus on the immune responses elicited in the skin, lungs and intestine by this and related parasites.

eradication[47]. Other parasites like *Trichuris muris* have been used to understand T cell activation and tissue changes in the intestinal epithelium at the colonic boundary seen in human whipworm infection[48,49], while *Schistosoma* infection has provided information on the role of dendritic cells in inducing T_H2 immunity[50,51]. Recently, work using the *H. polygyrus* chronic infection model has enabled the molecular identification and characterization of some of the biologically active molecules secreted by adult worms that bind with high fidelity cytokine receptors and work to regulate the host immune system to enable chronic infection[52].

In real world settings, helminth infections have often been associated with impaired immune responses in humans and animals against mycobacteria[53], intradermal BCG vaccine[54] and tetanus vaccine[55]. However, in experimental co-infection models, helminths have also been shown to have potential protective role against secondary infection with Influenza A and pneumonia virus of mice (PVM), and protective effect against primary infection with respiratory syncytial virus (RSV) and murid gamma herpes virus 4 (muHV-4)[56–59]. Furthermore, in countries where helminth infections are still endemic, a lower incidence of severe atopic diseases has been observed due to the possible induction by the parasitic worm of Type 2 linked regulatory mechanisms[60–64]. These parasite-induced regulatory mechanisms have been recently associated with decreased severity of COVID-19 in a cohort of African patients[65]. In support of these observations, a chronic infection model using *H. polygyrus* showed reduced inflammation in a model of asthma[66], experimental autoimmune encephalomyelitis (EAE)[67] and contact hypersensitivity[68]. These findings have supported the proposal that helminth parasites could have a beneficial effect in regulating host inflammatory responses and have led to clinical trials using live parasites to treat conditions like Crohn's disease, multiple sclerosis, asthma, and celiac disease[69]. In humans the complexity of the immune system in conjunction with multiple parasitic infections and presence of co-morbidities make the relationship between asthma and helminth infections difficult to untangle. For instance, *Ascaris lumbricoides*, a roundworm that migrates through the lung, has been identified as a risk factor for asthma and atopic diseases which is opposite to the situation with *N. americanus* infection, which with a similar life cycle, but which has a negative association with asthma[70–73]. Furthermore, helminth-endemic areas have the highest incidence of malaria, HIV and tuberculosis indicating potential helminth induced impairment on the host immune defenses against viruses, bacteria and other parasites[74]. Certainly, in co-infection models increased mortality following challenge with West Nile virus[75] or virus reactivation with γ-herpesvirus[76] has been shown. In summary, the mechanisms by which helminth parasites can modulate immune responses at distal tissue and mucosal sites is still largely unidentified, making the field of parasite immunomodulation a productive area for future research endeavour.

HELMINTH INFECTION INDUCED IMMUNE RESPONSES IN THE SKIN

For many helminths the skin is the first barrier they have to breach to gain entry to the host with several types of skin immune cells reported to confer some protection against invasion and maintenance of barrier integrity at the skin surface[77]. However, to date natural skin infection studies have proven difficult to model with one of the most commonly used models of helminth infection *N. brasiliensis* parasites bypassing the skin penetration phase of the parasite with subcutaneous injection. Experiments using percutaneous administration of *N. brasiliensis* larvae have demonstrated recruitment of neutrophils and eosinophils to areas of parasite penetration with recent elegant studies showing that larvae can sense the presence of inflammatory cells in the skin remaining longer in their protective sheaths before travelling more quickly to the lung once ex-sheathed[78]. In other studies

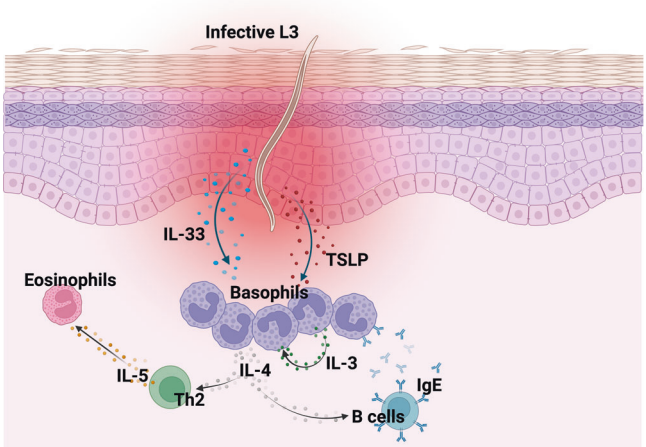

Fig. 2 Basophil responses in the skin. Infective L3 penetrate the skin causing damage of the epithelial cells. Alarmins such as IL-33 and TSLP are released from damaged epithelial cells. Both IL-33 and TSLP can activate basophils, which can release IL-4. IL-4 is necessary for 1) the development of T_H2 cells and the release of IL-5 involved in eosinophil recruitment, and 2) B cell IgE class switching. Basophil activity is directed against the parasite upon binding of IgE through high affinity receptors and trapping infective larvae. TSLP together with IL-3 induces recruitment of basophils at the site of skin inflammation.

innate immune cells such as neutrophils and eosinophils have been shown to be required for immobilization and killing of *S. ratti* larvae in the skin and infected tissues[79], while *S. stercoralis* induces neutrophils extracellular traps (NETs) in vivo that trap and kill the parasite[80].

Helminth induced eosinophil responses in the skin

The presence of high numbers of eosinophils in blood and tissues is considered a hallmark of parasite infection and blood eosinophilia is clinically used as a diagnostic marker of parasite infection in humans[20]. Eosinophils are bone-marrow-derived cells that are recruited to the site of infection by IL-5 and eotaxin and can be specifically identified by the chemical staining of their cytoplasmic granules. Granules are rich in cationic proteins, RNAses and antimicrobial agents and for this reason, eosinophils have been studied as effector cells in human diseases and parasitic infection[81]. Interestingly the eosinophils that infiltrate the skin after *N. brasiliensis* injection show evidence of increased degranulation, and being associated with the larvae that remain trapped in the skin and having a clear role in reducing the number of larvae reaching the lungs[82]. Although a lower number of parasites were observed in the gut of this IL-5/eosinophil transgenic model, and parasites were less fecund, the gut infection was cleared at the same time of wild-type mice[83]. In a different study, using IL-5-deficient mice, which lack or are unable to mobilise eosinophils, resistance against *N. brasiliensis* is impaired in both primary and early secondary infection[84]. This indicates the importance of IL-5 in eosinophil recruitment and the role of IL-5/eosinophils in anti-helminth immunity in the skin. In models of *T. spiralis* infection which involve infection and long term survival of parasites in host muscle tissues, depletion of eosinophils did not affect the intestinal parasitic burden but did lead to greater numbers of viable larvae being detected in the muscle tissue[85]. Interestingly the eosinophils in the muscle tissue surrounding the parasite produced IL-10 in the early stage of infection which had the effect of protecting the encapsulated intracellular larvae and supporting chronic infection[86]. Taken together these studies identified an important role for eosinophils in anti-helminth immunity depending on the parasite and infective tissue stage. However, caution must be observed using experimental models due to the inadequacy of the strategies used to deplete or enhance eosinophils, especially with respect to the inability of the depletion strategies to discriminate between eosinophil subtypes that have functions beyond the observed in vitro killing of parasitic larvae[8,87]. Subsets of eosinophils have been shown to secrete a wide range of cytokines (e.g. IL-4, Il-6, IL-10, and IL-13)[88,89], are involved in liver regeneration[90], and in remodeling of the airways in diseases such as asthma[81].

Helminth induced basophil responses in the skin

Parasitic infections have been key to understanding the role of basophils in type 2 immune responses (Fig. 2). Basophilia has been described as a feature in several rodent parasite models and in humans their abundance is used as a hallmark feature of helminth infections[91]. Basophils from patients infected with *Ascaris*, *Strongyloides*, or *Schistosoma* can secrete histamine in response to parasite antigen[92]. Basophil precursors reside in the bone marrow and respond to IL-3 and TSLP upon helminth infection[91]. Furthermore, *N. brasiliensis* models showed that basophils are required to induce protection upon secondary infection by trapping the larvae in the skin, and this is orchestrated by IgE-activated basophils and M2-polarised macrophages[93]. This study helped to identify basophils as a source of IL-4 during primary infection, placing basophils as a potentially important player in initiating type 2 immune responses, in contrast to the $CD4^+$ T cells that are the major IL-4 producer during re-infection[34,93,94]. In the absence of basophils, clearance of parasites is impaired in both *N. brasiliensis* and *H. polygyrus* infections, due to a lack of basophil-derived IL-4 and IL-13 and reduced expansion of Th2 cells[95]. In a *S. venezuelensis* model, which migrates through the skin similarly to *N. brasiliensis*, basophils had a primary role in trapping larvae in the skin during primary infection, but had no effect during secondary infection[96]. However, studies using *S. ratti* indicated that the absence of basophils can be compensated for by other immune cells, such as mast cells. The authors observed no differences in T_H2 responses in basophil-depleted mice[97]. Experiments with different parasite species indicate that the role of basophils is model-dependent and should be evaluated individually. In a pathological context, basophils have been observed in inflamed human and murine skin during atopic dermatitis and early IL-4 production is required for ILC2 recruitment and activation[98]. However, basophil-derived IL-4 and M-CSF can activate M2 macrophages to induce dermal repair[99], therefore basophils have been shown to both promote skin damage as well as skin repair.

Schistosoma infection induced skin immune responses

When comparing the three main *Schistosoma* species able to infect humans interesting differences in skin responses are observed leading to quite different host skin penetration times for the parasite. This difference appears to be related to the variation in inflammatory mediators released by *S. mansoni* and *S. haematobium*, when compared to the slower migrating *S. japonicum*[100]. Investigations of *Schistosome* larvae, called cercariae, have also helped in understanding the interplay between the optimal immune response that controls the infection, whilst preventing tissue damage and threatening the survival of the host. Cercariae penetrate the skin and secrete excretory/secretory (E/S) products that help maintain the infection as well as regulate immune responses. For instance, E/S products affect the functionality of Langerhans cells and dendritic cells through prostaglandins, IL-4, and IL-13[101,102]. Percutaneous infection by *S. mansoni* induced a transient increase in expression of inflammatory cytokines such as TSLP and IL-33, which was associated with increased inflammatory cellular infiltrates in vivo[103]. While IL-33 plays a key role in orchestrating immune responses in the lung and intestine, TSLP seems to be more important in activating ILC2s in the skin[104].

Chronic helminth infection in the gut can influence skin immune responses

Infection with the strictly enteric helminth *H. polygyrus* has been shown to modulate the skin environment in a number of murine models. Chronic infection with *H. polygyrus* induces a strong systemic T_H2 immunity with the survival of the parasite in the host gut being determined by the expansion of T_{REG} and B_{REG} cells, and induction of a DC subset that expands T_{REG} over T_H2[15,105]. Interestingly, despite the fact that *H. polygyrus* is confined to the lamina propria of the small intestine and the lumen of the small intestine, it or its secreted products appear able to modulate skin inflammation in a mouse model of atopic dermatitis, reducing neutrophil recruitment through reduction of inflammatory chemokines/cytokines[68]. Additionally, chronic infection with *H. polygyrus* inhibited the allergen-induced hyperplasia of skin-draining lymph nodes. Similarly, intradermal BCG vaccination in *H. polygyrus* infected mice is reduced, with lower lymphocyte cells in the draining lymph node[106]. Interestingly, although these antigen-induced immune responses were inhibited in those mice infected with *H. polygyrus* alone there was a low level of CD4+ T cell expansion and eosinophil recruitment detected in the skin. Chronic *H. polygyrus* infection also induced increased expression of skin-homing receptors (e.g. CCR9, CCR4, and CCR10) in CD4+ T cells in the mesenteric LN (mLN), that subsequently migrated to the skin of infected mice and persisted even after deworming[107]. These gut helminth-induced changes in the composition of the immune cell infiltrate in the skin could potentially affect responses to vaccination or other pathogens and could be a further mechanism used by helminth parasites to protect the host from other invading parasites or limit the number of parasites that the host accommodates to the survival advantage of the host and parasite.

NATURAL HELMINTH INFECTION VERSUS EXPERIMENTAL MODELS OF HELMINTH INFECTION

One of the caveats to consider when using experimental parasite infections to model real world human helminth infection is the consideration of the natural routes of host entry and the level of infection that occurs. In endemic areas or the wild, humans and animals are constantly in contact with parasites and re-infection by low numbers of parasites is common. In experimental models, a high dose of parasite is often administered, termed a bolus infection which has been informative in understanding the immune cell types involved in the immune response but not necessarily the role they play in immunity and tolerance. To mimic real-world situations, experimental infections have been performed with low, regular parasite dosing, termed a "trickle infection". In the case of *Schistosoma*, a trickle infection of cercariae in the skin induces a different immune response compared to a bolus infection[102,108,109]. Injection of *S. mansoni* weekly in the ear pinna in mice, induced recruitment of non-regulatory FoxP3$^-$ CD4$^+$ T cells in the skin and the production of IL-10 is required to limit dermal immune responses to other invading parasites, and possibly also to other pathogens[109]. IL-10 production is essential in maintaining homeostasis. In the process of resolving inflammation, IL-10 can be produced by several T cell subsets and B cells, and it is strongly associated with immunomodulation by helminth parasites[64,110]. The absence of IL-10 in mice induced an increased inflammatory infiltrate in the skin during cercariae migration, showing the importance of IL-10 in reducing inflammatory responses[111]. In addition, *S. mansoni* stimulated the production of prostaglandin E_2 (PGE_2), possibly from keratinocytes, and consequently induced IL-10 in the skin[111]. Using trickle infection in models using *N. brasiliensis* in rats and *A. ceylaniucum* in hamsters allowed an increase in parasite burden followed by a steady decline, indicating the generation of a partial protective immune responses. The parasites established a longer infection[112], but to date, no immunological studies have been performed in trickle *N. brasiliensis* infection. Trickle infection with *T. muris* in mice resulted in slower induction of immunity, associated with partial expulsion and a shift from T_H1 to T_H2 responses[113], while trickle infection with *S. ratti*, induced little difference in the generation of type 2 immune responses affecting the production of IL-4, IL-13, and IgG[114].

HELMINTH INFECTION INDUCED IMMUNE RESPONSES IN THE LUNG

After penetrating the skin, *Ancylostoma spp*, *Strongyloides spp*, *Ascaris spp*, *N. americanus*, and *N. brasiliensis* parasites migrate through the lungs before reaching the intestine. During the migratory phase, *A. lumbricoides* induces persistent airway hyperresponsiveness (AHR) and airway remodeling in mice, that resembles allergic airway disease observed in human asthma[115]. In human exposures, infection with *Ascaris* has been linked to lower lung function and increase risk of asthma[72,73]. Severe *S. stercoralis* infection in human is associated with acute respiratory distress syndrome (ARSD), acute respiratory failure and pulmonary hemorrhage, however the majority of patients are asymptomatic or present with mild gastrointestinal symtoms[116]. The migratory phase of *N. brasiliensis* infection causes extensive damage and hemorrhage in the lung parenchyma with large neutrophilic infiltrate, but tissue repair is promoted once the parasite exits the lungs[117], possibly driven by TGF-b-responsive myeloid cells and the production of trefoil factor 2 (TFF2)[118,119]. Emphysema-like pathology and activated macrophages were observed long term in mice infected with *N. brasiliensis*[120], suggesting long term effect of hookworm infection in the lung environment. However, lung emphysema, hemorrhage and pulmonary pathology have been associated with high dose of infective larvae transiting the lung, and not observed with lower dose of parasite[121], possibly lung pathology observed in some infected human reflect high burden of larvae transiting the lungs.

Role of lung neutrophils during helminth infection

Neutrophils are primarily associated with antimicrobial or antifungal responses, and they are not well characterized during parasitic infections. However, significant numbers of neutrophils infiltrate the lungs of *Nb*-infected mice two days post infection (dpi) in an IL-17-dependent manner[122,123]. Furthermore, *Ancylostoma caninum* can secrete a neutrophil inhibitory factor (NIF) protein that can reduce neutrophilic inflammation[124]. Furthermore, depleting neutrophils increased *N. brasiliensis* adult worm burden in the gut, suggesting a potential role for neutrophils in defense against *N. brasiliensis*[78,122]. Similarly, Chen et al. showed impairment in worm expulsion in the absence of neutrophils. They showed that neutrophils can instruct macrophage polarization and these neutrophils displayed a specific gene expression profile, characterized by markers associated with type 2 immunity e.g. *Il13* and *Il33*[125]. IL-17A is a key cytokine for neutrophil recruitment with IL-17 responses being associated with pathology in human schistosomiasis[126], and an important component of Type 2 immune responses in some cases of asthma[127]. Recently, Ajendra et al. showed that early production of IL-17A induced down-regulation of IFNγ and this was required for the generation of optimal type 2 immune responses during *N. brasiliensis* infection. However, IL-17A produced in the later stage of infection negatively regulated type 2 immune response[128], showing a novel role for IL-17A in the regulation of type 2 immunity. Vice versa, type 2 immune responses can regulate T_H17 cells that express a functional IL-13R, reducing expression of RORγt and production of IL-17 and IL-21[129].

Initiation of type 2 immune responses in the lung during helminth infection

Murine helminth infection models have substantially enhanced our understanding of the agents and factors involved in the initiation of type 2 immunity. When *N. brasiliensis* and

S. venezuelensis migrate through the lung it has been clearly demonstrated that the alarmin IL-33 is released in significant amounts and appears to be important for initiating type 2 immune responses in the lung. IL-33 is normally released by damaged epithelial cells, and it acts on several immune cells that express the receptor for IL-33 (ST2). The IL-33 cytokine acts as an alarmin and it has broad effects on T_{REG}, CD8 + T cells, NK cells as well as ILC2 and T_H2[130,131]. IL-33 has also been shown to have a role in asthma development in early life[132], in allergen-induced asthma[42,133] and is associated with type-2 cytokines in asthmatic patients[134]. Furthermore, in a clinical trial of therapeutic anti-IL-33 monoclonal antibody beneficial outcomes were achieved in atopic dermatitis patients with reduced eosinophilia and skin neutrophil recruitment[135]. IL-33 is also known to rapidly activate ILC2s to secrete IL-5 which is important for eosinophil recruitment, and secrete IL-13 which is involved in mucus production and airway hyperresponsiveness[133] (Fig. 3). Neurotransmitters have recently been identified and additional contributors or regulators to Type 2 immune responses. Mucosal sites such as the lungs and the gut are highly innervated, and ILC2s can respond to neuromedin U (NMU), a neuropeptide produced by cholinergic neurons. The parasitic burden during *N. brasiliensis* infection is increased in Nmur1-/- mice, suggesting that NMU has an important role in the generation of protective type 2 immune responses[26,31]. In addition, ILC2s can synthesize acetylcholine (ACh), a neurotransmitter that influences the immune system (Fig. 3). The lung migration of *N. brasiliensis* increased the expression of choline acetyltransferase (ChAT) on lung ILC2s, the enzyme involved in the production of ACh. Pulmonary $ChAT^+$ ILC2s can be induced by IL-25 and IL-33, and ACh production is required for optimal anti-helminth type 2 immune responses[30,136]. In support of the importance of this novel pathway in the induction of optimal type 2 immune responses, parasitic nematodes can produce acetylcholinesterase[44], which could be involved in suppressing the effect of ACh to allow the parasite to establish infection in the host. ACh has a broad effect on several immune cells, such as eosinophils, lung macrophages, and DCs[137]. DCs treated with ACh induce expression of OX40L, which is involved in the promotion of T_H2 responses, and induces production of IL-4, IL-5, and IL-13 by T cells[138].

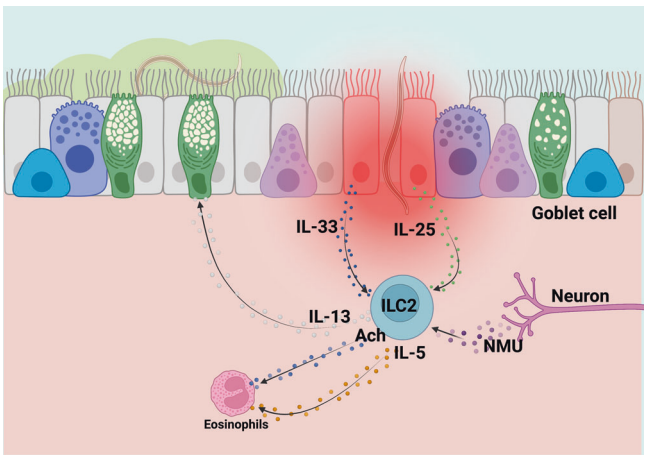

Fig. 3 Immune responses against invading parasite in the lung. Hookworm larvae can cause extensive damage during the lung migratory phase. The release of IL-33 and IL-25, from damaged epithelial cells, and NMU from neurons drives the activation of ILC2s. Activated ILC2s release IL-5 and ACh, involved in eosinophils recruitment, and IL-13 that acts on goblet cells and increases mucus production. Both the presence of activated eosinophils and increased mucus production help with the killing and removal of parasites.

Furthermore, ACh antagonists have been used to treat asthma and chronic obstructive pulmonary disease (COPD), ameliorating mucus production and airway inflammation[30]. Neuroimmune interactions are starting to be explored in the context of helminth infections. Neuroendocrine cells are localized in the lungs and intestine. Therefore, by using lung/gut-dwelling parasites as a model, we can gain insight into the role of neurotransmitters and neuropeptides in type 2 immune responses.

Type 2 responses involved in anti-helminth immunity

IL-13 is a key cytokine produced during type 2 immune responses to parasites, it has been shown to be crucial for expulsion of parasites from the gut[33,139,140], as well as tissue repair and fibrosis[123]. T_H2 cells induced by parasites have been associated with the production of IL-13, with, ILC2s being an innate source of IL-13[11,12,141]. IL-13 induces goblet cell hyperplasia and mucus production and has been linked to collagen synthesis and fibrotic deposition during *S. mansoni* infection or egg challenge[142,143], indicating the broad role IL-13 plays in type 2 immunity. In the absence of IL-13, vascular damage and lung injury is exacerbated during early *N. brasiliensis* infection, suggesting a protective role for IL-13, while it was required for complete eosinophil recruitment the lung[144]. IL-13 signals through IL-4 receptor alpha (IL-4Rα), sharing this receptor with IL-4. IL-13 and IL-4 both signal through STAT6 and for this reason it has been suggested that the cytokines could have a redundant function[145]. Both cytokines are rapidly induced after infection, and they are both necessary to induce tissue repair through macrophage activation[146]. IL-4/IL-13-deficient mice showed impairment in helminth expulsion[147], but while IL-4 seems to play an important role in expulsion of *H. polygyrus*[46], IL-13 may play a major role in driving *N. brasiliensis* clearance[33]. In addition, in experimental asthma model the role of IL-13 and IL-4 did not overlap as IL-4-independent type 2 immune responses have been reported[148,149]. Several other factors can influence anti-helminth immunity, such as the surfactant protein A (SP-A), in a mechanism dependent on IL-4Rα. Lack of SP-A was associated with increased worm burden, egg production, and impaired repair processes. SP-A deficient mice had increased lung damage, with a higher number of red blood cells and neutrophils in the bronchoalveolar lavage (BAL) of infected mice, along with reduced expression of resistin-like molecule α (RELMα), YM1, and arginase by macrophages[150]. Recently, arginase 1 (Arg1) was shown to be highly expressed in alveolar macrophages following *N. brasiliensis* infection. Interesting, during infection monocytes are rapidly recruited in the inflamed lung environment where they acquired an alveolar macrophage-like phenotype. These macrophages expressed SiglecF, CD11c and Arg1, and they can kill *N. brasiliensis* larvae in vitro possibly depleting arginine, an essential amino acid for parasite metabolism[151].

Effect of helminth induced immune responses on coinfections

In a previous section of this review the issue of the immune responses stimulated by a helminth infection could potentially be a strategy of the established worm to protect its host from further infection by other competing parasites. Mouse models using *Trichinella spiralis* demonstrate that the parasite induces a systemic response in distal tissues with increased mucus production observed in the lungs of mice infected with *T. spiralis*, which is dependent on ILC2-derived IL-13. Similarly, intestinal-dwelling helminths *H. polygyrus* or *Hymenolepis microstoma* showed a similar increase of mucin production in the lung[152], and this mucus production is thought to reduce subsequent infections by *N. brasiliensis*[152]. Co-infection models indicate that intestinal helminths can protect the host from other types of microbial infections. Using *H. polygyrus*, Filbey et al. showed in *H. polygyrus* infected mice that infective lung migrating *N. brasiliensis* and *T. muris* larvae were killed by a mechanism involving IL-33 activated $CD4^+$ T cells and IL-5 production[153]. In another model using respiratory syncytial virus

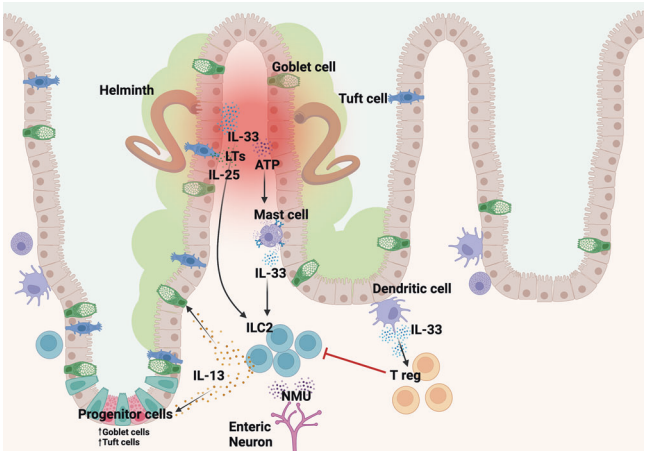

Fig. 4 Intestinal ILC2 activation during helminth infection. Adult hookworm can establish chronic infection in the intestinal tract. Several factors contribute to the activation of intestinal ILC2s. IL-33 released from epithelial cells and from ATP-activated mast cell can directly activate ILC2s. IL-25 and leukotrienes (LTs) produced by tuft cells, and NMU by enteric neurons induce production of IL-13. IL-13 induces hyperplasia of goblet cells and mucus production, and it acts on progenitor intestinal cells to promote goblet cells and tuft cells development. In contrast, IL-33 released from DCs induces expansion of $ST2^+$ T_{REG} that suppress ILC2s activation, reducing type 2 immune responses.

(RSV), *H. polygyrus* was able to induce protection through expression of type I interferon genes and interferon-stimulated genes in the lungs, by a process involving the microbiota but independent from adaptive and T_H2 immunity[58].

Helminth induced immune responses in the gut a focus on mucus

The metaphorically elegant term "weep-and-sweep" is often used to describe the effector mechanisms associated with localized gut immunity to intestinal helminths. *N. brasiliensis*, *H. polygyrus*, and *T. muris* are widely used to study immune responses in the gut. IL-4 and IL-13 are key players of this response, inducing smooth muscle hypercontractility with the involvement of enteric nerves and immune cells such as alternative activated macrophages[32,154,155]. Several other immune cells and cytokines are also involved in the anti-helminth type 2 immune responses in the gut. The intestinal environment undergoes significant tissue remodeling during parasitic infections, with the expansion and hyperplasia of goblet cells observed in multiple nematode infections[156–159]. Goblet cells are the main source of mucins, the major family of glycoproteins that comprise the mucus barrier and provide its viscoelastic properties[160]. MUC2 is the major mucin of the intestinal mucus gel, forming insoluble net-like structures mediated by covalent linkages between different mucin monomers[160]. The mucus barrier plays an important role in homeostasis and defense mechanisms, it protects epithelial cells from pathogens, and modifications are associated with pathologies such as cancer and ulcerative colitis[161]. In mice, the loss of mucins or their components, induced mice to develop spontaneous colitis or inflammation that resembled colitis[162,163]. This indicates an important role for mucins in the pathophysiology of certain diseases. In the response against parasites, the mucus layer is believed to be involved in trapping parasites, reducing motility and nutrient uptake, blocking the parasite to establish infection in the gastrointestinal tract[160]. The expulsion of *T. muris* is dependent on Muc2 expression[164] with Hasnain et al. showed that the absence of Muc2 delayed worm expulsion, leading to an increase in the immune properties of the mucus barrier[164]. Similarly, the cytokines IL-4 and IL-13 have been shown to stimulate goblet cells to produce resistin-like molecule β (RELM-β) that has a protective effect against *N. brasiliensis* and *H. polygyrus* but no protective effect is observed against *T. muris* infection[165,166]. IL-13 is predominantly produced by ILC2s and T_H2 cells that can be activated by several host-derived factors such as IL-33. ILC2s have been identified as a rapid innate source of IL-13 at steady state. During *N. brasiliensis* and *H. polygyrus* infections, T_H2 cells that express the epidermal growth factor receptor (EGFR) can be activated by IL-33 in a TCR-independent manner to release IL-13 and play a role in host protection against infection[167].

Helminth induced immune responses in the gut, a focus on alarmins and leukotrienes

Recently the role of IL-33 in gut immunity has been investigated with Shimokawa et al. showing that IL-33 can be released by dead cells in the intestine, with the concomitant release of ATP from damaged cells activating mast cells to release IL-33 leading to increased ILC2 activation and IL-13 production[168] (Fig. 4). Recently, a novel tissue specific role for IL-33 has been identified in immunity to helminth infection with a deficiency of IL-33 in intestinal epithelial cells (IECs) resulting in delayed parasite clearance and reduced number of ILC2s in the small intestine when challenged by *N. brasiliensis* infection[169]. Interestingly, mice lacking IL-33 in the DC compartment showed enhanced type 2 immune responses, with a lower parasite burden after both *N. brasiliensis* and *H. polygyrus* infection. DC-derived IL-33 was required to induce $ST2^+Foxp3^+$ T_{REG} that suppress type 2 immune responses[169] (Fig. 4). The authors showed an important mechanism in the induction/regulation of type 2 immune responses, observing that the release of IL-33 is highly tissue context dependent, and this can have a strong influence in the generation of immune responses. Another host factor that has recently been a focus in helminth infections is the alarmin IL-25 produced by tuft cells in the intestine[13,14,170]. Intestinal tuft cells are specialized IECs that act as secondary chemosensory cells, with apical microvilli, and express a variety of structural markers, taste receptors, and enzymes for prostaglandins and leukotrienes production[171]. Chemosensory cells express common transcriptional factors and have been identified in several tissues including the intestine, thymus, gallbladder, and airways[172]. Furthermore, they have been identified in the ovine stomach, where they expand during helminth infections, indicating that the expansion of tuft cells is a conserved mammalian mechanism that allows a host to be aware of, and respond appropriately to parasite infection strategies[173]. In the airways, tuft cells have been shown to play a role in allergic type 2 immune responses with their activation by allergens triggering the production of IL-25 and leukotrienes. This in turn activates ILC2s and DCs to drive eosinophil recruitment, $CD4^+$ T cells expansion, production of IL-13, and goblet cell hyperplasia in the lung[172]. Similarly, leukotrienes can be produced by tuft cells after *H. polygyrus* and *N. brasiliensis* infection in the intestine. Tuft cells can sense the parasite and rapidly produce IL-25 and leukotrienes that activate ILC2s (Fig. 4). The absence of leukotrienes synthesis in tuft cells has been shown to result in delayed parasite clearance[174]. Additionally, at steady state IL-25 has been shown to regulate homeostatic IL-13 expression, as IL-25-deficient mice have a reduction in IL-13 expression[14]. IL-13 produced by immune cells also acts in a positive feedback loop, as it increases goblet cell and tuft cells numbers[170] (Fig. 4). Drurey et al. have recently shown that *H. polygyrus* can reduce expansion of tuft cells in a *N. brasiliensis* co-infection model, and *H. polygyrus* E/S products were able to block the effects of IL-4/IL-13 in tuft cells and goblet cells gene expression and expansion[175]. In this study, authors showed that *H. polygyrus* infection downregulated several genes involved in cell differentiation of goblet cells, Paneth cells, and endocrine cells, suggesting that the parasite modulated several cells involved in helminth defense[175]. IL-13 is a key cytokine involved in mucus production and IL-13-deficiency prevented goblet cell hyperplasia in the lung[152]. In addition,

IL-13 has been shown to have a critical role in resistance to intestinal helminth infection[147,176]. ILC2-derived IL-13 has been shown to drive intestinal goblet cell hyperplasia upon IL-33 injection[177], however there is a lack of research on the role of IL-13 and goblet cell hyperplasia in the gut during helminth infections. Using *N. brasiliensis* and *T. muris*, Turner et al. showed that IL-22-deficiency impaired anti-helminth immunity despite a strong induction of IL-5, IL-13, and IL-4 in the intestine[178]. IL-22 deficient mice showed a reduction in goblet cells and delayed worm expulsion, suggesting that IL-22 acts directly on epithelial cells to induce mucin expression[178]. IL-22 is a member of the IL-10 cytokine family, and it mediates epithelial defense, tissue repair, and wound healing processes. Increased levels of IL-22 have been reported during *N. americanus* infection[179] and IL-22$^+$ CD4$^+$ T cells have been observed during *T. trichiura* infection[180]. Turner et al. reported a novel role for IL-22 in the induction of goblet cells and mucus production, following previous studies showing IL-4/IL-13 independent goblet cell hyperplasia during infection with the nematode *Syphacia obvelata*[181].

Helminth infection induced regulation of type 2 immune responses in the gut

An important feature of the host response to helminth infection is that the magnitude of inflammation and activation of immune cells must be tightly regulated to enable efficient killing and removal of harmful levels of parasites and their products, whilst not going overboard and limiting host tissue damage. This is true for the induction and regulation of Type 2 immune responses, as well as Type 1 immune responses. Several factors have been shown able to dampen Type 2 immune responses, like IL-10, TGFβ, IL-13 decoy receptor (IL-13Rα2), and RELMα. Goblet cells and tuft cells express CRTH2, the receptor for prostaglandin D2 (PGD2). Prostaglandins are eicosanoids, bioactive lipids with pro- and anti-inflammatory activity, derived from arachidonic acid[27,182]. The pro-inflammatory role of PGD2 has been shown in the lungs, and intestinal tuft cells have the potential to produce PGD2 with the possibility to be involved in anti-helminth immunity. Oyesola et al. showed that in the intestine the PGD2-CRTH2 pathway limited Type 2 immune responses. Mice lacking CRTH2 showed enhanced *N. brasiliensis* clearance which was associated with increased goblet cell hyperplasia, indicating a novel role for PGD2-CRTH2 pathway in influencing epithelial cells responses during type 2 immunity[183]. As mentioned in the previous section on helminth induced lung immune responses, neurotransmitters and neuropeptides have been shown able to induce and regulate type 2 immune responses. The intestinal environment is highly innervated, and several immune cells are co-localized with enteric neurons[184]. A typical example is the subset of enteric neurons which express NMU and co-localize with ILC2s, providing a rapid activator of ILC2s and promoting intestinal type 2 immune responses[26,31] (Fig. 4). In contrast to NMU, the β2-adrenergic receptor (β_2AR) pathway has been shown to downregulate Type 2 immune responses. ILC2s express β_2AR, and deficiency of β_2AR in mice enhanced type 2 immune responses but did not affect ILC2 development[185]. Increased eosinophilia and goblet cells hyperplasia were observed following *N. brasiliensis* infection in β_2AR-deficient mice, with enhanced worm expulsion[185]. These findings indicate that the nervous system has evolved adrenergic and cholinergic neurons that respectively downregulate and activate intestinal ILC2s[26,31,185], and have the potential to play an important role in inflammatory responses and tissue repair during both helminth infection and host immunopathologic diseases. Another consideration is the important role enteric neurons play in regulating homeostatic and physiological mechanisms in the intestine (e.g. intestinal motility). Enteric neurons need to be protected from damage due to their reduced proliferation and regeneration capacity with Ahrends et al. recently identifying that IL-4 and IL-13 produced during *S. venezuelensis* infection were required to induce neuroprotection. Helminth-induced neuroprotection was dependent on IL-5-mediated recruitment of duodenal eosinophils, and their IL-4/IL-13 production[186]. Long-term neuroprotection was induced due to modification in the progenitor compartments in the bone marrow after *S. venezuelensis* infection. This study identified a novel role for eosinophil-derived IL-4 and IL-13 in intestinal neuroprotection[186]. In addition, a recent study by Progatzky et al. described a novel role for IFNγ in promoting homeostasis and tissue repair after intestinal damage by *H. polygyrus* infection, highlighting the role of enteric glial cells (EGCs) in immunity and repair[187]. Disrupting the IFNs pathway increased eosinophils, neutrophils, and monocytes inflammation, which was associated with a delay in granulomas resolution. The authors identified that EGCs produced CXCL10, which was required for tissue repair after infection[187].

Challenges to studying gut immune responses during helminth infections

One of the biggest challenges when studying immune responses in the gut tissue during helminth infection has been isolating viable immune cells from the lamina propria (LP)[188,189]. These difficulties are largely due to the infection induced changes to intestinal physiology, with increased mucus production and thickening of the gut wall[189]. Immune responses in the intestine have been mainly performed by studying cells in the mLN or peritoneal lavage. However, two protocols have been recently optimized to obtain viable cells from the lamina propria of mice infected with *H. polygyrus* enabling in depth interrogation of cells by high-dimensional flow cytometry[188,189]. Focusing on the inflammatory infiltrate, Webster et al. reported IL-13$^+$ and IL-5$^+$ CD4$^+$ T cells in the LP of mice infected with *H. polygyrus*, increasing by day 7 post infection, in parallel to an increase in neutrophils and DCs. Similarly, Ferrer-Font et al. showed that several immune cells are increased by day 7 post infection. Neutrophils are recruited to the intestine but return to normal levels by day 14. In contrast, on day 7 and 14 eosinophils are still infiltrating the LP, as are RELMα$^+$ macrophages[188]. These protocols are useful to enable investigation of local immune responses against helminths, and in combination with the use of transgenic mice, they can help clarify the role of immune cells in anti-helminthic immune responses.

Even more challenging is the study of local tissue specific immune responses in parasitized humans. Human hookworm studies have been performed in the past, as well as clinical trials for the treatment of inflammatory disorders[190]. Studies in individuals infected with *N. americanus* showed a transient increase of Th2 cytokines in whole blood cultures, while low levels of T_H1 cytokines or IL-10 were detected[191]. In a controlled human infection using 50 *N. americanus* larvae, blood eosinophilia was observed in the two individuals examined, and cytokine/chemokine release followed a pattern that allowed authors to distinguish the infective phase of the parasite. A slight increase in IL-10, CCL17, and IL-13 were observed during the larvae migratory phase, with an increase of IL-10 in the pre-patency phase when the parasites start reaching the gut[192]. However, this study focused on systemic immune responses, the authors did not examine local immune responses. Gaze et al. characterized systemic and mucosal responses during *N. americanus* infection in humans. PBMCs and biopsies from the duodenum from infected individuals showed increased production of type 2 cytokines such as IL-4, IL-13, IL-5, IL-9, as well as IL-10, and TGF-β, in response to *N. americanus* excretory/secretory (NaES) products[179]. Some parasitic infections are well tolerated by their host, leading to the trial of parasites as therapeutic agents for pathologies like ulcerative colitis (UC) and Crohn's disease. *T. trichuria* has shown potential therapeutic effect in both Crohn's disease and UC[193,194]. Broadhurst et al. provided a comprehensive study from an individual affected by UC. Tissue from an UC lesion

showed a prominent inflammatory infiltrate, with T helper cells producing IL-17 and increased pro-inflammatory genes. Infection with *T. trichiura* induced the emergence of IL-22$^+$ T cells in the mucosa. The disease went into remission, possibly due to the promotion of T_H2 immune responses and IL-22 production[180].

CONCLUDING REMARKS

Experimental helminth infection models have begun to help decipher the role of immune cells and cytokines involved in tissue specific Type 2 responses both in the context of immunity, tissue repair and tolerance of the parasite by the host. Significant differences in these responses have been observed depending on the parasite species and route of administration and the tissues involved in the infection. The stage is now set to ask what are the next questions needed for better understanding the immune responses induced in the host by helminth infections? Firstly, we believe that a better understanding of the local responses during chronic helminth infection is required. Although inflammatory and morphological changes are associated with chronic helminth infection there is not the same degree of pathology as seen in allergic inflammation in atopic disease, possibly due to the immunomodulatory effect that adult parasites have on cells of the host immune system. Another key area that needs to be further explored and characterized is the effect of helminth infection on the host microbiota. Metabolites produced by the microbiota are known to have a positive effect on suppressing inflammation and promote health, possibly not only at the site of infection but also at distal tissue sites such as skin, lung and gut. Furthermore, in recent years the phenomenon of "trained innate immunity" has come to the fore. Studies involving *Fasciola hepatica* products suggest that macrophages and monocytes can be trained to have an anti-inflammatory phenotype[195,196]. Although, the question of whether infection with helminths can induce changes on the myeloid compartment or bone marrow stem cells remain unanswered to date future studies need to address whether helminth infection in early life translates to more permanent effects during adulthood. Finally, an important goal is to identify whether the immunomodulatory effects of helminth parasites can be translated into therapies for treating human disease. Safety concerns associated with live parasitic infection and high immunological variability among human populations limit clinical trials. However, a better understanding of the effect of helminth infections in human is needed, and this can be achieved by using safe infection models, with controlled conditions and standardized sample collection methods. In the past few decades, the world of immunology has rapidly evolved. Recent technological advances allowed the very detailed phenotyping of immune cells including the analysis of their metabolic state, and a snapshot of gene expression at single-cell level. The ability to block expression of specific genes in mice through either transient or stable gene deletion at germline level has enabled Type 2 immune responses to parasite infections to be studied in the absence of specific immune cells or cytokines. This has much improved understanding of the mechanisms involved in disease settings as well as anti-helminth immunity. The improvement of protocols to study local immune responses in the intestine of infected mice and humans in combination with technological advances for studying changes to the microbiome will help build a comprehensive picture of the role of different immune cells in type 2 immunity, and the possibility of discovering new immune cell subsets and pathways involved in inflammation, homeostasis, and tissue repair.

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AUTHOR CONTRIBUTIONS

F.V. wrote the manuscript. G.L.G provided feedback and editing the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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