



Eosinophils and helminth infection: protective or pathogenic?

E. Mitre¹ · A. D. Klion²

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Abstract

Since the earliest descriptions of this enigmatic cell, eosinophils have been implicated in both protective and pathogenic immune responses to helminth infection. Nevertheless, despite substantial data from in vitro studies, human infections, and animal models, their precise role in helminth infection remains incompletely understood. This is due to a number of factors, including the heterogeneity of the many parasites included in the designation “helminth,” the complexity and redundancy in the host immune response to helminths, and the pleiotropic functions of eosinophils themselves. This review examines the consequences of helminth-associated eosinophilia in the context of protective immunity, pathogenesis, and immunoregulation.

Keywords Helminth · Eosinophil · Parasite · Immune response

Introduction

The association between eosinophils and helminth parasites was first documented in the late 1800s by Müller and Rieder who described peripheral eosinophilia in two patients with hookworm infection [1]. This observation was extended soon thereafter to other intestinal helminths and trichinosis, raising the hypothesis that a “poison” secreted by parasites attracted eosinophils to the site of tissue damage [1]. Since that time, helminth-associated eosinophilia has been implicated in both protective immune responses and disease pathogenesis in a wide variety of helminth infections. Although the availability of novel mouse models, including eosinophil-free transgenic mice, and other technologic advances have helped dissect many of the mediators and pathways involved in parasite-host interactions, the relationship between eosinophils and helminth infection remains incompletely understood. Moreover, recent appreciation of the role that eosinophils play in orchestrating immune responses to pathogens and

maintaining homeostasis has added an additional layer of complexity. In the following manuscript, helminth-associated eosinophilia will be explored from multiple perspectives using data from animal models and humans to illustrate the dual, and sometimes conflicting, roles of the eosinophil in protective immunity and pathogenesis.

The eosinophil response in helminth infection

Peripheral eosinophilia is one of the hallmarks of helminth infection, and eosinophil accumulation at the site of helminth infection has been described in multiple host species, ranging from zebrafish [2] to humans. That stated, the degree of eosinophilia can vary dramatically from host to host and parasite to parasite. Whereas host factors, including genetics [3–5], prior helminth exposure, and/or concomitant allergic disease [6], may contribute to individual variability in the level of eosinophilia observed in response to a specific parasite, the helminth itself is without doubt the most important determinant of the degree, location, and nature of the eosinophilic response overall.

Helminth parasites are complex, multicellular organisms that have evolved to survive, often for long periods of time, in a susceptible host. They have diverse and complicated lifecycles which can involve the sequential or concomitant exposure of a single host to multiple antigenically distinct developmental stages during the course of infection. For example, in *Schistosoma mansoni* infection, free-swimming

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✉ A. D. Klion
aklion@niaid.nih.gov

¹ Department of Microbiology and Immunology, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

² Human Eosinophil Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

cercariae penetrate the skin, develop into schistosomula that enter a blood or lymphatic vessel, and then migrate through the lung to the liver and mesenteric veins where they develop into adult worms that can reside for years, releasing eggs, which then traverse into the intestinal lumen for environmental release (or are trapped in surrounding tissues) [7]. These different stages of the parasite often elicit discrete immune responses that can be generalized or tissue-specific and may evolve over time (Fig. 1). With some exceptions, eosinophilia is most prominent early in infection and in the setting of tissue invasion or damage. Clinically relevant examples include the dramatic eosinophilia seen in acute schistosomiasis (as compared to that in chronic disease) [8] and the kinetics of the eosinophil response in experimental hookworm infection [9]. Although eosinophilia typically decreases or even resolves over time in many chronic helminth infections, this is not universal. Moreover, release of parasite antigens during anthelmintic treatment may provoke a new or exacerbated eosinophilic response.

The precise nature of the signals that initiate and maintain eosinophilia in helminth infection is incompletely understood. In the case of tissue-invasive parasites, physical damage leading to the release of host-derived alarmins, including IL-33, IL25, and TSLP, likely plays a major role in initiation of the Th2 inflammatory response [10]. This has been convincingly demonstrated in many different experimental models, including IL-33 deficient mice infected with *Nippostrongylus*

brasiliensis [11, 12] or *Strongyloides venezuelensis* [13], where the absence of IL-33 leads to a selective defect in ILC2-derived IL-13 expression and decreased eosinophil recruitment to the lung. Other host molecules may also play a role, including ADP, which is released during tissue damage and has been shown to recruit and activate eosinophils through the purinergic receptor P2Y12 in experimental schistosomiasis [14]. In the intestinal tract, specialized chemosensory tuft cells can respond directly to the presence of helminths by releasing IL-25, which activates ILC2 cells to produce Th2 cytokines that drive tissue eosinophilia [15, 16]. Finally, various parasite-derived molecules, including chitins [17], lipids [18], glycans [19], and other proteins [20] have been shown to either increase or suppress eosinophil activation and recruitment and may be important in determining the nature of the initial immune response.

Once infection has been established, eosinophils often accumulate near helminth parasites or at sites of parasite-induced tissue damage. Whereas CCL11 (eotaxin-1) and its receptor CCR3 are clearly important in this process and have been the best studied, an array of chemokines have been implicated in helminth-associated eosinophil recruitment [21, 22] and CCR3-independent migration of eosinophils towards nematodes has been described [23].

The immune response to helminth infection is extremely complex and our understanding of the cells and mediators continues to evolve (reviewed in [24]). Nevertheless, studies

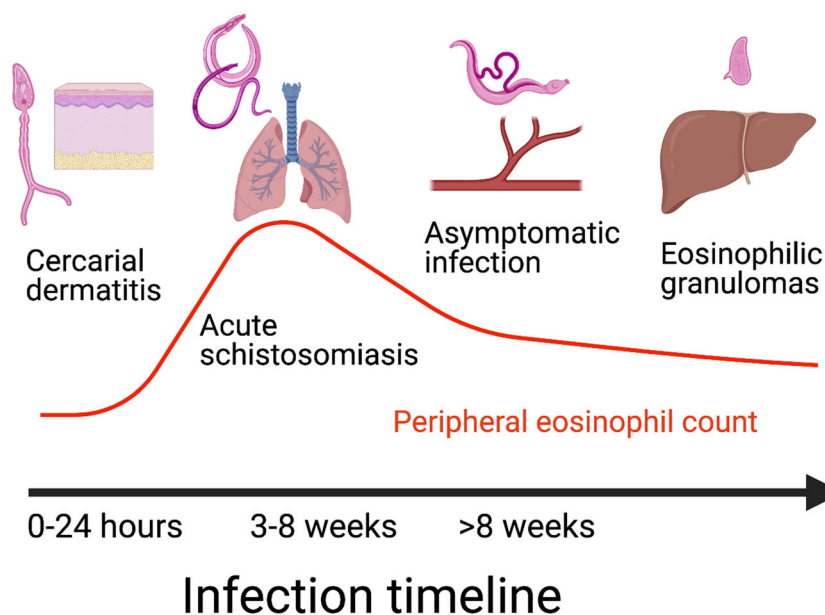


Fig. 1 Temporal and stage-specific factors during *Schistosoma mansoni* infection. Eosinophil responses during helminth infection vary temporally and are dependent on multiple factors including lifecycle stage of the parasite and anatomic location. Initial penetration of the skin by cercariae, which rapidly develop into migrating schistosomula, can result in an acute inflammatory reaction in the dermis within 24 h after exposure. Juvenile worms then migrate through the lung before reaching their final destination in the portal venous circulation and

beginning to lay eggs. Approximately 3–8 weeks after infection, some infected individuals develop a transient acute illness characterized by fever, pulmonary infiltrates, abdominal pain, and marked peripheral eosinophilia (acute schistosomiasis or Katayama fever). Chronic infection is often clinically inapparent; however, development of eosinophilic granulomas around eggs can cause periportal fibrosis in the liver and eosinophilic granulomatous colitis in the intestinal tract (created with [BioRender.com](#))

in humans and experimental models consistently point to IL-5 as a central regulator of eosinophilia and eosinophil activation [25, 26]. While much of the IL-5 produced during helminth infection appears to come from IL-4-driven induction of T helper 2 cells, murine studies have demonstrated that both IL-4-dependent and IL-4-independent pathways contribute to IL-5 production and eosinophilic responses in helminth infections [27–29]. For example, alarmin-activated ILC2 cells can produce IL-5 that acts directly on eosinophils [13, 30]. A simplified summary of the immunological pathways involved in the early eosinophil effector response to helminth infection in the intestinal tract is provided in Fig. 2. The general paradigm is similar in other anatomic locations, such as the lung, although tissue-specific differences clearly exist.

Eosinophil activation is a central feature of helminth infection in both humans and experimental mouse models and has been associated with enhanced killing of helminths *in vitro* [31]. During helminth infection, eosinophils can be activated through a variety of mechanisms, including cross-linking of surface immunoglobulin [32, 33], cytokine stimulation, and

exposure to parasite-derived lipids [18]. Upon activation, eosinophils can release a panoply of mediators and cytotoxic products, including specific granule proteins (major basic protein (MBP), eosinophil-derived neurotoxin (EDN), eosinophilic cationic protein (ECP) and eosinophil peroxidase (EPO)), cytokines, chemokines, leukotrienes, Charcot-Leyden crystals, and reactive oxygen intermediates, which can contribute to parasite killing and modulation of the immune response. These mediators and products can be released by exocytosis or selectively secreted by intact eosinophils through piecemeal degranulation, a complex regulated process whereby preformed mediators and granule proteins are shuttled to the eosinophil surface through a vesiculotubular network [34]. Alternatively, activated eosinophils have been shown to release eosinophil extracellular traps (EETs), composed of decondensed DNA studded with eosinophil granules and Charcot-Leyden crystals [35], in response to a variety of stimuli, including helminth infection. EET release can occur by two different mechanisms, one in which EETs containing nuclear histone H1-bearing DNA are released in the setting of

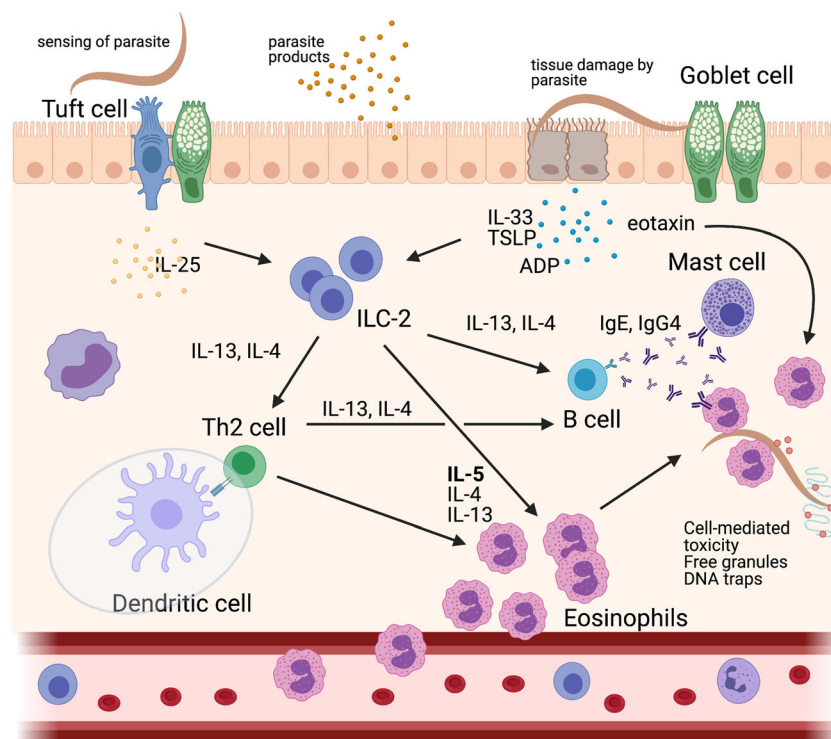


Fig. 2 Immunological pathways driving eosinophilic responses to helminths. This figure is a simplified depiction of our current understanding of the initiation of eosinophilic responses to helminth infection in the intestinal tract. Parasite antigens are initially sensed directly by chemosensory Tuft cells or as a result of damage to mucosal epithelial cells. This leads to release of “alarmins,” including IL-25, IL-33, thymic stromal lymphopoietin (TSLP), and adenosine diphosphate (ADP) which activate innate lymphoid cells type 2 (ILC-2s). ILC2-derived IL-13 (and IL-4) can then drive CD4⁺ T cell polarization towards a T-helper 2 (Th2) phenotype and activate tissue-resident dendritic cells to migrate to local lymph nodes and induce Th2 cell differentiation. Both ILC2s and Th2 cells can induce eosinophil

development, recruitment, and activation through the release of IL-5 (as well as IL-4 and IL-13). IL-5 and eotaxins (together with other chemokines and parasite products not shown) recruit eosinophils to the site of the parasite; they can be activated through antibody-dependent and antibody-independent mechanisms and damage helminths through release of eosinophil granule proteins, eosinophil extracellular traps, and formation of eosinophilic granulomas. Not shown in this figure are the many feedback loops or the ways that eosinophils themselves contribute to the immune response through secretion of cytokines and other mediators that recruit other inflammatory cells and amplify or downmodulate the immune response (created with [Biorender.com](https://www.biorender.com))

cell death [36] and a second where mitochondrial DNA-containing EETs are released from viable eosinophils [37]. In a recent report, murine and human eosinophils were shown to release mostly mitochondrial EETs in response to microfilariae of *Litomosoides sigmodontis* and *Dirofilaria immitis*, respectively, resulting in marked reduction of microfilaria motility in vitro and enhanced clearance when injected intravenously into infection-naïve mice [38].

Whereas most in vitro studies suggest that specific antibody plays a crucial role in eosinophil-mediated helminth killing [39, 40], helminth-associated eosinophil activation in vivo has been demonstrated to occur through both antibody-dependent and independent mechanisms. This has perhaps been most clearly demonstrated in the *N. brasiliensis* model, where the absence of eosinophil degranulation in *Rag-I*^{-/-} mice that lack B and T cells was restored by reconstitution with CD4⁺ T cells [41]. More recent data in the *N. brasiliensis* model suggest that IL-33-stimulated, IL-5-producing CXCR6⁺ST2⁺ memory T cells are the cells responsible for the accumulation of eosinophils strongly expressing MBP in the lungs [42].

Eosinophils as effector cells in the anthelmintic response

Despite substantial evidence that activated human eosinophils traffic to the site of infection and can damage helminths in vitro, the extent to which eosinophils actually protect against helminth infections in humans remains somewhat enigmatic. This is largely due to the correlative nature of available data, such as the association between high blood eosinophil counts and protection against re-infection with *S. mansoni* [43, 44] and the inverse relationship between peripheral eosinophil counts and *Loa loa* blood microfilaria levels [45]. Although eosinophil-depleting agents, including antibodies to IL-5 and IL-5 receptor, are now in clinical use and may begin to shed light on the protective role of eosinophils in human helminth infection, there is little to no experience using these agents in helminth-endemic populations to date. Consequently, our current understanding of the role of eosinophils in protective immunity to helminths is based primarily on data from murine models.

It is important to note that there are several limitations to murine models that impact the applicability of findings to the human system. First, murine helminth infections often display significant biological differences compared to the human infections they are designed to study. For example, whereas *N. brasiliensis* exhibits the same general lifecycle in mice as *Strongyloides stercoralis* and hookworms do in humans, *N. brasiliensis* is typically cleared in mice after about 2 weeks, whereas *S. stercoralis* and hookworms survive for years in humans [46]. This may reflect decreased susceptibility of the human parasites to the host immune system. Similarly, the

different anatomic locations of adult *L. sigmodontis* parasites, which reside in the pleural space in mice [47], and adult filarial parasites of humans, which are found in the lymphatic vessels, skin, and soft tissues in humans, may influence the accessibility of these helminths to host immune attack. Second, murine models designed to deplete or increase eosinophils often have off target effects on other cell types. For example, eosinophil-deficient Δ dblGATA mice lack basophils [48], IL-5 deficient mice have reductions in B-1 cells [49], and IL-5 transgenic strains have supraphysiological levels of eosinophils (at 65 to 265 times greater than wild-type mice) and also exhibit modest increases in neutrophils, lymphocytes, and monocytes [50]. Finally, mice themselves may not be ideal for determining the role of eosinophils in helminth immunity because of species-specific differences between mouse and human eosinophils, including low or absent expression of the high and low affinity IgE receptors, Fc ϵ RI and Fc ϵ RII, on murine eosinophils [33, 51] and the lack of a murine ortholog of galectin-10, a major constituent of human eosinophils involved in the formation of eosinophil extracellular DNA traps [35, 51]. Despite these limitations, murine and human immune responses to helminth infection are remarkably similar, and the ability to manipulate these responses in murine models can provide important insights not easily appreciated from human studies.

Given the large number and variety of helminths, the extent to which eosinophils protect against these parasites is likely to be highly variable and species-specific [52–55], precluding a simple answer to the question of whether or not eosinophils are protective. Thus, in the following review of murine studies, the protective effects of eosinophils are assessed on a helminth-by-helminth basis, focusing on studies that deplete eosinophils with anti-IL-5 antibodies or use genetically modified mice: IL-5 transgenic strains (which have high baseline levels of eosinophils) [50, 53], IL-5 and IL-5R α deficient mice (which have 2–3-fold reductions in eosinophil levels and fail to develop eosinophilia in the context of helminth infections) [56], and the eosinophil-deficient Δ dblGATA and PHIL mouse strains [55, 57, 58]. A summary of findings is provided in Table 1, and a detailed breakdown of study results per helminth species is shown in Table 2. Eosinophil transfers and strains of mice deficient in CCR3, eotaxin-1, or eosinophil granule proteins are not comprehensively examined, although some relevant studies are included. Additionally, in the tables on secondary infection, challenge infections after primary exposure to helminth antigens are excluded.

Worms for which eosinophils appear to impart little to no protective immunity

Available evidence suggests that eosinophils do not play an essential role in primary or secondary immunity to *Hymenolepis diminuta*, *Schistosoma* species, *Fasciola*

Table 1 Categorization of worms by susceptibility to clearance by eosinophils based on mouse studies

Helminth	Category	Type of host	Location in mice
<i>Eosinophils appear to impart little to no protective immunity</i>			
<i>H. diminuta</i>	Cestode	Aberrant	Intestinal
<i>Schistosoma</i> species	Trematode	Natural	Extra-intestinal
<i>F. hepatica</i>	Trematode	Aberrant	Extra-intestinal
<i>T. muris</i>	Nematode	Natural	Intestinal
<i>T. canis</i>	Nematode	Aberrant	Extra-intestinal
<i>Eosinophils appear to impart protection for secondary, but not primary, infection</i>			
<i>T. spiralis</i>	Nematode	Natural	Intestinal + Extra-Intestinal
<i>Eosinophils appear to impart protection for primary, but not secondary, infection</i>			
<i>H. polygyrus</i>	Nematode	Natural	Intestinal
<i>Eosinophils appear to contribute to clearance of primary and (when studied) secondary infection</i>			
<i>M. corti</i>	Cestode	Natural	Extra-intestinal
<i>B. malayi</i>	Nematode	Aberrant	Extra-intestinal
<i>L. sigmodontis</i> *	Nematode	Permissive**	Extra-intestinal
<i>O. lienalis</i> *	Nematode	Aberrant	Extra-intestinal
<i>A. suum</i>	Nematode	Aberrant	Intestinal and Extra-Intestinal
<i>N. brasiliensis</i> *	Nematode	Permissive**	Intestinal and Extra-intestinal
<i>S. ratti/venezuelensis</i>	Nematode	Permissive**	Intestinal and Extra-intestinal
<i>A. cantonensis</i>	Nematode	Aberrant	Extra-intestinal
<i>Worms for which the role of eosinophils remains unclear</i>			
<i>S. stercoralis</i> ***	Nematode	Aberrant	Extra-intestinal

*Investigations were conducted on secondary as well as primary infection

**Rats are natural hosts. Certain mouse strains are permissive

***Was included in text in discussion of other *Strongyloides* species, and thus in the category of helminths for which eosinophils appear to contribute to protective immunity

hepatica [56], *Trichuris muris*, and *Toxocara canis*. Of these, the best studied are *Schistosoma* species and *T. canis* (Table 2).

Much of the early in vitro data demonstrating parasite killing by rodent and human eosinophils was generated using schistosomula, the post-infection larval stage of schistosomiasis [59]. Nevertheless, primary infection studies of *S. mansoni* in eosinophil-depleted and eosinophil-deficient mice have consistently exhibited no differences in liver fluke numbers compared to control mice [60, 61], and one study actually reported increased parasite numbers in IL-5 transgenic mice [62]. Similarly, despite data in humans suggesting a correlation between eosinophilia and resistance to secondary infection [43, 44], murine studies suggest that eosinophils are not essential in this process [60, 62, 63]. These findings are consistent with histological and electron

microscopy analyses of murine skin samples after secondary percutaneous challenge, which demonstrate that abundant eosinophilic infiltration of the skin is not associated with reduction in worm burden [64].

As an ascarid, *T. canis* has both extra-intestinal and intestinal phases during infection of dogs, its definitive host. In humans and mice, however, larvae migrate in extra-intestinal tissues where they cause an eosinophilic inflammatory reaction and ultimately die. Although peripheral and tissue eosinophil levels are often dramatic in toxocariasis, studies of *T. canis* in mice consistently show no effect of eosinophil depletion on worm killing. Numbers of larvae recovered from host tissues were not altered in IL-5 transgenic mice [65, 66] or IL-5 KO mice [67] after primary infection or following depletion of eosinophils with anti-IL-5 antibody following secondary challenge [68].

Table 2 Eosinophil studies in murine models. Results from the literature are listed by effect and individual parasite. Color coding: blue, no evidence for eosinophil-mediated clearance of worms; red, evidence

for eosinophil-mediated clearance of worms; green, evidence for eosinophil-mediated increase in worm numbers

Primary Infection of Cestodes					
Helminth	Model type	Route of infection	Outcome measured	Effect	Reference
<i>Hymenolepis diminuta</i>	IL-5 KO	oral administration of cysticercoids	# worms in intestinal tract	No effect	56
<i>Mesocostoides corti</i>	IL-5 KO	i.p. injection of metacystodes	# larvae in peritoneal cavity and liver	No effect	49
	IL-5 KO	i.p. injection of metacystodes	# larvae in peritoneal cavity and liver	No effect	56
	Δ dblGATA	Intracranial injection of metacystodes	# larvae in brain	Increased at 4 weeks p.i. but not at 2 weeks p.i.	99
Secondary Infection of Cestodes					
Helminth	Model type	Route of infection	Outcome measured	Effect	Reference
none reported					
Primary Infection of Trematodes					
Helminth	Model type	Route of infection	Outcome measured	Effect	Reference
<i>Fasciola hepatica</i>	IL-5 KO	oral administration of metacercariae	# flukes in liver	No effect	56
<i>Schistosoma japonicum</i>	Anti-IL-5 antibody	s.c. injection of cercariae	# worms in portal veins and # eggs in liver 7 or 10 weeks p.i.	No effect	151
<i>Schistosoma mansoni</i>	Anti-IL-5 antibody	percutaneous exposure to cercariae	# worms in portal veins	No effect	60
	IL-5 transgenic	percutaneous exposure to cercariae	# worms in portal veins	Increase	62
	IL-5 transgenic	percutaneous exposure to cercariae	# worms in portal veins	No effect	63
	Δ dblGATA and PHIL	percutaneous exposure to cercariae	# worms in portal veins and eggs per gram in liver tissue	No effect	61
Secondary Infection of Trematodes					
Helminth	Model type	Route of infection	Outcome measured	Effect	Reference
<i>Schistosoma mansoni</i>	anti-IL-5 antibody	percutaneous cercariae after exposure to irradiated cercariae	# worms in portal veins	No effect	60
	IL-5 transgenic	percutaneous cercariae after exposure to irradiated cercariae	# worms in portal veins	No effect	63
	IL-5 transgenic	percutaneous cercariae after exposure to irradiated cercariae	# worms in portal veins	Increase	62
Primary Infection of Intestinal Nematodes with no extra-intestinal phase					
Helminth	Model type	Route of infection	Outcome measured	Effect	Reference
<i>Heligmosomoides polygyrus</i>	Δ dblGATA and PHIL	oral gavage with L3 larvae	# adult worms in intestine and egg production per worm	No effects on # adult worms, decreased egg production	78
	IL-5 KO	oral gavage with L3 larvae	# adult worms in intestine and egg production per worm	Increase	56
	Δ dblGATA	oral gavage with L3 larvae	# adult worms in intestine	Increase	77
<i>Trichuris muris</i>	anti-IL-5	oral gavage with eggs	# adult worms in intestine	No effect	152
	Δ dblGATA	oral gavage with eggs	# adult worms in intestine	No effect	153
Secondary Infection of Intestinal Nematodes with no extra-intestinal phase					
Helminth	Model type	Route of infection	Outcome measured	Effect	Reference
<i>Heligmosomoides polygyrus</i>	anti-IL-5 antibody	oral gavage with L3 larvae after primary infection	# adult worms in intestine and intestinal egg counts	No effect	80
	Δ dblGATA	oral gavage with L3 larvae after primary infection	# adult worms in intestine	No effect	78

Primary Infection of Extra-Intestinal Nematodes

Helminth	Model type	Route of infection	Outcome measured	Effect	Reference
<i>Angiostrongylus cantonensis</i>	anti-IL-5 antibody	oral gavage with L3 larvae	# worms in brain or lungs	Increase	83
	IL-5 transgenic	oral gavage with L3 larvae	# worms in brain	> 50% decrease	84
	IL-5 transgenic	oral gavage with L3 larvae	# worms in brain	30% fewer at 5 and 10 days p.i., 80% fewer at d 25 p.i.	82
	IL-5R α KO	oral gavage with L3 larvae	# worms in brain	> two-fold increase	82
<i>Filaria - Brugia malayi</i>	IL4R α /IL5 KO	i.p. injection of L3 larvae	# adult worms and mfs in peritoneum	conversion of IL4R KO mice from resistant to susceptible with high # of adult worms and peritoneal mfs at 12 weeks p.i. in double KO	27
	Δ dblGATA	i.p. injection of L3 larvae	# adult worms and mfs in peritoneum	Increase	28
	PHIL	IV injection mfs	# blood mfs at days 5,10, 20 p.i.	Increase in mf numbers	90
<i>Filaria - Litomosoides sigmodontis</i>	IL-5 transgenic	s.c. injection of L3 larvae	# worms in pleural space	dramatic (85%) reduction in adult worms 60 d p.i.	88
	IL5 KO	s.c. injection of L3 larvae	# worms in pleural space	No effect	86
	IL5 KO	s.c. injection of L3 larvae	# L3, L4, and adult worms in pleural space	No effect on # adult worms Delayed L3 maturation	87
	IL5 KO IL4R α /IL5 KO	natural infection by vector O. bacoti	# adult worms in pleural space # mfs in blood	Increased # adult worms and mfs in both KO strains Greater increase in #mfs in IL4R α /IL5 KO	29
	PHIL	s.c. injection of L3 larvae	# L3, L4 and adult worms in pleural space	No effect on # adult worms Delayed L3 maturation	87
	Δ dblGATA	natural infection by vector O. bacoti	# adult worms in pleural space and # mfs in blood	Increase in # adult worms and mfs	29
	Δ dblGATA + HR1 blockade	s.c. injection of L3 larvae	# of adult worms in pleural space	Reduction in worm numbers after HR1 blockade is reversed in Δ dblGATA mice. No effect of Δ dblGATA alone on worm numbers.	89
<i>Filaria - Onchocerca lienalis</i>	anti-IL-5 antibody	s.c. injection of mfs	# mfs in skin	Increase	91
<i>Toxocara canis</i>	IL-5 transgenic	oral gavage of eggs	# worms in lungs and intestine	No effect	65
	IL-5 transgenic	oral gavage of eggs	# worms in liver, brain, and muscle tissues 28 d p.i.	No effect	66
	IL-5 KO	oral gavage of eggs	# worms in lungs	No effect	56

Secondary Infection of Extra-Intestinal Nematodes

Helminth	Model type	Route of infection	Outcome measured	Effect	Reference
<i>Filaria - Litomosoides sigmodontis</i>	IL5 KO	s.c. injection of L3 larvae after exposure to irradiated larvae	# worms in pleural space	Increase	86
<i>Filaria - Onchocerca volvulus</i>	anti-IL-5 antibody	L3 larvae in chambers after exposure to irradiated larvae	#L3s in chambers	Increase	154
<i>Filaria - Onchocerca lienalis</i>	anti-IL-5 antibody	s.c. inoculation of mfs 100 days after primary infection	# mfs in skin	Increase	91
<i>Toxocara canis</i>	Anti-IL-5 antibody	oral gavage of eggs after primary infection	# larvae in liver 14 d p.i.	No effect	68

Primary Infection of Nematodes with Intestinal and Extra-Intestinal phases

Helminth	Model type	Route of infection	Outcome measured	Effect	Reference
<i>Ascaris suum</i>	Δ dblGATA	oral gavage of eggs after allergic sensitization of respiratory tract	# larvae in lungs	Reduction in worms after allergic sensitization is reversed in Δ dblGATA mice. No effect of Δ dblGATA alone on # of worms.	6
<i>Nippostrongylus brasiliensis</i>	IL-5 transgenic	s.c. injection of L3 larvae	# intestinal worms days .	Fewer worms, though no difference in time to complete clearance	66
	IL-5 transgenic	s.c. injection of L3 larvae	# intestinal and lung worms	Fewer worms	97
	IL-5 transgenic	s.c. injection or intra-air skin pouch injection of L3 larvae	# larvae in skin, # larvae in lungs, # adult worms in intestine, egg counts	Decrease in # of lung L3s and adult worms. Increased trapping of larvae in skin.	95
	IL-5 KO	s.c. injection or intra-air pouch injection of L3 larvae	# L3s in lung and # adult worms in intestine	No effect on # of L3 larvae in lungs or # of adult worms. Increase in fecal egg counts	95
	Δ dblGATA	s.c. injection of L3 larvae	# larvae in lungs at d 2 p.i., #intestinal adult worms d 7 p.i., egg counts d 6	No effect on # of L3 larvae in lungs or # of adult worms. Increase in fecal egg counts	95
	Δ dblGATA	s.c. injection of L3s	# adult worms in intestine 7 d after challenge	No effect	96
<i>Strongyloides ratti</i>	IL-5 KO	s.c. injection of larvae	# intestinal worms plus fecal egg and larval counts	Increase in # of adult worms as well as fecal egg and larval counts	93
<i>Strongyloides stercoralis</i>	PHIL	s.c. implantation of larvae in cell-permeable chambers	# larvae in chambers	No effect	94
<i>Strongyloides venezuelensis</i>	anti-IL-5 antibody	s.c. injection of larvae	# larvae in lungs, # adult worms in intestines	No difference in # of larvae in lungs. Increase in # adult worms in intestine	92
<i>Trichinella spiralis</i>	anti-IL-5 antibody	oral gavage with L1 stage larvae	# larvae in muscle	No effect	70
	IL-5 transgenic	oral gavage with L1 stage larvae	# adult worms in intestine # larvae in muscle	No effect	74
	IL-5 KO	oral gavage with L1 stage larvae	# adult worms in intestine # larvae in muscle	Slight increase in # of adult worms at d16 but no difference in time to clearance. No difference in # of larvae in muscle .	155
	IL-5 KO	oral gavage with L1 stage larvae	# adult worms in intestine	No effect	71
	Δ dblGATA and PHIL	oral gavage with L1 stage larvae	# adult worms in intestine # larvae in muscle	No effect on adult worm #. Decrease in number of larvae in muscles in both eos deficient models.	72
	Δ dblGATA and PHIL	oral and IV challenge with L1 stage larvae	# larvae in muscle	Decrease in number and size of larvae in muscle	73

Secondary Infection of Nematodes with Intestinal and Extra-Intestinal phases

Helminth	Model type	Route of infection	Outcome measured	Effect	Reference
<i>Nippostrongylus brasiliensis</i>	IL-5 transgenic	s.c. injection of L3 larvae	# larvae in lungs, #worms in intestine, egg counts	Lower # of lung L3s and adult worms at day 3 p.i. compared to WT mice. Similar complete clearance by day 7 p.i.	95
	IL-5 KO	s.c. or intra-air skin pouch injection of L3 larvae after primary infection	# larvae in skin, # larvae in lungs, # worms in intestine, egg counts	Increased # of lung larvae and intestinal worms day 3 p.i. No change in complete clearance of worms by day 7 p.i.	95
	Δ dblGATA	s.c. or intra-air skin pouch injection of L3 larvae after primary infection	# larvae in skin, # larvae in lungs, # worms in intestine, egg counts	Increased # of lung larvae and intestinal worms day 3 p.i. No change in complete clearance of worms by day 7 p.i.	95
	Δ dblGATA (with or without CD4 T cell depletion)	s.c. injection of L3s at 4 weeks after clearance of primary infection	# worms in intestine	No effect on adult worm numbers d10 p.i. EXCEPT when CD4 cells were also depleted	96
<i>Strongyloides stercoralis</i>	anti-IL-5 antibody	s.c. implantation of larvae in cell-permeable chambers after two primary infections given by s.c. injection	# larvae 1 day after challenge	Increase L3 #s in chambers No effect on tissue-migrating larvae	156
	PHIL	s.c. implantation of larvae in cell-permeable chambers after two primary infections given by s.c. injection	# larvae in chambers 1 day p.i.	No effect	94
<i>Trichinella spiralis</i>	IL-5 KO	oral gavage with L1 stage larvae after a primary infection	# adult worms in intestine	Increase	71
	Δ dblGATA	oral gavage with L1 stage larvae after a primary infection	# adult worms in intestine # larvae in muscle	No change in adult worm numbers Increased # larvae in muscle	75

Worms for which eosinophils likely impart protection for secondary, but not primary, infection

Trichinella spiralis is a nematode with both intestinal and extra-intestinal phases. *T. spiralis* most often infects pigs, bear, and wild carnivores but can also infect and complete its lifecycle in mice. While the role of eosinophils in control of *Trichinella* has long been considered somewhat enigmatic [69], the preponderance of data obtained from studies using IL-5 transgenic, IL-5 deficient, Δ dblGATA, and PHIL mice, as well as mice depleted of eosinophils with anti-IL-5 antibody suggest that eosinophils do not protect the host from primary infection (and may in fact promote larval survival in muscle) [70–74].

In contrast, experimental models do suggest that eosinophils play a role in protecting against secondary infection. In one study, IL-5 knockout mice developed a peak intestinal worm burden twice that of control mice and exhibited slower clearing of intestinal worms [71]. Moreover, secondary infection in Δ dblGATA mice resulted in increased numbers of muscle larvae (the opposite of the findings in primary infection) but no differences in adult worm burden [75]. In the

same study, eosinophil transfer into Δ dblGATA mice reduced muscle larvae numbers to those of wild-type mice, albeit only when given with serum from an exposed animal, consistent with prior data demonstrating the role of helminth-specific antibodies in eosinophil killing of *Trichinella* larvae [76].

Worms for which eosinophils likely impart protection for primary, but not secondary, infection

Heligmosomoides polygyrus is a nematode that naturally infects mice and establishes chronic infection in the intestinal tract. Of the three primary infection studies reviewed, two found dramatic increases of adult worm numbers at day 21 in eosinophil-deficient mice [56, 77]. The third study noted no difference, although necropsy was performed at day 14 [78], which may have been too early to see an effect [79]. Of note, egg production per adult female worm was found to be lower after primary infection of both Δ dblGATA and PHIL mice in the same study, suggesting that the presence of eosinophils may enhance worm maturation [78]. Secondary infection studies showed no effect of eosinophil depletion on parasite clearance [78, 80].

Worms for which eosinophils appear to contribute to clearance of primary and (when studied) secondary infection

Eosinophils do appear to play a protective role in the response to most nematodes with an extra-intestinal phase of infection, including filariae, *Ascaris suum*, *N. brasiliensis*, *Strongyloides* sp., and *Angiostrongylus cantonensis*. Of these, perhaps the most clearcut example is non-permissive aberrant infection with the rat parasite *A. cantonensis*, which causes larval persistence and highly morbid eosinophilic meningitis in mice (and in humans) [81]. In all studies reviewed, eosinophils were associated with enhanced clearance of *A. cantonensis* worms from the brain and meninges, with 50–80% fewer worms in transgenic IL-5 mice and a 2-fold increase in IL-5R α knockout mice [82–84]. Although limited to one study, eosinophils also appear to be important in the protective immunity to *A. suum*, as demonstrated by the reversal of enhanced larval killing in the lung following presensitization with house dust mite in eosinophil-deficient Δ dblGATA mice [6].

Filariae are vector-borne tissue invasive nematodes that cause chronic diseases such as elephantiasis and river blindness in humans. A variety of approaches have been used to study the host immune response to filarial parasites in mice, including permissive infection with the rodent filaria *L. sigmodontis* [47], non-permissive infection with the human filarial pathogen *Brugia malayi* [85] or the cattle parasite *Onchocerca lienalis*, and diffusion chamber models in which *O. volvulus* larvae are placed in chambers implanted in the subcutaneous tissue. Although adult worm numbers were similar after subcutaneous injection of *L. sigmodontis* L3 larvae into either IL-5 KO or PHIL mice compared to wild-type controls [86, 87], adult worm burdens and circulating micro-filarial counts were increased when the same mice were infected using the natural mite vector, *Ornithonyssus bacoti* [29]. Consistent with the latter result, IL-5 transgenic mice exhibited a dramatic (85%) reduction in adult worms in the pleural space 60 days after infection [88] and the eosinophilic granulomas around dying worms and worm clearance observed in wild-type mice treated with a histamine 1 receptor inhibitor were absent in Δ dblGATA mice [89]. Similar to these findings, eosinophil-deficient mice demonstrate increased worm burdens after infection with *B. malayi* [28, 90]. Finally, IL-5 antibody-treated mice infected with the cattle parasite *O. lienalis* exhibited delayed clearance of skin microfilariae, especially during secondary infection [91].

Similar to the data in filarial infection models, permissive models using *S. ratti* or *S. venezuelensis* suggest that eosinophils confer some protective immunity, with increased numbers of adult worms, fecal eggs, and larvae in IL-5 deficient and anti-IL-5 antibody treated mice [92, 93]. In contrast,

diffusion chamber experiments using the human parasite *S. stercoralis* found no difference in larval recovery in eosinophil-deficient PHIL mice compared to wild-type mice after primary or secondary infection [94].

In contrast to the data in filarial infection, eosinophils appear to contribute to, but are not required for, clearance of *N. brasiliensis* in the mouse. Whereas studies in IL-5 KO and Δ dblGATA mice found no differences in worm numbers after primary infection and complete clearance of worms by 7–10 days after secondary infection [95, 96], the absence of eosinophils was associated with increased fecal egg counts after primary infection and with higher counts of migrating larvae and intestinal worms at an early timepoint (3 days) after secondary infection [95]. Moreover, IL-5 transgenic mice consistently exhibit reduced worm numbers in primary and secondary infection, demonstrating that eosinophils have the ability to control *N. brasiliensis* worms [66, 95, 97]. Of note, increased numbers of L3 larvae were found in the skin 4 h after percutaneous infection of IL-5 transgenic mice, suggesting that eosinophil-mediated clearance occurs at time of tissue migration [95]. Strong supporting evidence that eosinophils work in a redundant manner with other processes (specifically T cells) to eliminate *N. brasiliensis* worms is provided by a study of secondary infection in Δ dblGATA mice in which the ability of Δ dblGATA mice to eliminate worms as readily as wild-type mice was lost when Δ dblGATA mice were also depleted of CD4 T cells [96].

Studies in cestodes are extremely limited. Whereas the data from intraperitoneal injection studies of *Mesocostoides corti* in IL-5 deficient mice shows no effect of eosinophils on infective larvae [98] (similar to what was observed in *H. diminuta*), intracranial injection of the infective metacystode larva, which can be used to model human neurocysticercosis, resulted in a doubling of brain parasite numbers in Δ dblGATA mice at 4 weeks after infection [99]. While eosinophils appeared to play a role in partially controlling parasite numbers in this model, wild-type mice with lower parasite numbers actually experienced a more rapid course of disease with earlier death, likely due to eosinophil-mediated inflammation in the brain [99].

Eosinophil enhancement of helminth survival

Whereas most data from experimental models suggest that eosinophils have no effect or serve to limit helminth infection, it is becoming increasingly clear that eosinophils can also promote helminth survival and/or maturation in some settings. For example, eosinophils appear to cause accelerated maturation of the filarial parasite, *L. sigmodontis*, as evidenced by altered L3:L4 larva ratios in IL-5 transgenic, IL-5 KO, and PHIL mice [87, 88]. Similarly, while eosinophil absence does not impact adult worm numbers of the intestinal nematode *H. polygyrus*, primary infection of Δ dblGATA and PHIL

mice resulted in increased egg production per female worm [78]. Finally, primary *T. spiralis* infection of Δ dblGATA and PHIL mice resulted in reduced number and size of larvae in the muscle cells of eosinophil-deficient mice, consistent with a beneficial effect of eosinophils in this model [72, 73]. Through an elegant set of experiments, Huang et al. demonstrated that eosinophils promote larval growth by an IL-4 dependent mechanism whereby local interferon-driven inflammation is suppressed and nutrient metabolism is optimized [100].

Variability in helminth susceptibility to eosinophils

Parasitologists have long sought to develop a unifying theory to explain the variability in helminth susceptibility to eosinophils observed in vivo in experimental models. Proposed explanations have included restriction of eosinophil killing to 1) secondary but not primary helminth infections, 2) zoonotic infections, 3) helminths that transit rapidly through extra-intestinal tissues, or 4) extra-intestinal but not intestinal stages [53, 55]. Taking all of the reviewed studies into account, none of these explanations consistently explains the findings. Although eosinophils appear to contribute to clearance of primary infection in many helminth infections, clearance does not correlate with the status of the host as natural or aberrant (Table 1). Eosinophils contribute to clearance of both rapid-transit helminths, such as *N. brasiliensis*, and chronic tissue-dwelling parasites, such as *L. sigmodontis*. Finally, two studies found more than a doubling of the worm burden after primary infection of the intestinal helminth *H. polygyrus* in eosinophil-deficient mice [56, 77], and there is evidence that the eosinophil contribution to clearance of *S. venezuelensis* occurs primarily during the intestinal stage [92]. One interesting trend is the lack of effect of eosinophils in protective immunity to trematode infection, although only *Schistosoma* species and *F. hepatica* have been studied to date (Tables 2).

Although the examples above suggest that the specific helminth and its lifecycle are not major determinants of susceptibility to eosinophils in vivo, a number of factors likely contribute to the observed heterogeneity of results. First, the specifics of the mouse model used is clearly one factor, as illustrated by the differences in outcome when *L. sigmodontis* larvae are administered intravenously or via the natural mite vector [29, 86, 87]. Perhaps most important, however, is the general redundancy of the immune response to helminth infection, which may obscure the role of eosinophils in some settings, as in *N. brasiliensis* infection, where eosinophils are required for worm clearance only when Th2 CD4+ responses are prevented from developing [96]. Finally, under evolutionary pressure to survive, many helminths have likely developed strategies to avoid eosinophil-mediated killing, such as cuticular shedding [101] and direct or indirect suppression of eosinophil function. Consistent with this last hypothesis, chronic

infection with *L. sigmodontis* infection results in downregulation of surface expression of FcγR1 (the high affinity receptor for IgG) on eosinophils decreasing the ability of eosinophils to be activated by immune complexes [102].

Helminth-induced eosinophilia and immunoregulation

Chronic helminth infection in humans and experimental animals is associated with downmodulation of immune responses to bystander antigens, a finding that has been attributed primarily to expansion of T regulatory cells (Tregs) and immunomodulatory monocytes, increased levels of regulatory cytokines, and B cell class switching to IgG4 (reviewed in [24]). This, coupled with epidemiologic data suggesting an inverse relationship between the prevalence of helminth infection and various autoimmune, inflammatory, and metabolic disorders [103–107], has sparked interest in the potential use of helminth infection and/or helminth products as a potential therapeutic intervention. Despite the observed decrease in eosinophilia in the setting of chronic helminth infection, recent studies suggest that eosinophils play an integral role in helminth-associated immunoregulation in several of these disorders.

Helminth-induced eosinophilia and Type 2 cytokine responses have been consistently reported to downmodulate Th1 and Th17 inflammation and improve disease manifestations in murine models of inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis. In a study of 2,4,6-trinitrobenzene sulfonic acid-induced experimental colitis, pre-infection of mice with living schistosomes or subcutaneous immunization with the schistosome protein, 28 kDa glutathione *S*-transferase, was associated with induction of a local and systemic Th2 cytokine response and protection from colitis that was abrogated by depletion of eosinophils [108]. Similarly, in two separate murine models of rheumatoid arthritis, *N. brasiliensis* infection led to eosinophil accumulation in the joints and an IL-4/IL-13-dependent reduction in arthritis and protection from bone loss [109]. Finally, *Fasciola* excretory-secretory extracts induced protection from experimental autoimmune encephalitis that was associated with IL-5-dependent systemic and central nervous system eosinophilia and recapitulated by the administration of IL-33 [110]. Despite these convincing results in experimental models, the outcomes of clinical studies using *T. suis* or *Necator americanus* to treat patients with inflammatory and autoimmune disorders have not been compelling to date (Table 3). Although one placebo-controlled double-blind trial in patients with ulcerative colitis demonstrated a reduction in the ulcerative colitis disease activity score in helminth-treated patients, meeting the primary study endpoint, overall clinical improvement was modest with only 3/30 patients achieving a score of 0–1 as compared to 1/24 in the placebo group [116].

Table 3 Outcomes of clinical studies using helminth infection for the treatment of inflammatory disorders

Disease	Helminth	Study design* duration	N	Primary outcome**	Effect	Significant increase in eosinophilia	Reference
Multiple sclerosis	<i>T. suis</i>	OL 10 months	16	MRI	+	Y	[111]
Multiple sclerosis	<i>T. suis</i>	OL 12 weeks	10	MRI	-	Y	[112]
Multiple sclerosis	<i>N. americanus</i>	DBPC 9 months	75	MRI	-	Y	[113]
Crohn's disease	<i>T. suis</i>	DBPC 12 weeks	252	CDAI	-	Y	[114]
Crohn's disease	<i>T. suis</i>	DBPC 6 months	36	Clinical symptom diary	-	Not reported	[115]
Ulcerative colitis	<i>T. suis</i>	DBPC 12 weeks	54	UCDAI	+	Y	[116]
Celiac disease	<i>N. americanus</i>	OL 52 weeks	12	Post-challenge histology	+	Y	[117]
Celiac disease	<i>N. americanus</i>	DBPC 21 weeks	20	Post-challenge histology	-	Y	[118]
Celiac disease	<i>N. americanus</i>	DBPC 94 weeks	54	Symptoms and post-challenge histology	+/-	Y	[119]
Asthma	<i>N. americanus</i>	DBPC 16 weeks	32	Airway reactivity***	-	Y	[120]
Asthma	<i>N. americanus</i>	DBPC 12 weeks	30	Airway reactivity***	-	Y	[121]

*OL open label, DBPC double-blind, placebo-controlled

**MRI magnetic resonance imaging, CDAI Crohn's disease activity index; UCDAI ulcerative colitis disease activity index

***as measured by the maximum fall from baseline in the provocative dose of inhaled AMP required to reduce the forced expiratory volume at 1 second by 10%

Epidemiologic studies in humans have consistently demonstrated an inverse relationship between helminth infection and metabolic parameters, including hyperglycemia, insulin resistance, and elevated serum lipids [103–105]. Moreover, reversal of this beneficial effect of helminth infection has been documented at the population level following praziquantel therapy for schistosomiasis [122] and in individuals infected with soil-transmitted helminths following treatment with albendazole and/or ivermectin [123, 124]. Although the precise mechanism underlying these findings is unknown, the resolution of depressed baseline levels of adipocytokines and proinflammatory cytokines and concomitant worsening of glycemic control following anthelmintic therapy in patients with strongyloidiasis suggest that helminth-associated modulation of the cytokine milieu is involved. In their landmark study in 2011, Wu et al. demonstrated that murine eosinophil secretion of IL-4 plays a crucial role in preserving glucose homeostasis by maintaining the M2 macrophage pool in white adipose tissue [125]. Of note, *N. brasiliensis* infection was associated with increased numbers of eosinophils in adipose tissue and improved glucose tolerance in obese mice in this study. Chronic helminth infection has subsequently been shown to improve insulin sensitivity and glucose homeostasis in other mouse models (reviewed in [126]), an effect that was recently recapitulated in obese mice

using recombinant Omega-1, a glycoprotein component of schistosome egg antigen [127].

Eosinophil pathogenesis and post-treatment eosinophilia

Despite numerous reports of blood eosinophilia in patients with helminth infection, the role of helminth-induced eosinophilia in disease pathogenesis was not appreciated until 1945 when H.I. Spector made the association between intestinal helminth migration through the lung and eosinophilic pulmonary infiltrates (Loeffler's syndrome) [128]. Innumerable examples of eosinophilic infiltration and granule protein deposition at tissue sites of helminth destruction in humans and in animal models soon followed. Despite considerable variability at the individual level, the degree of blood and tissue eosinophilia often correlates both with parasite killing and with host pathology, creating a clinical conundrum particularly in the setting of enhanced eosinophil-mediated pathology following anthelmintic therapy. Overlap between the pathways involved in parasite containment, tissue repair, and fibrosis presents an additional challenge [129]. Finally, whereas the pathology associated with chronic helminth-induced eosinophilia most commonly occurs locally in direct response to the presence of a helminth or helminth antigens (e.g., chronic

eosinophilic dermatitis in onchocerciasis or eosinophilic meningitis in angiostrongyliasis), systemic manifestations, including eosinophilic endomyocardial fibrosis [130, 131], have been described. The following section will use salient examples to describe the potential role of eosinophils in three different types of helminth-associated pathology: eosinophilic hypersensitivity pneumonia, eosinophilic granulomatous disease, and post-treatment reactions.

Tropical pulmonary eosinophilia

Although eosinophilic hypersensitivity reactions are most common early in helminth infection as developing parasites migrate through the lung (e.g., eosinophilic pneumonitis complicating hookworm infection or acute schistosomiasis [132]), these early reactions typically resolve once infection has been established. In contrast, tropical pulmonary eosinophilia (TPE) is a chronic hypersensitivity reaction to dying microfilariae in the pulmonary microcirculation (similar to sowda, the hyperreactive form of onchocerciasis where microfilariae reside in the skin). TPE occurs in < 1% of patients with lymphatic filariasis and is characterized by high levels of peripheral eosinophilia and eosinophilic alveolitis that can progress to interstitial lung disease and pulmonary fibrosis if left untreated [133]. Histologic studies of lung tissue typically show patchy interstitial eosinophilic infiltrates early in disease with gradual development of predominantly histiocytic focal granulomatous inflammation and fibrosis [134]. Microfilariae are rarely detectable in lung biopsies [135], consistent with a dual role for eosinophils in destruction of microfilariae and tissue pathology. Studies using mice genetically deficient in eosinophils or eosinophil granule proteins have demonstrated a role for both eosinophils and EPO in airway hyperresponsiveness and lung pathology in a *B. malayi* challenge model reminiscent of TPE [90], and neutralizing antibodies to $\alpha 4$ and $\beta 7$ integrins, which block eosinophil transmigration, activation, and survival during inflammation, have been shown to reduce lung eosinophilia and pathology in a similar murine model [136]. More recently, acidic calcium-independent phospholipase A2 (aiPLA2) has been implicated in this process [137]. Consistent with the murine data, patients with TPE appear to have compartmentalization of the eosinophilic response to the lung, with markedly increased levels of the eosinophil granule protein, EDN, in bronchoalveolar lavage fluid as compared to serum [138].

Eosinophil-rich granuloma formation in schistosomiasis

A second example of eosinophil-associated pathology, where the role of eosinophils is less clear, is the development of eosinophil-rich granulomas around dying parasites. Whereas eosinophil-rich granulomas have been described in a variety

of helminth infections, including toxocariasis, angiostrongyliasis, fascioliasis, and anisakiasis, they have been best studied in the context of egg deposition in the lung and presinusoidal capillary venules of the liver in schistosomiasis where their formation can lead to collagen deposition, pulmonary and periportal “pipestem” fibrosis, and ultimately cor pulmonale and portal hypertension [7]. Studies in mice experimentally infected with schistosomes have clearly demonstrated an initial proinflammatory response followed at 6–8 weeks by a dramatic increase in type 2 cytokines and eotaxins with influx of eosinophils and alternatively activated M2 macrophages to sites of egg deposition, tissue damage, and epithelial cell release of alarmins (IL-33, TSLP, and IL-25) that in turn promote tissue eosinophilia and granuloma formation. However, despite experimental data suggesting that eosinophils play a crucial role in destroying eggs in the livers of infected mice [139] and early studies of schistosomiasis in IL5^{-/-} mice which demonstrated eosinophil depletion in liver granulomas and a 40% reduction in fibrosis [140], subsequent studies have demonstrated no effect on liver granuloma formation or fibrosis in eosinophil-depleted Δ dblGATA or TgPHIL mice [61]. Whether this is because eosinophils play a redundant role or no role at all in the pathogenesis of chronic hepatic fibrosis in schistosomiasis remains unclear. It is worth noting that direct activation of human eosinophils by schistosomal lipids has been reported in vitro with resultant leukotriene synthesis and secretion of pre-formed TGF- β , suggestive of a direct role for eosinophils in the modulation of fibrosis in human schistosomiasis [18]. The site of inflammation may be an important factor, however, since eosinophilic granulomas in the intestine in experimental schistosomiasis appear to enhance transit of eggs into the intestinal lumen [141].

Post-treatment reactions in loiasis

Peripheral eosinophilia is common in the 1–2 weeks following treatment of many helminth infections. While typically self-limited and without sequelae in intestinal helminthiasis, severe reactions have been described following treatment of tissue-invasive helminthiasis, including filariasis and neurocysticercosis. In filariasis, microfilaricidal treatment with diethylcarbamazine or ivermectin induces a rapid rise in serum IL-5 levels accompanied by a transient decrease followed by a dramatic increase in peripheral eosinophilia and eosinophil activation that is temporally associated with microfilarial clearance and the development of post-treatment reactions [142–144]. Although the role of eosinophils in the pathogenesis of post-treatment reactions in onchocerciasis and lymphatic filariasis is confounded by the concomitant release of parasite antigens and bacterial products (from endosymbiotic *Wolbachia* species), severe post-treatment reactions, including fatal encephalopathy, have been described in patients with loiasis despite the fact that *L. loa*

does not harbor the intracellular bacteria [142]. Indeed, inflammatory cytokines that are produced in response to gram-negative bacteria, such as TNF, IL6, and IL17A, are not elevated in patients with loiasis following microfilaricidal treatment [142]. Moreover, data from a baboon model of hypermicrofilaremic loiasis demonstrated an association between neurologic findings following ivermectin administration and eosinophil and macrophage infiltration in the brain parenchyma with blockage of capillaries and microvascular damage [145], suggesting that IL-5 production in response to parasite antigen release and the resultant eosinophilia are responsible for post-treatment reactions in loiasis. A placebo-controlled, double-blind pilot trial of the anti-IL5 antibody reslizumab prior to diethylcarbamazine treatment was conducted in 8 patients with loiasis to directly address this hypothesis. Although reslizumab completely abolished the rise in serum IL-5 levels and blunted the eosinophil response post-treatment, adverse events were mild and similar in the two groups [146]. Further studies using agents that more completely suppress eosinophilia are needed to clarify the role, if any, eosinophils play in post-treatment reactions in loiasis.

Post-treatment reactions in schistosomiasis

As in filariasis, treatment of schistosomiasis leads to a rapid rise in IL-5 levels and a concomitant decrease in circulating eosinophils the depth of which is correlated with pre-treatment infection burden [147]. Eosinophil levels and serum levels of parasite-specific IgE subsequently rise above baseline; however, unlike filariasis, transient hypersensitivity reactions are rare, and basophil histamine release is, in fact, suppressed for up to 21 days [148]. Of note, a robust early eosinophil response has been shown to correlate with decreased reinfection at 20 months post-treatment. Although the mechanism underlying this relationship is unknown, incubation of venous blood from *S. haematobium* infected patients pre- and post-treatment with cercarial, egg and adult worm antigens demonstrated changes in the egg and adult antigen-induced cytokine profiles that were associated with decreased susceptibility to reinfection [149].

Conclusions/remaining questions

Eosinophils are multifunctional cells that can selectively secrete cytokines, chemokines, and other mediators in response to helminth infection, contributing both to effector functions and the maintenance of homeostasis [150]. Major challenges in defining the precise role of eosinophils in the immune response to helminth infection include the biologic diversity and complexity of helminth parasites. A better understanding of these responses is important not only for the development of

strategies to prevent infection and limit pathology, but also in the context of targeted therapeutics that deplete eosinophils and may have unexpected effects in individuals at risk for helminth infection. Lastly, the role of helminth-induced eosinophilia in the immunomodulation of autoimmune and inflammatory disorders is an emerging area of research, which promises to increase our understanding of host-parasite relationships and provide novel strategies for the control of inflammatory diseases.

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Declarations

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