International Immunology, Vol. 30, No. 3, pp. 93–102
doi:10.1093/intimm/dxy002
Advance Access publication 13 January 2018

Host responses to intestinal nematodes

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Received 30 November 2017, *editorial decision* 9 January 2018; *accepted* 10 January 2018

Abstract

Helminth infection remains common in developing countries, where residents who suffer from the consequences of such infections can develop serious physical and mental disorders and often persist in the face of serious economic problems. Intestinal nematode infection induces the development of T_h2-type immune responses including the B-cell IgE response; additionally, this infection induces an increase in the numbers and activation of various types of effector cells, such as mast cells, eosinophils and basophils, as well as the induction of goblet cell hyperplasia, anti-microbial peptide production and smooth-muscle contraction, all of which contribute to expel nematodes. Innate immunity is important in efforts to eliminate helminth infection; cytokines, including IL-25, IL-33 and thymic stromal lymphopoietin, which are products of epithelial cells and mast cells, induce T_h2 cells and group 2 innate lymphoid cells to proliferate and produce T_h2 cytokines. Nematodes also facilitate chronic infection by suppression of immune reactions through an increased number of T_{reg} cells. Immunosuppression by parasite infection may ultimately be beneficial for the host animals; indeed, a negative correlation has been found between parasite infection and the prevalence of inflammatory disease in humans.

Keywords: helminths, IgE, IL-13, mast cells, T_h2

Introduction

The 2015 Nobel Prize in Physiology or Medicine was awarded to Satoshi Omura, William Campbell and Youyou Tu (1, 2). Omura and Campbell developed the revolutionary therapeutic drug, ivermectin (3, 4), to cure both onchocerciasis (river blindness) and lymphatic filariasis; Tu developed a new malaria treatment, artemisinin (5). Awarding the Nobel Prize for development of anti-parasitic drugs indicates that parasitic infections remain highly important targets for medical research. Indeed, according to a World Health Organization (WHO) survey, >1 billion people worldwide are currently infected with intestinal parasites (6). When infected with parasites, many individuals develop a chronic infection, which often manifests as severe anaemia and malnutrition and is dependent on the type and number of parasites (7). The infection of children with parasites may induce developmental disorders and delay cognitive development; for some children, these infections may become lethal.

Parasites include the unicellular eukaryotes, protozoa (e.g. malaria, toxoplasma, amoeba) and the multicellular helminths, which are classified as trematodes, cestodes and nematodes (nematodes include trichinella, hookworm, ascarid, filaria) (8). There is a wide variety of methods and sites of parasitic infections; similarly, there is a wide variety of host immune responses that are dependent upon the nature of the infecting parasite. However, there are some general trends within parasitic infections: T_h1-type immune responses develop in response to protozoan infections (9), whereas T_h2-type immune responses develop in response to helminthic infections (10). T_h2 immune cells aid the immune response through production of T_h2 cytokines. These T_h2 cytokines induce the production of antibodies, particularly IgE, and promote an increase in the number of eosinophils and basophils in blood and tissues (11). Furthermore, in mucosal tissues, such as the gastrointestinal tract, T_h2 cytokines induce goblet cell hyperplasia and mucin production, as well as the accumulation of mast cells (12, 13).

In addition to the immune response induced by T_h2 cells, the broader mechanism of anti-helminthic innate immunity is under active investigation. Notably, group 2 innate lymphoid cells (ILC2s), activated by cytokines from epithelial cells, have received much attention as a powerful source of T_h2 cytokines (14, 15). Moreover, various immune responses have developed to attack infecting parasites, but many helminths acquire the ability to escape these immune responses (16); thus, the infection becomes chronic (17). This recent knowledge of innate type and acquired type immune responses against helminths was largely obtained by intensive studies on intestinal nematode infections. Thus, in this article, we focus on immune responses to common intestinal nematodes of experimental animals.

Intestinal nematodes strongly induce a T_h2-type immune response

The importance of T cells in the anti-parasitic response was originally demonstrated in classical experiments where nude mice infected with various helminths showed their inability to expel infected parasites normally (18–20). In normal hosts infected with helminths, naive T cells differentiate into T_h2 cells. During infection by *Trichuris muris* (*T. muris*), mice with a dominant T_h2-type immune response are resistant to the infection, whereas mice with a dominant T_h1-type immune response are susceptible to the infection (21). This indicates that T_h2 cell differentiation is important for protection against helminths (Fig. 1).

T_h2 cells are induced by parasitic infection and produce T_h2 cytokines, including IL-3, IL-4, IL-5, IL-9 and IL-13, which activate effector mechanisms that are necessary to eliminate parasitic intestinal helminths (22–26). Mice that lack IL-4 and IL-13 production develop chronic infections, even when the mice are genetically resistant to infection (27). Conversely, administration of an antibody that neutralizes IFN-γ and thus enhances the T_h2-type immune response, to mice with a susceptible genetic background causes consistent expulsion of the worms (21).

Although it is unclear why naive T cells differentiate into T_h2 cells in hosts infected by helminths, there are several possible reasons. First, helminths exhibit very few TLR ligands that induce dendritic cells to produce IL-12, which is important for differentiation of T_h1 cells. Second, parasites might produce excretory/secretory (ES) molecules that suppress IL-12 production while enhancing production of cytokines that inducing T_h2 cells [e.g. thymic stromal lymphopoietin (TSLP), IL-25 and IL-33] from non-hematopoietic epithelial cells (28–30). Under these circumstances, T_h2 cells and T_h2 cytokines work to induce the activation of many cell types with anti-helminthic functions, including mast cells, eosinophils, basophils and epithelial cells (discussed below). Furthermore, IL-4 induces B cells to produce antibodies, including IgE. These effector cells and molecules act synergistically to expel infected helminths.

We note that ILC2s are an important source of T_h2 cytokines, inducing substantial production of IL-5, IL-9 and IL-13 in response to the IL-33 released from nematode-damaged epithelial cells. Recently, Cardoso *et al.* (31) reported that a neuropeptide, neuromedin U (NMU), is produced by mucosal neurons stimulated either by IL-33 or by *Nippostrongylus brasiliensis* (*N. brasiliensis*) ES products. NMU strongly stimulates activation of ILC2s, inducing T_h2 cytokine production (32), and contributes to protection against *N. brasiliensis* infection (33) (Fig. 1).

Functions of mast cells

IL-3 and IL-9, products of activated T_h2 cells, synergistically induce the accumulation of mucosal mast cells (MMCs) in the mucosa of the small intestine (34). These IL-3- and IL-9-stimulated MMCs release chondroitin sulfate, preventing nematode adhesion to, and penetration of, the mucous membrane (Fig. 2A) (35). *Strongyloides* spp. are expelled by this mechanism (36–38). *Strongyloides venezuelensis* (*S. venezuelensis*) is a convenient infection model of human *Strongyloides*; its adult worms invade the intestinal

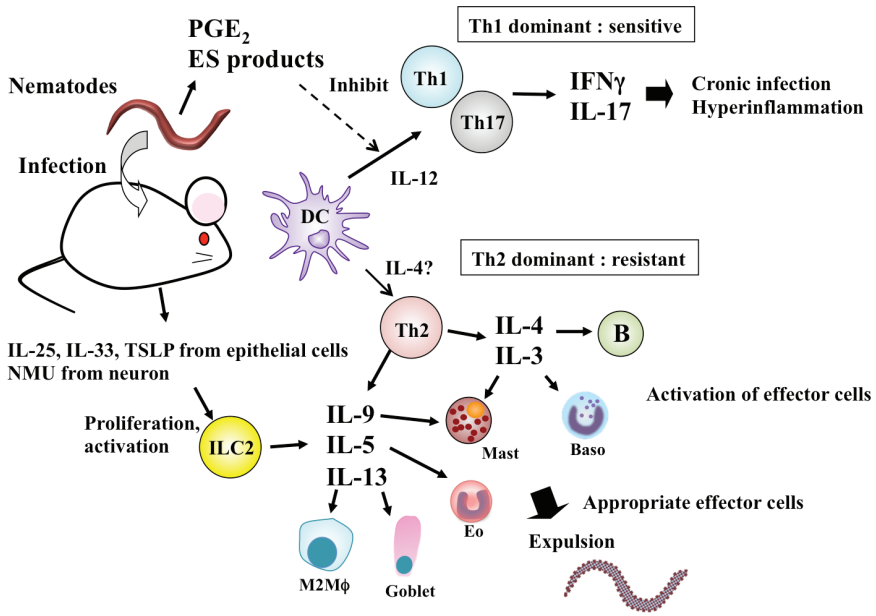

Fig. 1. T_h2-dominant immune responses protect host animals from nematode infection. When nematode larvae infect host animals, the worms stimulate or damage epithelial cells, which then produce epithelial cell-derived cytokines. Parasites release ES products, including PGE_2, which suppresses the induction of IL-12 from dendritic cells (DCs). ES products also stimulate the release of NMU from neurons. Epithelial cell-derived cytokines and NMU cooperatively activate ILC2s to produce T_h2 cytokines. Antigen-captured DCs induce development of T_h2 cells, which can then produce T_h2 cytokines. T_h2 cytokines activate multiple effector cells including mast cells, basophils (Baso), eosinophils (Eo), goblet cells, M2 macrophages (M2Mϕ) and B cells; some of these effector cells contribute to expulsion of the helminths dependently on the type of helminths, for instance goblet cells induce expulsion of *N. brasiliensis* and mast cells are important in expulsion of *S. venezuelensis*.

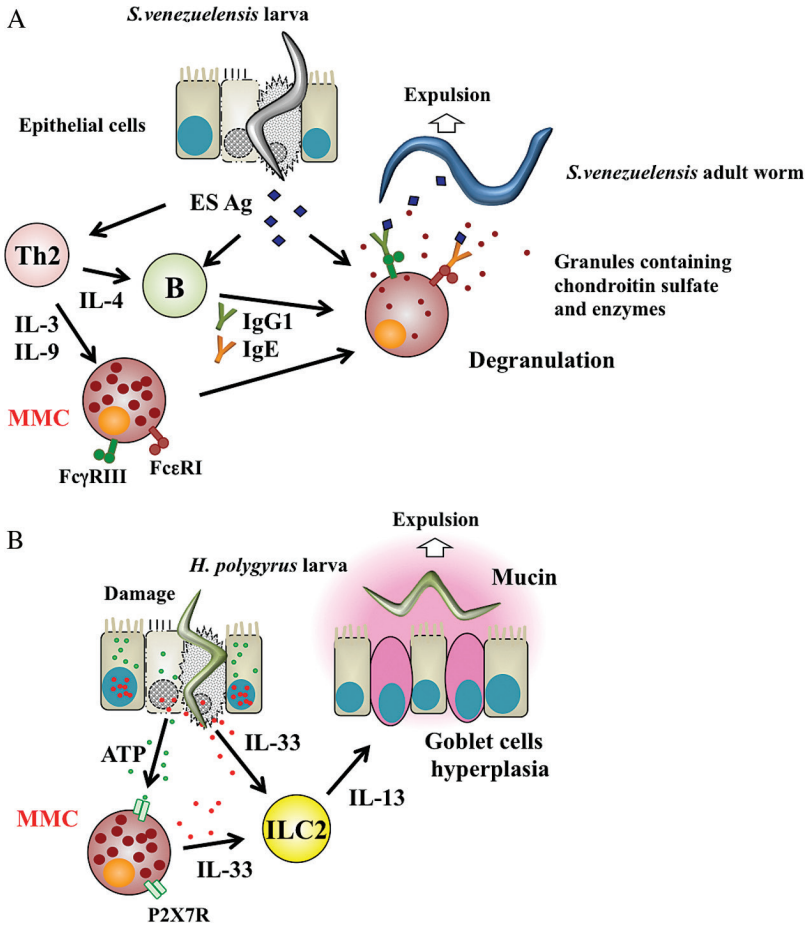

Fig. 2. Role of mast cells in the expulsion of nematode infection. (A) T_h2 cells produce IL-3 and IL-9, which induce proliferation and differentiation of MMCs. MMCs express both FcεRI and FcγRIII, which can bind nematode ES antigen (ES-Ag) using IgE and IgG1, respectively, resulting in activation of the MMCs to release granule contents and expel *S. venezuelensis*. (B) MMCs produce IL-33 upon activation of P2X7R by ATP from damaged epithelial cells; this IL-33 activates ILC2s to produce IL-13 resulting in induction of goblet cell hyperplasia to protect against *H. polygyrus* infection.

mucosa and excrete large amounts of eggs into the intestinal lumen (39). However, when a T_h2-type immune response is induced, these adult worms are expelled from the intestinal tract after ~12 days of infection, largely by action of MMCs (38). However, even when MMCs are present, clearance of the infection is delayed in Fc receptor γchain (FcRγ)-deficient mice (37). This indicates that antibodies are necessary for parasite expulsion by MMCs; however, the critical antibody isotype remains unknown.

Recently, we investigated this aspect, using mice deficient in activation-induced cytidine deaminase (AID), who have no capacity to switch immunoglobulin classes during infection (40). Thus, they can produce IgM, but not IgG, IgA or IgE, when infected with *S. venezuelensis*. Further, they required a longer period (>9 additional days) for parasite expulsion, compared with wild-type mice. T_h2 cells and MMCs exhibit normal development in both wild-type and AID-deficient mice (41). Additionally, during infection with *N. brasiliensis*, AID-deficient mice are able to expel *N. brasiliensis*, suggesting that their goblet cell development remains intact. Therefore, we purified IgG1 and/or IgE from the sera of normal mice that had been infected twice with *S. venezuelensis*; we administered these purified antisera to AID-deficient mice. Both isotypes promoted expulsion of parasites in a dose-dependent manner (41).

Furthermore, a combination of IgG1 and IgE collaboratively augments the capacity of AID-deficient mice to expel *S. venezuelensis* (41). IgE constitutes a trace (~1/200) compared with the concentration of IgG in blood, but demonstrates a strong effect; in normal mice, both IgG and IgE work together to eliminate *S. venezuelensis*. Thus, the FcRγ-mediated activation of MMCs by cooperative efforts of IgG1 and IgE is important for elimination of *S. venezuelensis*.

We previously reported that C57BL/6 mice, after treatment with IL-18 and IL-2, are able to promptly expel surgically implanted adult *S. venezuelensis* worms (38). These mice developed mucosal mastocytosis and exhibited high levels of serum mMCP1, a marker of MMC activation. These results revealed that proper activation of MMCs is important for expulsion of *S. venezuelensis*.

Notably, the protective function of mast cells is observed in the late stages of infection, where T_h2 cells stimulate various cell types through the activity of T_h2 cytokines (42). In contrast, during defence against the rodent nematode

Heligmosomoides polygyrus (*H. polygyrus*), mast cells are required for the early T_h2 immune response (43, 44). $Kit^{W}/Kit^{W\text{-}v}$ mice lacking mast cells cannot sufficiently induce T_h2 immune responses against *H. polygyrus*. These studies also demonstrated the importance of IL-25, IL-33 and TSLP from mast cells. Shimokawa *et al*. also reported the importance of IL-33 production from mast cells, and further noted that Spi-B-deficient mice possess an increased number of mast cells and are thereby resistant to *H. polygyrus* (45). These mast cells utilize ATP stimulation to produce IL-33, which activates ILC2s to produce IL-13 and goblet cell hyperplasia (Fig. 2B).

Parasite infection and eosinophils

The accumulation of eosinophils in nematode-infected sites was shown in classical experiments (46). Later, investigators discovered the relationship between parasitic infection and pulmonary eosinophilia (Löffler's syndrome) (47). Although the mechanism of this eosinophil accumulation was unknown for many years, we described this mechanism using an *S. venezuelensis* infection model. First, we demonstrated that nasal administration of IL-33 could induce pulmonary eosinophilia, even in Rag2-deficient mice (48). Next, we examined whether *S. venezuelensis* could induce pulmonary eosinophilia in wild-type and Rag2-deficient mice (49).

Some parasitic intestinal nematode larvae, including *S. venezuelensis* and *N. brasiliensis*, do not travel directly to the intestinal tract upon percutaneous or oral infection; instead, they arrive at the lung via the bloodstream, then penetrate the alveolar cavity and ascend to the throat, where they are swallowed with sputum. Finally, they reach the small intestine and begin maturation (50, 51). Thus, injury of the lung tissue is induced by parasitic larvae, stimulating release of IL-33 from type II alveolar epithelial cells (ATIIs). This IL-33 induces ILC2s to accumulate, proliferate and produce IL-5 and IL-13, which combine to induce pulmonary eosinophilic inflammation (Löffler's syndrome) (Fig. 3) (49).

In vitro experiments demonstrated that eosinophils have the ability to kill schistosomula in combination with antibodies and complement (52, 53). Importantly, IgE and eosinophil cytotoxicity (antibody-dependent cellular cytotoxicity) has been widely reported as a mechanism for helminth exclusion (54). However, the *in vivo* role for IgE and eosinophils is not yet clear because expression of high-affinity FcεRIα is not often found in murine eosinophils, the most common experiment animal model.

During *N. brasiliensis* infection of eosinophil-deficient mice and normal wild-type mice, comparable numbers of adult worms harboured in the intestinal tract are detected in both types of mice; however, increased number of eggs are detected only in faeces of the eosinophil-deficient mice (55). During *H. polygyrus* infection, eosinophil-deficient mice harbour more worms than wild-type mice do (56). In microfilarial infection achieved by intravenous administration of *Brugia malayi*, the population of microfilaria decreases shortly after infection in wild-type mice, whereas the population remains stable after infection in eosinophil-deficient mice (57).

Thus, eosinophils contribute in a limited manner to host defence, as shown by the lack of effect in infectious models of *Schistosoma mansoni* (58), *Strongyloides stercoralis* larvae (59) and *T. muris* (60), though eosinophils are able to kill the larvae of all these species *in vitro*. Conversely, it has been reported that eosinophils may promote infection (61). New larvae of *Trichinella spiralis* (*T. spiralis*) formed in the intestinal tract migrate to muscles, where they invade muscle fibres and become capsular larvae (62). Here, T_{reg} cells are induced by eosinophil-produced IL-10; larvae can thus survive because IL-10 suppresses production of nitric oxide (NO). However, eosinophil-deficient mice exhibit insufficient T_{reg} cell differentiation, enhanced IFN-γ expression, enhanced NO production and a reduced cystic larvae population (63). Furthermore, larvae of *Litomosoides sigmodontis* (*L. sigmodontis*), a rodent filaria, grow more rapidly in the presence of eosinophils, suggesting that eosinophils support the growth of larvae (64).

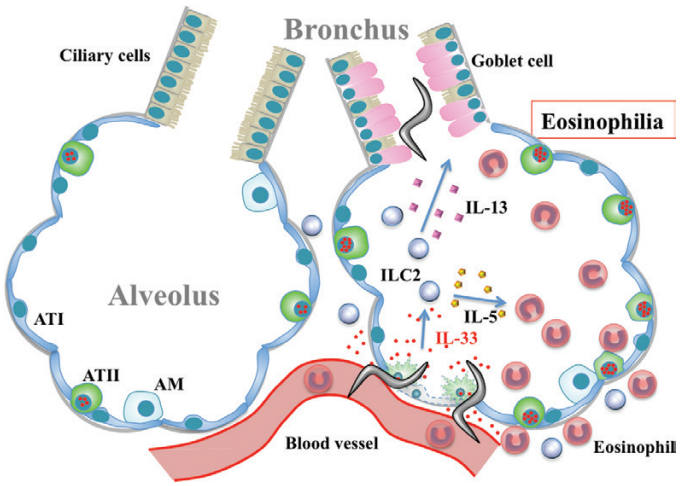

Fig. 3. Mechanism of Löffler's syndrome. *Strongyloides venezuelensis* larvae infect host animals through the skin, then migrate to the lung via the bloodstream (shown at the bottom of the figure). When the larvae reach the lung, they penetrate blood vessels and alveolar walls by disrupting the endothelial and epithelial cell layers. The dead cells release damage-associated molecular patterns such as IL-33, which stimulates ILC2s to proliferate and produce T_h2 cytokines. IL-5 and IL-13 cooperatively induce eosinophilia in the lung. AM, alveolar macrophage; ATI, type I alveolar epithelial cell; ATII, type II alveolar epithelial cell.

Once a host is infected by a parasite, it can gain immunity against the parasite, and thus become resistant to re-infection by the same parasite (65, 66). When wild-type mice are re-infected with *N. brasiliensis*, parasite larvae are captured in the skin and fewer larvae are able to reach the lung, whereas eosinophil-deficient mice allow many larvae to reach the lung (55). Eosinophils may support parasitism of *T. spiralis* during primary infection; however, eosinophils work during re-infection to inhibit migration of new larvae and proliferation of intramuscular larvae (61). Parasite-specific antibodies support eosinophil-mediated infection resistance. Antibodies support *in vitro* activities of eosinophils against *T. spiralis* larvae: binding, degranulation and killing (67). Antibodies have also been shown to synergize with basophils and M2 macrophages to inhibit movement of *N. brasiliensis* and *H. polygyrus* (68); eosinophils may function similarly to control parasites. Eosinophils can release DNA to capture antigens (similar to neutrophils); this has been demonstrated *in vitro* during capture of *Haemonchus contortus* larvae (69).

Protective immunity of basophils to parasitic infection

Min *et al*. (70) reported an ~50-fold increase in number of IL-4-producing basophils in the liver and lungs of mice infected with *N. brasiliensis*, as well as a focused role of basophils in the host response.

In order to clarify the *in vivo* function of basophils, the basophils were removed using antibodies for FcεRIα chain (MAR-1) (71) or for CD200R3 (Ba103) (72); this was used in some parasite infection models. Oral administration of whipworm eggs (*T. muris*) in a resistant murine model leads to goblet cell hyperplasia in the intestinal epithelium at 21 days post-infection; it also causes development of T_h2 cells in mesenteric lymph nodes, thus expelling the worms (21). In this model, basophils also increase in a TSLP-dependent manner. However, depletion of basophils through MAR-1 antibody administration shifts the dominant cell balance in normal mice from T_h2 to T_h1; this leads to suppression of goblet cell proliferation in the small intestine epithelium, of mucin production and of production of resistin-like molecule-β (RELMβ), thereby prolonging the infection. Thus, in the absence of basophils, host animals fail to develop a T_h2-type immune response and cannot substantially expel worms (73, 74).

In contrast, although Ba103-mediated basophil removal suppresses T_h2 cell development, IgE production and eosinophil proliferation during filarial *L. sigmodontis* infection, there is no effect on the population of infected filaria (75).

Thus, interesting results have been obtained, supporting previous hypotheses that basophils influence T_h2 differentiation (73, 76–78). However, since FcεRIα and CD200R3 are also expressed on mast cells, this method may not provide sufficient specificity. To resolve this problem, genetically modified basophil-deficient mice were developed (e.g. Mcpt8-DTR, Mcpt8Cre, BasTreck) (79). Even when basophils were removed in Mcpt8-DTR mice by administration of diphtheria toxin, infection with *N. brasiliensis* induced conventional differentiation of T cells into T_h2 cells, as well as normal antibody production and eosinophil induction; importantly, the worm burden was also unaffected. This indicates that basophils are not involved in the host immune response to primary infection by *N. brasiliensis* (80).

Basophils are, however, important in the immune response to re-infection by *N. brasiliensis*. When *N. brasiliensis* re-infects wild-type mice, the larvae are captured intra-dermally and blocked from migration to the lungs. Additionally, basophils and monocytes accumulate around larvae captured within the skin. In contrast, during infection of basophil-deficient mice, larvae can migrate to the lungs as in primary infections. Notably, parasite-specific IgE binds to FcεRI on basophils. When parasite antigens interact with basophil-bound IgE, the basophils produce IL-4 and IL-13. This stimulates monocyte differentiation into M2 macrophages, production of the arginine-degrading enzyme arginase 1 and the capture of larvae in skin (Fig. 4). Thus, during re-infection, the antibody-dependent immune response blocks infection of *N. brasiliensis* (68).

However, basophils do not completely block invasion of *N. brasiliensis* in the skin, as some larvae can pass through the lungs and migrate to the intestinal tract. In this case, basophils also protect against parasitic infection of the small intestine. Binding of parasite antigen to FcεRI-bound parasite-specific IgE causes basophils within the small intestine to produce IL-4. The IL-4 then increases proliferation and activation of T_h2 cells, resulting in elimination of the worms (Fig. 4). Basophils also induce T_h2 enhancement in the intestinal tract during *H. polygyrus* infection (81).

Mast cells are important for resistance against *S. venezuelensis* infection; this was determined by studies of c-Kit mutant mice that lack mast cells (82). Involvement of basophils has been suggested, since infection with worms is more prolonged in c-Kit mutant IL-3-deficient mice where mast cells and basophils cannot increase (36). Recently the role of basophils was analysed in a basophil-deficient mouse model (Mcpt8-DTR), where an increased number of eggs were observed in faeces and an increased number of adult worms were observed in the small intestine; however, prolonged infection, as seen in mast cell-deficient mice, was not noticeable. Furthermore, *S. venezuelensis* infects skin, as does *N. brasiliensis*, but basophils do not protect against re-infection by *S. venezuelensis* (83).

Activation of non-immune cells by T_h2 cytokines

T_h2 cytokines, including IL-13 (produced by local T_h2 cells and ILC2s), act on non-immune cells and are involved in the expulsion of helminths (Fig. 5) (26, 84). In the gastrointestinal tract, IL-13 directly acts on intestinal epithelial cells to induce goblet cell hyperplasia and mucin production, which prevent helminth adhesion to the intestinal surface and wash them away (85).

Activated epithelial cells (Paneth cells) also secrete antimicrobial peptides, including RELMβ (86). The RELMβ is important for eliminating parasites (e.g. *N. brasiliensis* and *H. polygyrus*) that live in the lumen; however, it is ineffective against nematodes such as *T. spiralis* entering the epithelium. IL-13 and IL-9 expel helminths from the intestinal tract by activating intestinal smooth muscle cells to enhance peristalsis (87, 88). In addition, enhancement of epithelial cell turnover is an important host response against helminth infection.

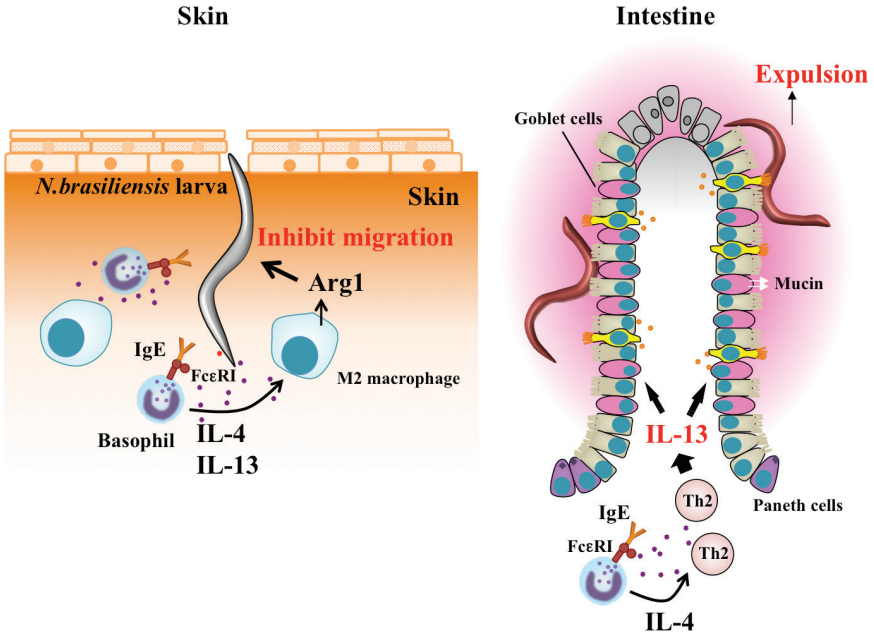

Fig. 4. Contributions of basophils during re-infection by nematodes. On re-infection by *N. brasiliensis* larvae in the skin, basophils are rapidly recruited to the infected site. In the presence of IgE, basophils produce IL-4 and IL-13. IL-4 stimulates macrophages to differentiate into M2 macrophages and induces arginase 1 (Arg1) production, which inhibits larval migration to the lung. Some larvae that escape from the basophil-mediated skin trap can migrate to the intestine, where basophils also recognize worm antigens by IgE–FcεRI and produce IL-4. IL-4 stimulates T_h2 cell accumulation and the production of T_h2 cytokines that activate effector cells for expulsion of the parasite.

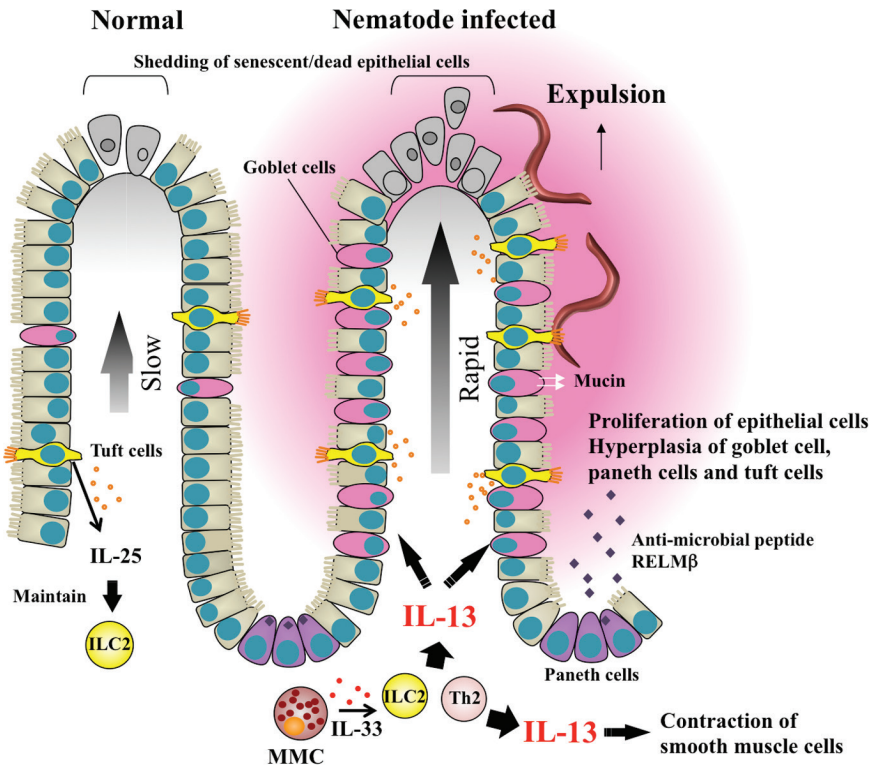

Fig. 5. IL-13 is a central mediator in the intestine for expulsion of nematodes. IL-13 from T_h2 cells or ILC2s stimulates epithelial cells in the intestine. Activated epithelial cells proliferate and differentiate into Paneth cells, goblet cells and tuft cells. Paneth cells produce anti-microbial peptides, such as RELMβ; goblet cells secrete massive amounts of mucin into the intestinal lumen; tuft cells produce IL-25, which activates ILC2s. Enhanced proliferation of epithelial cells hastens the migration of epithelial cells towards the tips of villi, where senescent or dead epithelial cells are shed. Additionally, IL-13 acts on smooth muscle cells to increase peristalsis. These cooperative effects remove nematodes from the intestinal mucosa.

Epithelial cells actively divide near the base of the villi, differentiate into absorptive epithelium and goblet cells and migrate towards the tip of the villi, where senescent epithelial cells drop off from the tip (89). During *T. muris* infection, this epithelial cell replacement is enhanced by the action of IL-13 and amphiregulin, thereby eliminating adherent worms and reducing the epithelial area where they can grow (90, 91).

Furthermore, tuft cells in the intestinal epithelium constitutively produce IL-25 to maintain ILC2s in the lamina propria. IL-4 and IL-13 induce tuft cell hyperplasia and enhance the production of IL-25, contributing to the expulsion of *N. brasiliensis* (92, 93).

Immune regulation by helminth infection

Importantly, many parasitic infections become chronic because of various immune evasion strategies developed by parasites that have coexisted with humanity for millennia. An important parasite strategy is to control the host immune system. Various ES products released by helminths, including prostaglandins, induce T-cell development into a parasite-favourable type by regulating activity of antigen-presenting cells through suppressed IL-12 production (94, 95).

In host animals, many parasitic infections increase numbers of T_{reg} cells, which are central to immune regulation (96). Since T_{reg} cells suppress extreme T_h2 and T_h1/T_h17 responses, this can attenuate immune activity against helminths. Though immune regulation is a common feature of chronic parasitic infection, it is also advantageous for the host. During *Schistosoma* infection, if T_h1/T_h17-type inflammation is continuous and outcomes include hepatic disorders, splenomegaly and portal hypertension, which may result in death; however, by changing to T_h2-type inflammation, severe symptoms can be avoided.

Importantly, if the T_h2 immune response is excessive, it can also become pathologic, but excessive T_h2 inflammation can be suppressed by IL-10 and TGF-β, major products of T_{reg} cells (97). Conversely, low-specificity immunosuppression may be beneficial for the host in certain situations. A 'hygiene hypothesis' suggests that the living environment may be too clean in developed countries; thus, the near-complete elimination of pathogen infection may cause immune dysfunction, including allergies and autoimmune diseases (98–101). Although a decrease in parasitic diseases is not the only change associated with improved hygiene, there is evidence that immune cells in parasite-infected hosts are less responsive (102, 103) and that re-activity recovers when the parasites are exterminated (104). In addition, T_{reg} cells from helminth-infected hosts have been shown to suppress airway inflammation in a mouse asthma model (105).

Attempts have been made to utilize these anti-inflammatory effects to treat symptoms of autoimmune diseases and inflammatory bowel diseases (106). The current method is to infect patients with a small number of nematodes; thus far, it seems to be safe, but has not yet proven effective. Importantly, parasite infection is not entirely beneficial to the host. Often, it may reduce resistance against other infectious diseases or even exacerbate inflammatory diseases (107). In contrast, with further study of the mechanism of immune regulation by helminths, medical therapy may be possible using a parasite ES component, rather than the parasite itself (106). Thus, the risk of pathogenicity might be avoided, and the patient's physiological resistance to infection would also be maintained.

Conclusions

A host attempts to eliminate invading parasites through an epithelial barrier, innate immunity and acquired immunity; however, parasites can avoid and regulate immune responses, thereby creating an optimal environment for their own maturation and breeding while at the same time allowing the host to survive by avoiding excessive damage. The host is able to adjust its immune responses to expel the parasite without excessive self-damage, and to avoid excessive suppression that would impair its ability to protect against other pathogens. These conflicting immunological processes occur in many parasitic infections and are sufficiently controlled that one response does not become excessive, much like the response to commensal bacteria. Some parasites persist for several years; for many centuries, it has been suggested that infection by parasites is normal for humans.

Viral infection is still a widespread phenomenon and bacteria can be important symbionts with the human body. Thus, it is possible that parasites are the only pathogens that are rapidly decreasing in developed countries, thereby disturbing the balance between immune reactions and pathogen invasion; the rise of inflammatory diseases, including allergies and autoimmune diseases, is quite conspicuous. Perhaps clarification of the mechanism of immune regulation by parasite infection will contribute greatly to the treatment for inflammatory diseases. Moreover, elucidation of the immune regulatory mechanism may lead to the development of therapeutic methods to effectively eliminate life-threatening or nuisance parasites.

Funding

This work was supported in part by a grant from the Japan Society for the promotion of Science KAKENHI-C grant number 17K08813 (to K.Y.).

Acknowledgements

We thank Tadamitsu Kishimoto (Osaka University) for the kind donations to the Department of Immunology, Hyogo College of Medicine.

Conflicts of Interest statement: the authors declare no conflicts of interest.

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