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Protective immune mechanisms in helminth infection

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Abstract

Important insights have recently been gained in our understanding of how host immune responses mediate resistance to parasitic helminths and control associated pathological responses. Although similar cells and cytokines are evoked in response to infection by helminths as diverse as nematodes and schistosomes, the components of the response that mediate protection are dependent on the particular parasite. In this Review, we examine recent findings regarding the mechanisms of protection in helminth infections that have been elucidated in murine models and discuss the implications of these findings in terms of future therapies.

More than two billion people are infected with parasitic helminths[1]. Although infections by these pathogens are generally not fatal, they are associated with high rates of morbidity, with chronic infection often leading to anaemia and malnourishment[1]. Developed countries have controlled these infections through primary health-care programmes and effective public sanitation, but helminth diseases are still widespread in developing nations and often drug treatment does not protect against rapid re-infection. The need for effective vaccines to control these infections is compelling and at least a few clinical trials are currently underway[2,3]; however, one impediment towards development of an effective vaccine is a lack of understanding of the actual components of the immune response that mediate protection against helminths. In this Review, we examine the host protective mechanisms with regard to the cell types and molecules involved in helminth expulsion and in control of pathological inflammation that is associated with infection.

Helminth infections and the corresponding host immune responses are products of a prolonged dynamic co-evolution between the host and parasite. For parasites, it is advantageous to trick the host into developing an ineffective immune response, to find a suitable niche for maturation and propagation, and to do so without killing or unduly harming the host. Conversely, the host

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DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene

chitinase | FcεRI | IL.4 | IL.5 | IL.9 | IL.10 | IL.13 | IL.17 | IL.21 | IL.23p19 | STAT6 | TSLP

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has to ideally generate an effective immune response to expel the parasite, and minimize its harmful effects, while not sacrificing its ability to effectively respond to other pathogens. The host immune system evolved in the context of a parasite-replete environment, and the balance of immune effector and regulatory cell populations are at least partly a consequence of ongoing responses to infectious organisms that can often simultaneously invade host tissues. Although such dynamic host–pathogen interactions exist throughout much of the world, in industrialized countries infectious diseases are better controlled as a result of increased hygiene, the administration of vaccines at an early age and the widespread use of antibiotics. Although this has resulted in marked reductions in chronic and severe disease, recent studies indicate a possible adverse effect of this enhanced control of infectious diseases that leads to an increase in inflammatory disorders. One mechanism by which this unfavourable result occurs has been suggested by an extension of the hygiene hypothesis, which proposes that a dysregulated immune response might develop in individuals who were not exposed to chronic helminth infections, increasing the likelihood of the development of allergic and autoimmune diseases[4,5]. Studies have supported this model as the administration of helminths can downmodulate autoimmune and allergic inflammation, whereas clearance of the helminth infection can result in a resurgence of these diseases[5–9]. Understanding the helminth-induced immune regulatory mechanisms that control certain inflammatory diseases might point the way towards future treatments for these increasingly common immune disorders.

The protective immune response against many helminth parasites has been variously referred to as the type 2 response, T_H2 (T helper 2) response or T_H2-type response. Here, we use the term T_H2-type response to refer to the combined immune response, which includes both innate and adaptive components, to clearly distinguish it from the adaptive T_H2-cell response. T_H2-type responses are typically characterized by increases in the levels of interleukin-4 (IL-4) and other T_H2-type cytokines (including IL-5, IL-9, IL-13 and IL-21), activation and expansion of $CD4^+$ T_H2 cells, plasma cells secreting IgE, eosinophils, mast cells and basophils, all of which can produce several types of T_H2-type cytokine. The IL-17-related cytokine IL-25 (also known as IL-17E) is also associated with the T_H2-type response and can promote T_H2-cell differentiation and nematode parasite expulsion[10,11]. Whether IL-25 is also a T_H2-type cytokine or identifies another T_H-cell subset remains unclear[11]. By contrast, interferon-γ (IFNγ)-dominant T_H1-type responses are typically evoked by microbial infections, including bacteria and viruses, and are associated with increases in the numbers of T_H1 cells, cytotoxic $CD8^+$ T cells, neutrophils and macrophages. Although IL-10 was initially characterized as a T_H2-type cytokine, recent findings show that this cytokine is also produced [12,13] *in vivo*, and can by T_H1 cells and regulatory T cells downregulate both T_H1-type and T_H2-type responses[14]. Several cytokines that are preferentially expressed during the T_H2-type response, including IL-4, IL-13, IL-21 and IL-25, can also downregulate T_H1-type and T_H17-type responses and their associated inflammation.

In this Review we examine recent findings concerning the T_H2-type responses elicited by parasitic helminths with some emphasis on studies in mice infected with the intestinal nematode parasite *Heligmosomoides polygyrus* and the trematode parasite *Schistosoma mansoni*. Infection with these parasites triggers a T_H2-type response, although the resultant mechanisms of protection differ greatly, with each providing unique insights. In the highly polarized T_H2-type response to the hookworm model parasite, *H. polygyrus*, protective responses mediate parasite stress that leads to expulsion of the worm. In *S. mansoni* infection, the protective T_H2-type response primarily downregulates an otherwise pathological T_H1-type response. Therefore, the immune responses to these two helminth species exemplify distinct functions of protective T_H2-type immune responses, one leading to worm expulsion and the other contributing to the control of pathological inflammation.

Recent advances have provided new insights into our understanding of the protective T_H2-type response that occurs during infectious disease. In particular, macrophages and neutrophils, which are typically associated with antimicrobial immunity, are key players. It is also becoming apparent that the crosstalk between innate and adaptive components throughout the course of the immune response is important. Typically, studies have focused on the role of innate immunity in instructing and directing the adaptive effector immune response, but it is increasingly evident that T cells reciprocally provide signals that amplify and fine-tune the function of innate effector cells. Here, the inflammatory infiltrate that occurs at the host–parasite interface of these two tissue-dwelling parasite species and the possible mechanisms by which immune cells in the infiltrate contribute to the overall host protective response is discussed.

Granuloma formation in helminth infections

Granulomas are traditionally associated with localized T_H1-type inflammatory responses that develop around a nidus, such as an invading microorganism or parasite. In schistosomiasis, perioval granulomatous inflammation is mediated by $CD4^+$ T cells that are specific for antigens derived from parasite eggs. The initial T_H1-type response to the acute schistosome infection targets adult parasites, but typically transitions to a T_H2-type response after the parasite's eggs are produced. Both co-stimulatory molecules and B cells are required for this switch[15]. The failure to develop an effective T_H2-type response after egg deposition results in exacerbated granulomatous inflammation driven by T_H1 and T_H17 cells; this causes substantial damage to the surrounding hepatic parenchyma, and can result in death[16]. Typically, a well-established T_H2-type response prevails and is associated with mild lesions consisting of small and well-circumscribed granulomas composed of eosinophils, macrophages and lymphocytes with an increasingly fibrotic extracellular matrix (referred to herein as mild pathology). In chronic schistosomiasis, even the subsequent T_H2-type response eventually subsides and newly forming egg granulomas are diminished in size; this regulation of the immune response is termed 'immunomodulation'[16]. However, tissue fibrosis, which is largely stimulated by the cytokine IL-13, can also become pathological and therefore represents a potential downside of the ongoing T_H2-type response to chronic infection (reviewed in REF. [17]).

Granulomas can also develop during polarized T_H2-type responses, including those to infection with *H. polygyrus*[18,19]. The life cycle of *H. polygyrus* begins with the ingestion of third-stage larvae by the host; the larvae then travel to the small intestine, where they invade the submucosa and continue to develop for 8 days. The final stage of the life cycle involves the migration of the mature adult female and male worms back to the intestinal lumen where they mate to produce eggs that can then leave the host for subsequent transmission[15] (FIG. 1). Primary infection is chronic with established adult parasites in the gut lumen that can be eliminated by the administration of a helminth-specific drug. Subsequent challenge (secondary infection) triggers a $CD4^+$ T_H2-type memory response that mediates worm expulsion within 14 days[15]. It should be noted that other gut-residing nematode parasites, including *Trichuris muris*, induce a more mixed T_H1- and T_H2-type response, suggesting that other characteristics besides generalized enteric infection are responsible for the highly polarized T_H2-type response to *H. polygyrus*[15,20].

As the *H. polygyrus* larva develops in the gut submucosa, an immune-cell infiltrate with a defined architecture rapidly forms around it[19] (TABLE 1). The memory immune response, which occurs by 4 days after *H. polygyrus* ingestion, is characterized by neutrophils immediately surrounding the invading larva. Alternatively activated macrophages, which are present in larger numbers than neutrophils, enclose the parasite and neutrophils forming a granulomatous structure. At the border of the granuloma there is an accumulation of $CD4^+$ T cells, $CD11c^+$ dendritic cells (DCs) and eosinophils; however, basophils, mast cells, $CD8^+$ T

cells, γδT cells and B cells are absent[18,19,21]. Cytokine gene-expression analysis using laser capture microdissection has shown the development of a highly polarized T_H2-type response (high expression levels of IL-4 and IL-13, in the absence of IFNγexpression). By contrast, 4 days after primary inoculation with *H. polygyrus*, similar but markedly reduced populations of infiltrating cells are observed, with few $CD4^+$ T cells. Taken together, these findings indicate that a potent inflammatory response can rapidly develop around an invading nematode parasite during the memory T_H2-type response. These results indicate that, as in the T_H1-type response to many different microorganisms, highly activated neutrophils and macrophages are among the first cells to respond, which results in the rapid development of a granulomatous structure dependent on $CD4^+$ T_H2 cells. It has been proposed that the formation of granulomas around schistosome eggs facilitates the migration of the eggs through the intestinal wall[22]. Although the formation of a parasite-enveloping granuloma secludes the parasite, the immune cells contained in the granuloma still appear to cause parasite damage and probably also contribute to the healing process after the adult parasite migrates back to the intestinal lumen[18,23].

These granulomas, which are induced by very different parasite species, therefore share a number of similarities, including macrophages as the key infiltrating cell types and the dependence on a T_H2-type response for protective effects (TABLE 1). However, the immune response to *H. polygyrus* is strictly a T_H2-type response that develops over several days, whereas the response to *S. mansoni* is a more mixed-type response that develops over a prolonged period of time.

Innate effector cells in helminth infections

Innate immune cells are essential for both the initiation and effector phases of T_H2-type immune responses. $CD4^+$ T_H2 effector cells instruct and amplify the innate effector-cell response primarily through the secretion of cytokines; once activated, innate-cell populations in turn help to sustain and promote expansion of the T_H2 effector-cell population. This crosstalk results in an overall effector response composed of interacting cells that coordinate and fine-tune targeted effector functions against the invading helminth parasite.

Neutrophils and macrophages: first responders in T_H2-type inflammation?

Macrophages are conventionally associated with T_H1-type responses to infectious bacteria and viruses. Classically activated macrophages engulf and destroy microorganisms through pathways that are dependent on inducible nitric oxide synthesis (iNOS)[24]. Until recently, macrophages were thought to be relatively quiescent during T_H2-type responses, having a secondary role to eosinophils, basophils and mast cells. However, several studies have now shown pronounced alternative macrophage activation and rapid recruitment to sites of infection during T_H2-type responses to helminths [18,24–29]. IL-4, IL-13, IL-10 and IL-21 trigger the alternative activation of macrophages[24,30–32], which can readily be distinguished by the high expression levels of markers such as arginase-1, IL-4 receptor α-chain (IL-4Rα), the mannose receptor CD206 and the absence of iNOS expression[18,33].

Alternatively activated macrophages appear to have at least three principal functions: regulation of the immune response, wound healing and resistance to parasite invasion (FIG. 2). With regard to immune regulation, previous studies showed that macrophages from granulomas of schistosome eggs can downregulate T_H1 cells [34]; other studies have identified regulatory $Gr1^+F4/80^+$ macrophages[35]. More recently, *in vivo* studies have shown that life-threatening acute inflammation is largely controlled by alternatively activated macrophages, demonstrating their regulatory potential[26]. Similarly, alternatively activated macrophages that are elicited in response to filarial parasites preferentially downregulate the T_H1-cell response, through an IL-10-independent mechanism mediated partially by transforming growth factor-β (TGFβ)[28].

Given their large size, parasitic helminths can potentially cause significant tissue damage by migrating through and residing within specific sites. Alternatively activated macrophages might contribute to wound healing by clearing matrix and cell debris and by releasing cytokines, growth factors and angiogenic factors that promote fibroplasia and angiogenesis even at sterile sites[36] (FIG. 2). Some genes expressed by alternatively activated macrophages are associated with wound healing[37,38] (BOX 1), these include resistin-like molecules and extracellular matrix proteins[39].

In addition to wound repair, alternatively activated macrophages may also mediate more direct effects on tissue-dwelling helminths, for example, by targeting the glycan chitin that is frequently expressed by helminths, but not by mammals. The chitinase and fizz family member proteins (ChaFFs), which include chitinase and chitinase-like secreted proteins and are secreted by alternatively activated macrophages (BOX 1), are prime candidates for mediating host resistance[40]. Although antiparasitic properties for many of these proteins have not been described, some have surprising roles in mediating T_H2-type inflammation (BOX 1). Therefore, ChaFFs have evolved multiple functions that may contribute to resistance to helminth infection, including enzymatic and other activities that potentially damage certain parasites and promote the T_H2-type inflammatory response.

Alternative macrophage activation is important for protection against the tissue-dwelling life-cycle stage of *H. polygyrus*[18] (FIG. 1; TABLE 1); protective immunity against the parasite was blocked when hosts were depleted of macrophages or arginase-1 function was inhibited[18]. In this system, $CD4^+$ T cells and IL-4 are required for both alternative macrophage activation and parasite expulsion[15]. These studies underscore the inter-play between T_H2 cells and innate effector cells during protective T_H2-type responses, and suggest that T_H2-cell-derived IL-4 drives alternative macrophage activation, which then contributes to parasite clearance through an arginase-1-dependent pathway (FIGS 2,3).

Neutrophils are also activated and are recruited to sites of infection during tissue invasion by helminths[18,19] (FIG. 2). Classically and alternatively activated neutrophils have recently been distinguished following bacterial infections[41] and it will be important for future studies to determine the phenotypes of the neutrophils that are associated with helminth infection. Studies have suggested a possible role for neutrophils in mediating resistance to *H. polygyrus in vivo* and damaging parasites *in vitro*. More recent reports indicate an important role for neutrophils in the killing of the larval stages of *Strongyloides stercoralis*. It was shown that neutrophils were rapidly recruited to diffusion chambers containing *S. stercoralis* larvae, where they killed larvae in the absence of other cell types, although eosinophils were also required for optimal killing[42]. During infection with *S. mansoni*, neutrophils seem to have little effect, as their depletion did not influence the severity of disease[26]. Generally, however, neutrophils are increasingly recognized as important components of the T_H2-type response elicited during helminth infection. Following their rapid recruitment to sites of parasitic helminth invasion, neutrophils, working in coordination with other cell populations, including eosinophils and macrophages, can potentially directly damage tissue-dwelling helminths.

Box 1 ChaFFs and helminth infection

Chitinase and FIZZ (found in inflammatory zone) family members (ChaFFs) are recently described secretory proteins that are induced during T helper 2 (T_H2)-type responses and contribute to allergic asthma, fibrosis or helminth immunity[40,121]. Some of these molecules are related to enzymes that degrade chitin, a molecule that is common to some pathogens, including some helminth larvae and fungi[40,121]. Resistin-like molecules (RELMs) have sequence homology to resistin (also known as FIZZ3), a hormone released

by adipocytes that mediates insulin resistance[122]. The descriptions below of specific ChaFFs are primarily based on studies in murine models.

AMCase

AMCase (acidic mammalian chitinase) is a functional chitinase that is upregulated during T_H2-type inflammatory responses by interleukin-13 (IL-13) in lung epithelium and pulmonary macrophages in a model of allergic asthma[123], and at host–parasite interfaces during helminth infections[18,29,124]. Macrophages have been shown to express AMCase during *Heligmosomoides polygyrus* infection[18], *Brugia malayi* implantation[121] and in *Schistosoma mansoni* egg granulomas[32]. AMCase plays an effector role in promoting T_H2-type responses by inducing eotaxin and CC-chemokine ligand 2 (CCL2; also known MCP1)[123].

Ym1

This is a lectin with affinity for chitin. It lacks chitinase activity and is one of the most highly upregulated transcripts in macrophages during nematode and schistosome infection[32, 125]. It is also found forming spontaneous crystals in asthmatic lungs[126]. Its induction is dependent on IL-4 and signal transducer and activator of transcription 6 (STAT6) signalling[127]. It also binds heparin[136], suggesting that it mediates interactions between cells and the extracellular matrix. Ym1 may also be an eosinophil chemotactic factor[137].

RELMα

RELMα (also known as FIZZ1) has a diverse expression profile, including by lung, intestinal, and adipose tissues, as well as by macrophages. Macrophages express very high levels of RELMα mRNA when alternatively activated by infection with *S. mansoni*, *B. malayi*, *Nippostrongylus brasiliensis* or *Litomosoides sigmodontis*, as do other antigen-presenting cells[18,29,32,121]. RELMα seems to have multiple functions, such as inhibition of adipocyte differentiation (perhaps due to its homology with resistin), inhibition of the action of nerve growth factor (suggesting a role in immunoregulation) and stimulation of collagen production in myofibroblasts (providing a potential link between alternatively activated macrophages, fibrosis, and tissue repair[40]).

RELMβ

RELMβ (also known as FIZZ2) has a more restricted expression than RELMα, and is found expressed almost exclusively in the gastrointestinal tract where it is important for normal colonic function and for the T_H2-type response to helminth infection[128,129]. Upon infection with *Trichuris muris*, *Trichuris spiralis* or *N. brasiliensis*, intestinal goblet cells upregulate and secrete RELMβ under the control of IL-13 signalling through the type II IL-4 receptor. Immunofluorescent staining has shown direct interactions between RELMβ and the helminths *T. muris* and *Strongyloides stercoralis*, in which it binds to structures on the lateral alae, thereby interfering with helminth chemotaxis towards host tissues[128].

RELMγ

This is the least understood member of the family. Expressed in the lungs and in haematopoietic tissues, it might have a role in regulating promyelocytic development[130]. This protein is also found upregulated in nematode-infected intestines[131], although a role for RELMγ in these types of infection is unknown.

Eosinophils: in search of a function?

The innate immune cell populations typically associated with T_H2-type responses, eosinophils, basophils and mast cells, have an integral role in antihelminth responses and in the allergic

cascade[15,43]. Following helminth infection, eosinophil numbers increase dramatically in the blood[44], and these eosinophils rapidly migrate to the site of infection, where they degranulate, releasing eosinophil secondary granule proteins (ESGPs) (FIG. 2).

Until recently, eosinophil biology was examined by blocking or inhibiting IL-5, a $CD4^+$ T-cell-derived cytokine that is required for eosinophilia (FIG. 3). These studies generally showed continued resistance to a variety of helminths despite the reduced eosinophil numbers[45,46]. However, not all eosinophils were eliminated using these approaches, and other cell populations, including neutrophils[47], might also respond to IL-5, and their function might therefore have been altered by these treatments. More recently, several eosinophil-deficient mouse models have been developed. These include mice in which the eosinophil peroxidase promoter drives expression of the diphtheria toxin (referred to as TgPHIL mice), and mice that have deletion of a GATA1 binding sequence (referred to as ΔdblGATA mice)[48,49]. In these mouse models, primary responses to schistosomes[48] and to the intestinal nematode parasite *Nippostrongylus brasiliensis*[49] are unaffected. However, eosinophils mediated parasite damage during *N. brasiliensis* challenge, even in the absence of $CD4^+$ T cells[50]. Depletion of eosinophils with antibodies specific for CC-chemokine receptor 3 (CCR3) enhanced susceptibility to primary infection with *Strongyloides stercoralis*[42]. Similar results were obtained from a model of filarial disease, although mice deficient in ESGPs remained resistant[51], suggesting that eosinophils also mediate protection through an ESGP-independent mechanism. Eosinophils can also have a regulatory role through the production of cytokines, including IL-4 and IL-13 (REFS 52,[53])(FIG. 2), and can function *in vitro* to present antigens to T cells in a *S. stercoralis* model[54]; however, in general, eosinophil depletion does not appear to markedly impair the development of the *in vivo* T_H2-type response to most parasitic helminths[45,48,55]. A major effector function of eosinophils and their ESGPs might be in tissue remodelling and debris clearance following tissue injury, a general activity that might help to mediate the wound healing response following parasite tissue invasion[56] (FIG. 2).

Basophils and mast cells: they are activated, but are they primary players?

Following helminth infection, basophils increase in number in the blood and tissues. Following *N. brasiliensis* infection, IL-4-producing basophils are readily detected in the lungs, liver and spleen, but have not been detected in the lymph nodes or Peyer's patches[57,58]; it is possible that they infiltrate lymph nodes at an unidentified time. Basophils and eosinophils might be a major source of IL-4 at early stages of the T_H2-cell response (FIG. 2), suggesting that they promote the development of T_H2 cells or their recruitment to sites of inflammation[57,58]. To further understand basophil biology and the role of these cells in helminth infection, it will be important to develop an effective method for selectively depleting basophils *in vivo*.

Mast cells share many characteristics with basophils, including the cell-surface expression of the high-affinity Fc receptor for IgE (FcεRI) and the Toll-like receptors (TLRs) TLR2 and TLR4, the release of mediators upon activation and IL-4 secretion, they have also been shown recently to derive from a common progenitor[59]. However, unlike basophils, which circulate in the blood, mast cells reside in peripheral tissues and are thus well situated to respond immediately to invasive agents. Increased numbers of mucosal mast cells are often observed in affected tissues during helminth infections and this increase is dependent on T_H2-type cytokines that are primarily derived from $CD4^+$ T cells; specifically, IL-4-dependent mucosal mastocytosis is associated with a resistant phenotype to *H. polygyrus*[60]. Although mastocytosis is pronounced in the small intestine of mice inoculated with *H. polygyrus*, interestingly, increased numbers of mast cells are not observed in or near the granuloma in which the larval parasite develops[19]. Furthermore, previous studies have shown that mice lacking mast cells (referred to as w/w^v mice) are able to clear *H. polygyrus* infection (J.F.U. Jr, unpublished observations). Mast cells also do not appear to have a key role in

schistosomiasis, although they might contribute to the immune response at early stages of infection when the cercariae penetrate the skin[61].

A role for mast cells in helminth immunity has been described in *Trichinella spiralis*; studies using w/w^v mice or stem-cell factor (SCF)-specific antibodies that impair mast-cell function showed that SCF is required for mucosal mastocytosis during helminth infection, and is important for effective helminth expulsion[62,63]. Furthermore, mice deficient in mouse mast-cell protease 1 (mMCP-1; also known as β-chymase and Mcpt1) are unable to expel *T. spiralis* indicating the antihelminth properties of mast-cell cytoplasmic granules (FIG. 2); however, mMCP-1 has little effect on *N. brasiliensis* host resistance[64]. mMCP-1 might function to impair epithelial-cell barriers by degrading the tight junction protein occludin and thereby increasing luminal fluid flow[65,66].

Although most helminths induce pronounced basophil and mast-cell responses, the importance of these cells in mediating resistance to these parasites varies greatly. This variation may be related to the distinct microenvironments that are occupied by different intestinal nematodes. For example, adult *T. spiralis* — unlike adult *H. polygyrus* and *N. brasiliensis*, which inhabit the intestinal lumen — reside in intestinal epithelial-cell syncytia, raising the possibility that mast-cell mediators might be more important in expelling tissue-dwelling nematodes, possibly by increasing vascular permeability[67].

Other cell populations

Several non-leukocyte populations have recently been described as having a role in helminth infections. *In vitro* studies suggest that intestinal epithelial cells (IECs) secrete factors, including thymic stromal lymphopoietin (TSLP), that block the production of IL-12 by DCs and thereby inhibit the ability of DCs to promote T_H1-type responses[68]. These findings have been extended *in vivo* to show that IECs, at least partly through their production of TSLP, help to sustain the protective T_H2-type response to *T. muris* by inhibiting T_H1-type inflammatory responses[69]. As *T. muris* resides in epithelial-cell syncytia, physiological changes in this cell type may have particularly important implications with regard to resistance to this parasite. Indeed, studies have shown that the epithelial-cell turnover that is induced by T_H2-type cytokines acts as an ‘escalator’, expunging whipworms from the syncytia into the gut lumen[70].

Although natural killer (NK) cells have been shown to be activated during helminth infection[71,72], including gut-resident NK cells that were shown to produce IL-13 during *T. muris* infection of scid (severe combined immunodeficient) mice[73], the role of these cells in protective responses is unclear. Recent studies have implicated IL-25 in the promotion of host protective T_H2-type immune responses during intestinal nematode infections and also in the recruitment of a newly identified non-B-cell, non-T-cell population that expresses elevated levels of T_H2-type cytokine mRNAs to draining mesenteric lymph nodes. These cells express c-KIT but not FcεRI, and might represent a distinct lineage or perhaps a precursor population of mast cells or basophils that contributes to the development of the T_H2-type response[11] (FIG. 3).

Box 2 IL-4 and IL-13 in helminth infections

Direct effects of interleukin-4 (IL-4) and IL-13 on gut tissue during helminth infection

Sources

T cells are a primary source of IL-4 and IL-13, but B cells, basophils, eosinophils and mast cells might also contribute significantly at both the initiation and effector phases of the response.

Receptors

Type I IL-4 receptor. Type I IL-4 receptor (IL-4R) binds IL-4, it is a heterodimer of IL-4Rα and the common cytokine-receptor γ chain (γ_c), it is expressed on bone-marrow-derived cells, including T and B cells, mast cells, basophils, eosinophils and macrophages. It signals through Janus kinase-dependent tyrosine phosphorylation of the IL-4R and signal transducer and activator of transcription 6 (STAT6).

Type II IL-4R. This receptor binds IL-4 and IL-13, it is a heterodimer of IL-4Rα and IL-13Rα1, it is expressed on non-bone-marrow-derived cells, including epithelial cells, smooth muscle cells, endothelial cells and fibroblasts and also various bone-marrow-derived cells but not T cells[132]. It signals through Janus-kinase-dependent tyrosine phosphorylation of the IL-4R and STAT6.

A second IL-13R chain, IL-13Rα2, is soluble, not linked to STAT6, and might function as a decoy receptor to modulate IL-13 activity *in vivo*[133], with recent studies suggesting that it modulates IL-13-mediated muscle contractility[134], and downregulates fibrosis in schistosome granulomas[17].

Effects on non-bone-marrow-derived tissues

IL-4 and IL-13 induce increased contractility of intestinal longitudinal smooth muscle and also increased intraluminal fluid through increased intestinal permeability and responsiveness to mediators such as prostaglandin E2, which stimulates fluid secretion[135]. Similar STAT6-dependent effects are observed following infection with nematodes (such as *Heligmosomoides polygyrus, Trichuris spiralis* and *Nippostrongylus brasiliensis*)[85]. The secreted fluids may also include toxins which damage the intestinal parasite. Increased mucus secretion has been observed in *N. brasiliensis* infection[15], and IL-4 has been shown to stimulate Paneth-cell growth and secretion of antibacterial products which may also harm helminths[67]. In addition, IL-13 induces goblet-cell secretion of resistin-like molecule-β (RELMβ), which may bind cuticle structures thereby impairing chemosensory function[128].

IL-4 and IL-13 effector mechanisms may differ between helminth parasites

H. polygyrus. The IL-4-mediated protective response involves both macrophage effects on tissue-dwelling larvae and also probably direct effects of IL-4 (and also IL-13) on small intestinal tissue, thereby interfering with adult worm adherence and feeding.

N. brasiliensis. The IL-13-mediated response involves primarily non-bone-marrow derived cells, probably directly affecting the small intestine, which leads to modified worm adherence and feeding.

T. spiralis. IL-4 and IL-13 stimulate B-cell production of IgE, mastocytosis and basophilia. Mast-cell and basophil degranulation and release of IL-4 and IL-13, as well as other mediators, induces changes in the small intestinal tissue, creating an inhospitable environment for both luminal larvae and adults that dwell in intestinal tissues.

T. muris. IL-13 and, to a lesser extent, IL-4 stimulate rapid epithelial-cell turnover in the large intestine, essentially expelling parasites from their habitat (which are syncytia of epithelial cells)[70].

Schistosoma mansoni. IL-4 and IL-13 induce alternatively activated macrophages, which help to control the development of an underlying pathological T_H1- and/or T_H17-type inflammation[26,88]. IL-13, in particular, can contribute to fibrosis[17].

Adaptive effector cells: T and B cells

Helminths potently induce the development of effector T_H2 cells following infection. The ensuing cytokine response by T_H2 cells has broad effects, promoting antihelminth effector functions in a variety of bone-marrow-derived and non-bone-marrow-derived cell populations and tissues.

$CD4^+$ T helper effector cells: heterogeneous and essential

Effector T_H2 cells induced by helminths are characterized by the production of the cytokines IL-4, IL-5, IL-9, IL-13 and the recently identified T_H2-type cytokine IL-21, and the absence of IFNγ and IL-17 production (FIGS 3,4). In immune responses to *S. mansoni*, but usually not to *H. polygyrus*, T_H2 cells can also produce IL-10 (REF. 15). Following infection with different species of bacteria and viruses, naive T cells differentiate along a reciprocal pattern, with high levels of IFNγ and low levels of IL-4, that is largely shaped by adjuvant microbial pathogen-associated molecular patterns (PAMPs) that bind to TLRs and other innate receptors expressed by DCs and other antigen-presenting cells[74]. Recent studies show that helminths can also provide an adjuvant function, driving T_H2-cell differentiation *in vivo* to non-parasite antigens[75,76]. In this context, IL-2 mediates initial T_H2-cell differentiation whereas IL-4 is required for expansion of antigen-specific T_H2 cells. The source of IL-4 may include non-T cells, bystander T cells and the antigen-specific T_H2 cells that produce IL-4, promoting proliferation through an autocrine feedback loop. Indeed, autocrine IL-4 produced by antigen-specific $CD4^+$ T cells is sufficient to support T_H2-cell differentiation and expansion during *N. brasiliensis* infection[75]. The adjuvant structures on helminths that drive T_H2-cell differentiation are not yet clearly defined; however, intriguing data suggest that glycans[77, 78], lipids and lipoproteins[79,80], and perhaps proteases[81] expressed by certain helminths, might function as PAMPs to drive T_H2-cell differentiation. In a recent important study, chitin was identified as a potential T_H2-cell-stimulating PAMP[82]. The role of DCs in preferentially promoting T_H2-cell differentiation during helminth infection remains unclear, although several studies indicate that DCs activated following exposure to schistosome egg antigen (SEA) preferentially support T_H2-cell differentiation[83,84].

During helminth infections, T_H2 cells orchestrate the activation and expansion of leukocytes primarily through the production of cytokines, an essential function that serves to amplify and sustain the T_H2-type response. In addition, IL-4 and IL-13 can directly affect cell populations that express IL-4R but that are not derived from the bone marrow, such as small-intestine smooth-muscle cells, epithelial cells and myenteric neurons[67] (BOX 2; FIG. 3). IL-4R signalling is largely dependent on the actions of signal transducer and activator of transcription 6 (STAT6). *H. polygyrus* infection induces STAT6-dependent changes in epithelial-cell function, increased smooth-muscle contractility, increased mucus production, and enhanced fluids in the gut lumen [85–87] (BOX 2; FIG. 3). These studies suggest T_H2-cell derived IL-4 and IL-13 contribute in a STAT6-dependent manner to the 'weep and sweep' response that is characteristic of many intestinal helminth infections, in which increased luminal fluids (weep) and muscle contractility (sweep) are speculated to make the intestinal lumen an inhospitable environment for the helminth parasite. The weep and sweep response functions to decrease the fecundity of adult worms and increase the likelihood of live parasite expulsion, rather than to kill them. So, multiple host protective mechanisms might contribute to an effective *H. polygyrus* response, with macrophages targeting developing parasites during the tissue-dwelling phase, and cytokine-induced changes in gut physiology affecting adult worms in the intestinal lumen (BOX 2; FIG. 1). Blockade of the T_H2-type response during *H. polygyrus* infection does not default to a T_H1-type response; instead, the immune response is generally inhibited[21]. By contrast, infection with schistosomes elicits an early T_H1-type response, which typically changes to a T_H2-type response following parasite egg deposition[16,88].

The host-specific $CD4^+$ T-cell response to schistosome infection stimulates parasite development[89], and results in an inflammatory environment that is required for translocation of parasite eggs from the intravascular compartment into the intestinal lumen[22]. The controlled hepato-intestinal granulomatous inflammation around the eggs in this T_H2-type-polarized milieu might represent a compromise between the parasite and the vertebrate host, allowing the parasite to complete its life cycle while at the same time protecting the host from severe, lethal disease. In certain mouse strains, the host–parasite balance is not achieved, and this results in a severe pathological inflammatory response mediated by $CD4^+$ T_H1 and T_H17 cells[16,88,90].

T_H17 cells represent a recently discovered $CD4^+$ T-cell subpopulation, defined by their production of IL-17, that can mediate chronic inflammation in autoimmune diseases such as encephalitis and arthritis[91] (FIG. 4). T_H17 cells are stimulated by IL-23, a heterodimeric cytokine composed of the IL-12p40 and IL-23p19 subunits (in contrast to IL-12, which is an IL-12p40–IL-12p35 heterodimer)[92]. In schistosomiasis, exacerbation of egg-induced pathology that is associated with elevated IL-17 levels occurs after immunization with SEA in complete Freund's adjuvant of infected wild-type or IL-12p35-deficient C57BL/6 mice, and fails to occur in mice lacking IL-12p40 (REFS 90,[93]). These findings suggest that the IL-17–IL-23 pathway is critical for development of severe schistosomiasis, although a role for the IL-12–IFNγ pathway cannot be completely excluded. Consistent with this interpretation, CBA mice, which naturally develop extensive pathology, also have elevated IL-17 responses and the egg-induced pathology can be reduced using IL-17-specific antibodies[90]. More recent studies have shown that IL-6, TGFβ and IL-21 (REF. 94) are the key inducers of T_H17-cell differentiation, and that IL-23 serves as a survival and expansion factor for this subset of T cells[95–97].

These studies suggest that, in schistosomiasis, T_H2 cells primarily downregulate harmful T_H1- and T_H17-type inflammatory responses either directly or through innate immune cell populations (FIGS 2,4). By comparison, the T_H2-type immune response to *H. polygyrus*, which is not associated with an underlying T_H1-type response, instead contributes to parasite resistance and eventual helminth expulsion from the gut. The lack of harmful T_H2-cell-mediated pathology following *H. polygyrus* infection is probably a consequence of the relatively short 8 day period of tissue residence.

Regulatory T cells

Nematode infections can induce and expand naturally occurring regulatory T cells (T_{Reg} cells) in humans and mice[98–101], suggesting a role for these T_{Reg} cells in helminth-induced modulation of inflammatory diseases[102] (FIG. 4). Hyporesponsiveness associated with infection of mice with the filarial parasite *Litomosoides sigmodontis* was blocked following *in vivo* depletion of T_{Reg} cells, which resulted in increased killing of parasites[103]. These studies suggest that T_{Reg} cells induced during filarial parasite infection have an important role in immunosuppression induced by filarial parasites and in increased worm survival. Recently, $CD8^+$ lamina propria T cells induced by infection with *H. polygyrus* were shown to inhibit T-cell proliferation and the development of experimentally induced colitis[104], suggesting that other regulatory T-cell populations are also important in nematode infections. T_{Reg} cells have been suggested to have an important role in the suppression of the T_H1-type inflammatory response to SEA. Initial reports have suggested this effect was mediated through IL-10 (REFS 105,[106]); however, more recent findings indicate that these T_{Reg} cells can function through as yet unidentified IL-10-independent mechanisms as well[107–109]. T_{Reg} cells might also be instrumental in controlling T_H2-type responses in chronic *S. mansoni* infection[106,108]. Future studies should examine the role of the T_H2 cells, T_{Reg} cells, alternatively activated macrophages and perhaps other innate cell populations, in the control of T_H1- and T_H17-cell-

mediated inflammation and the upregulation of the T_H2-type response. It is possible that several or all of these different cell populations interact to mediate the evolution of a potentially pathological T_H1-type response into a protective T_H2-type response following egg deposition in chronic schistosomiasis.

B cells and antibody responses

During polarized T_H2-type responses, IL-4 mediates B-cell class switching to IgE, a primary mediator of acute allergic and asthmatic reactions that binds FcεRI on mast cells and basophils (FIG. 3). Antigen crosslinking of FcRεI-bound IgE triggers mast-cell degranulation and the release of soluble mediators[110]. IL-4 and IL-13 signalling through the IL-4R can increase the sensitivity of target cells to basophil- and mast-cell-derived mediators. Therefore, IgE effects are amplified in the presence of these T_H2-type cytokines and this results in enhanced responses including increased vascular permeability, smooth muscle contractility, and also the recruitment of T_H2-type effector cells, including eosinophils and T_H2 cells[67].

Interestingly, neither IgE nor mast cells appear to have an essential role in the development of the host protective immune response to either *H. polygyrus* or *N. brasiliensis*[87] (J.F.U. Jr, unpublished observations). By contrast, mast cells are required for protective immunity against *T. spiralis*; however, parasite-specific IgE does not have an essential role, as recent studies have demonstrated that effective expulsion is achieved in B-cell-deficient mice[111]. In these cases, T_H2-type cytokines and perhaps other factors must be sufficient for mast-cell degranulation.

Antibody classes other than IgE have been described in nematode infection. Secreted IgM was essential for timely expulsion of filarial parasites[112]. This is the primary antibody type that recognizes larval parasites, and might be produced in a T-cell-independent manner. As macrophages express Fc receptors for IgM, IgM might also be important for macrophage recognition of filarial parasites[113].

Schistosome infections elicit strong host antibody responses against multiple components of the parasite, the majority of which are glycan determinants[114]. Although it seems unlikely that the antibodies have a significant antiparasitic effect, B cells can generally support the establishment of the T_H2-type response[115], thereby contributing to reduced pathology in schistosomiasis[116,117], and correlations between IgE production and protective immune responses have been reported in human schistosomiasis[118]. Therefore, although the humoral antibody response is typically associated with T_H2-type responses during infectious disease, in many cases antibodies do not appear to have an essential role in helminth protective responses that either involve parasite expulsion or that down-regulate harmful T_H1-type responses. As it is clear that specific components of the T_H2-type response that actually mediate protection vary greatly with the specific parasitic helminth and developmental stage of the host[119], it is very possible that an essential role for antibodies will be identified as such parasitic infections are examined.

Concluding remarks and future directions

The T_H2-type response mediates protective responses to a wide variety of parasitic helminths. Activation and function of this response is dependent on ongoing crosstalk between innate and adaptive effector-cell populations. It is initiated by innate-cell populations that promote T_H2-cell differentiation. As the response progresses, T_H2 cells, primarily through cytokine production, amplify and instruct the innate cell populations, which reciprocate and help to sustain the T_H2 cells. The result is a potent, orchestrated response, involving a diverse population of leukocytes that secrete T_H2-type cytokines and other factors that promote helminth-specific immunity by directly affecting the parasite, triggering non-bone-marrow-

derived cells to undergo physiological changes, and further amplify the T_H2-type response. Although many of these effector cells are activated in response to most helminth infections, only certain cell types are actually effective against any one type of parasitic helminth. Individual effector-cell types might also have multiple functions that have an essential role in the response to some helminths and not others. Both the cell population and effector function mediating protection are at least partly dependent on the tissue site of parasite residence.

Current treatments for helminth infection include frequent administration of helminth-specific drugs such as praziquantel (for schistosomiasis) and benzimidazoles (for hookworm infection). Although these treatments have been effective, parasites could potentially develop resistance, and re-infect individuals shortly after drug administration. Therefore, identification of new helminth-specific therapies, with the ultimate development of effective vaccines, is urgently needed. A number of vaccine candidates are being tested in clinical trials with, as yet, little success[88,120]. The inefficacy of vaccines tested against helminths might in part result from too narrow a focus on single antigens and their ability to induce effective antibody responses. Ultimately, the most effective vaccines will probably elicit broad T_H2-type responses including potent cell-mediated and humoral components. The choice of adjuvant may be particularly important in eliciting these kinds of multi-faceted immune responses. In some cases, successful vaccines may be directed more towards suppressing harmful pathological immune responses than expelling the helminths. The recent advances in our understanding of how various innate and adaptive components of the T_H2-type response contribute to host protective responses provides a new set of compelling targets for the development of more effective therapies and vaccines.

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Glossary

Helminths

These are worms that are characterized by their body shape into cestodes (flat worms), nematodes (round worms) and trematodes (leaf-shaped worms).

Hygiene hypothesis

This hypothesis originally proposed that the increased incidence of atopic diseases in westernized countries was a consequence of living in an overly clean environment resulting in an under-stimulated immune system that responded inappropriately to harmless antigens. More recently it has been proposed that an absence of exposure to pathogens, in particular helminths, may predispose to both increased allergy and autoimmune disease.

T_H2-type response

(T-helper-2-type response). An immune response including innate and adaptive components that is elicited by helminth infections and many allergic reactions. Common features include expression of T_H2-type cytokines (IL-4, IL-5 and IL-13), eosinophilia, basophilia, mastocytosis, goblet-cell hyperplasia and IgE production.

T_H1 cells

(T helper 1 cells). This is a $CD4^+$ effector T cell mainly characterized by its expression of interferon-γ.

Heligmosomoides polygyrus

A natural mouse gastrointestinal trichostrongylid nematode parasite, used as a model of human intestinal nematode infection. Primary infections become established and chronic, and can be cleared by helminth-specific drug treatment. Challenge infections are naturally cleared by the host by day 14 post-infection, making this an excellent model of protective memory T-helper-2-type responses.

Schistosoma mansoni

A blood-dwelling trematode parasite that causes a major form of human hepato-intestinal schistosomiasis. Infection of mice with this parasite represents a well-established murine model of this disease.

Granuloma

A circumscribed inflammatory cell infiltrate surrounding a nidus. Its composition usually includes T cells and macrophages, and in the case of helminth infection, eosinophils.

T_H17 cell

(T helper 17 cell). This is a $CD4^+$ effector T cell that expresses interleukin-17 (IL-17), IL-6, tumour necrosis factor, IL-21 and IL-22, but does not express interferon-γ nor IL-4.

Alternatively activated macrophage

A macrophage stimulated by interleukin-4 (IL-4) or IL-13 that expresses arginase-1, mannose receptor CD206 and IL-4 receptor α. There may be

pathogen-associated molecular patterns expressed by helminths that can also drive alternative activation of macrophages.

Classically activated macrophage

A macrophage that is activated through Toll-like receptors and interferon-γ that expresses inducible nitric oxide synthase and nitric oxide.

Filarial parasites

These thread-like nematode parasites cause a wide range of diseases in humans, including River blindness (by *Onchocerca volvulus*) and elephantiasis (by *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*).

Chitinase and FIZZ family member proteins

(Chaffs). Proteins that are expressed by alternatively activated macrophages or goblet cells during T_H2-type responses. They include acidic mammalian chitinase (AMCase), Ym1, Ym2, resistin-like molecule (RELMα; also known as FIZZ1), RELMβ (also known as FIZZ 2) and RELMγ.

Strongyloides stercoralis

A parasitic roundworm (threadworm) of humans and other mammals.

Goblet cells

Mucus-producing cells found in the epithelial-cell lining of the intestine and lungs.

Allergic cascade

The sequence of events contributing to acute and chronic allergic reactions. Surface Fc receptors for IgE on mast cells are crosslinked, triggering the release of soluble mediators. Immediate vascular permeability and smooth muscle contractility is associated with acute allergic reactions, and eosinophils and T helper 2 cells are associated with chronic allergic reactions.

Nippostrongylus brasiliensis

A trichostrongylid intestinal nematode rodent parasite that is widely used as a model to study T-helper-2-type responses. In most inbred mouse strains, primary infection results in rapid expulsion of the parasite within 10–12 days.

Toll-like receptors

(TLRs). The best characterized family of receptors for pathogen-associated molecular patterns. Receptors in this family recognize bacterial cell-wall and membrane structures, flagella, bacterial DNA motifs, viral double-stranded RNA and other structures.

Pathogen-associated molecular patterns

(PAMPs). Conserved microbial structures recognized by innate receptors, including Toll-like receptors.

Regulatory T cell

(T_{Reg} cell). A type of $CD4^+$ T cell that is characterized by its expression of forkhead box P3 (FOXP3) and high levels of CD25. T_{Reg} cells can downmodulate many types of immune responses.

Class switching

The somatic-recombination process by which the class of immunoglobulin is switched from IgM to IgG, IgA or IgE. During T helper 1 (T_H1)-type responses,

B cells can class-switch to produce IgG2a whereas during T_H2-type responses B cells can switch to produce IgE.

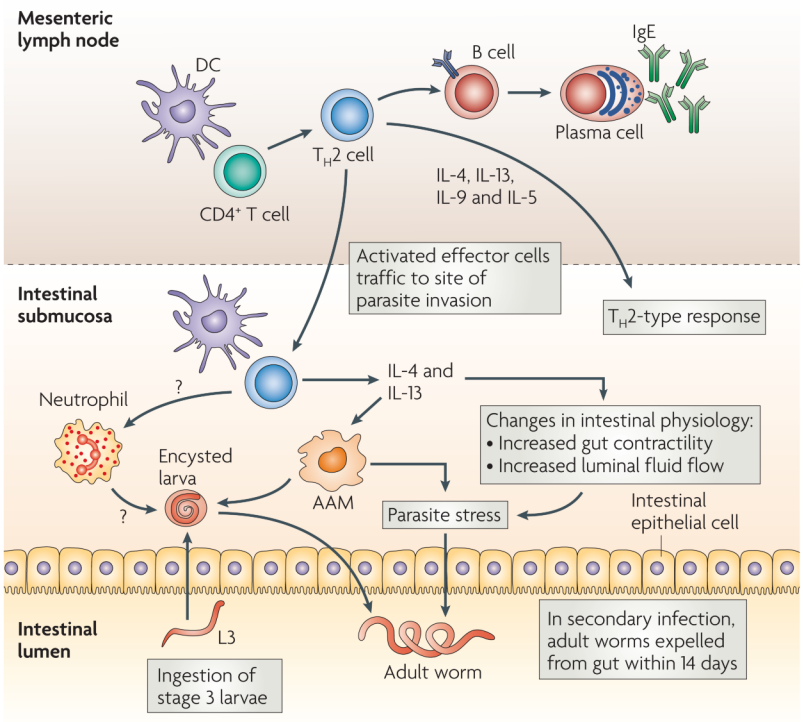

Figure 1. Protective T_H2-type response during intestinal nematode infection

Infective third-stage larvae (L3) are ingested by the host. They then travel to the duodenum, invade the epithelia, and reside in the submucosa for 8 days, after which they re-enter the lumen of the duodenum as adult nematodes. Primary infections become established and chronic, but can be cleared by antihelminthic drug treatment. Challenge (secondary) infections are naturally cleared by the host by day 14 post-infection, making this an excellent model of protective memory T helper 2 (T_H2)-type responses. Parasite antigens are presented to $CD4^+$ T cells in mesenteric lymph nodes and other gut-associated lymphoid tissues, driving the induction of T_H2 effector cells. These cells exert their effector functions through the production of a number of cytokines, including interleukin-4 (IL-4), IL-13, IL-9 and IL-5. T_H2 cells induce B-cell immunoglobulin class-switching to IgE. Shortly after activation, T_H2 effector cells migrate to the site of parasite residence in the submucosa. Within several days, a distinct immune-cell infiltrate appears which can damage the larval parasite after secondary, but not primary, inoculation. The infiltrate following secondary inoculation includes T_H2 cells, dendritic cells (DCs), neutrophils and alternatively activated macrophages (AAMs). The T_H2 cytokines IL-4 and IL-13 might also facilitate expulsion of adult parasites in the lumen by inducing changes in intestinal physiology.

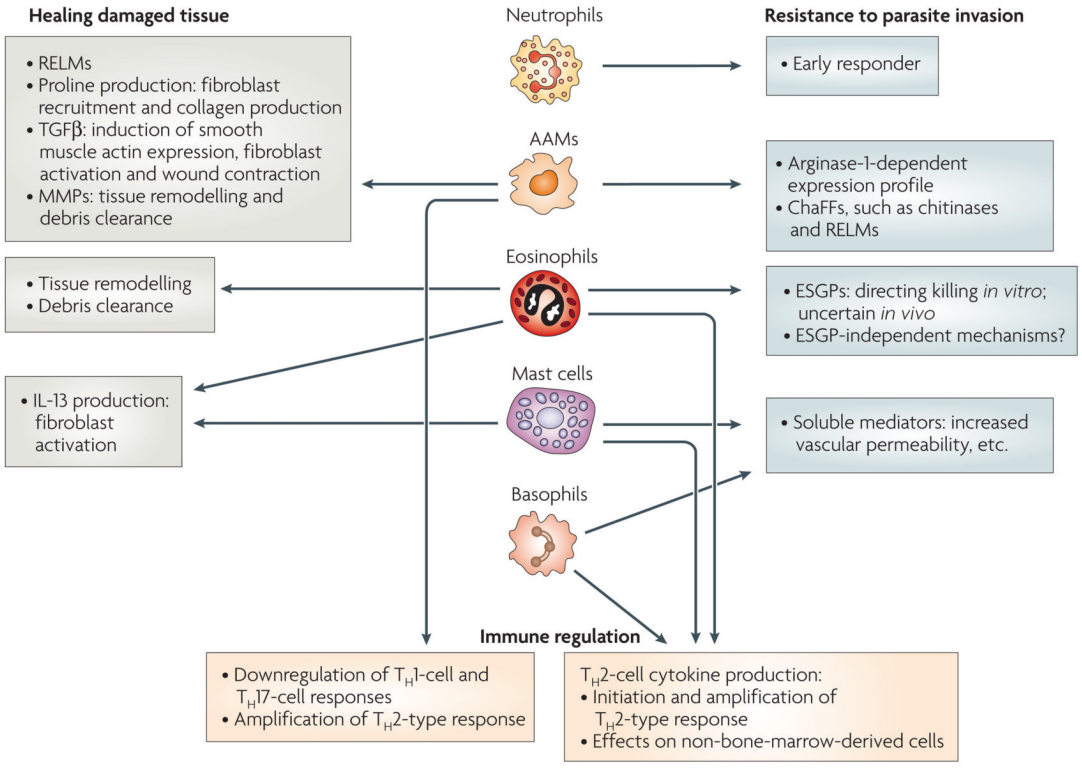

Figure 2. Functions of innate effector cells during the T_H2-type response

In general, the effector functions of innate immune cells during protective T helper 2 (T_H2)-type responses can include healing damaged tissue, mediating resistance to parasite invasion and regulating the immune response. Alternatively activated macrophages (AAMs) and eosinophils might contribute to the healing of tissue damage caused by invasive helminth parasites through the production of factors that initiate and promote the remodelling and restructuring of tissue. AAMs, eosinophils, basophils, mast cells and neutrophils can contribute to resistance to parasite invasion. AAMs and eosinophils can directly stress tissue-dwelling parasites. Basophils and mast cells produce soluble mediators (including leukotrienes, prostaglandins and histamine) that promote luminal fluid flow, nerve stimulation and gut contractility. Neutrophils are early responders to invasive helminths, and are localized adjacent to the parasites. AAMs can regulate the immune response by downregulating T_H1 and T_H17 cells and promoting T_H2 cells. Eosinophils, basophils and mast cells can produce T_H2-type cytokines including interleukin-4 (IL-4) and IL-13, and thereby amplify the T_H2-type response. ChaFFs, chitinase and FIZZ family members; ESGPs, eosinophil secondary granule proteins; MMPs, matrix metalloproteases; RELMs, resistin-like molecules, TGFβ, transforming growth factor-β.

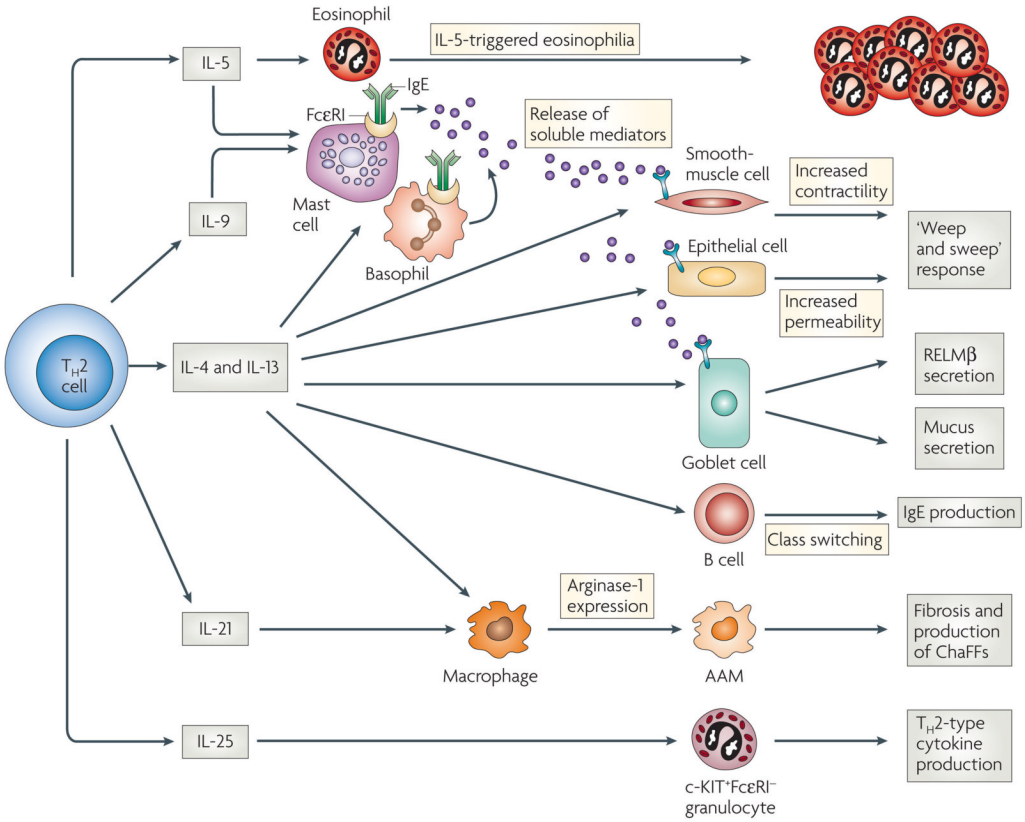

Figure 3. T_H2-cell functions during helminth infection

T helper 2 (T_H2) cells orchestrate the immune response primarily through the production of cytokines in the lymph nodes and periphery. Interleukin-5 (IL-5) triggers eosinophilia, and in conjunction with IL-4, IL-9, and IL-13, and the crosslinking of FcεRIs (high-affinity Fc receptors for IgE), can result in enhanced mast-cell and basophil development and release of mediators. IL-4 and IL-13 stimulate increased smooth-muscle-cell contractility, increased intestinal permeability and elevated goblet-cell mucous secretion. IL-4 and IL-13 also enhance responsiveness of these cell types to mast-cell-derived mediators. Collectively, these effects can contribute to the 'weep and sweep' response to intestinal helminths. IL-4, in conjunction with other signals, can induce class switching in B cells, leading to IgE production. IL-4, IL-13 and IL-21, can drive development of alternatively activated macrophages (AAMs), leading to upregulation of arginase-1 expression, and in some cases this might lead to fibrosis, as in chronic schistosomiasis. IL-25 expression stimulates a c-KIT$^+$FcεRI$^-$ population to migrate to lymph nodes and upregulate T_H2-type cytokine mRNAs. It is unclear whether IL-25 is a T_H2-type cytokine, or whether it is expressed by a distinct T_H-cell lineage. IL-21, also produced by T_H17 cells, is instrumental in the development of a T_H17-like response (not shown). ChaFFs, chitinase and FIZZ family members; RELM, resistin-like molecule.

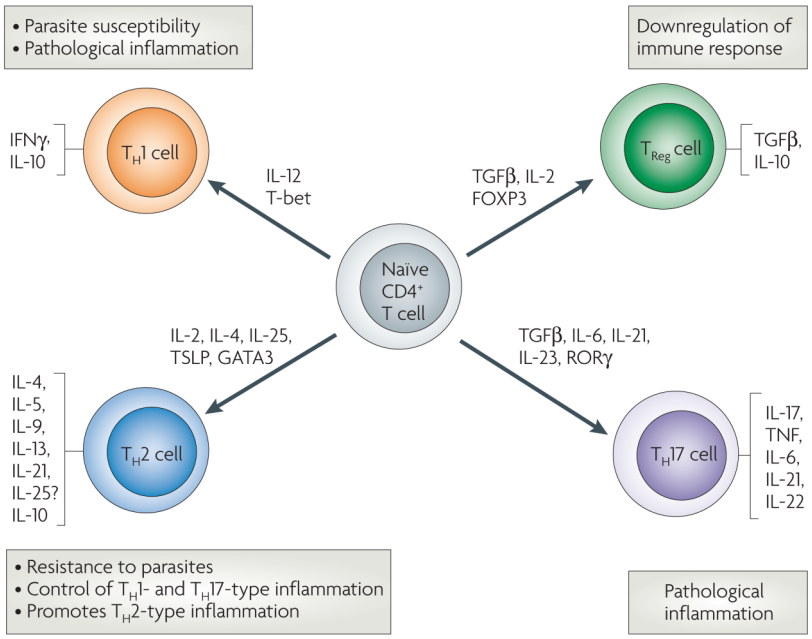

Figure 4. T helper and regulatory cells

Naive $CD4^+$ T cells can differentiate into several different types of effector and regulatory cells during helminth infection. Specific cytokines and transcription factors contribute to differentiation and expansion of these cell populations, and their differential activation plays a major role in determining whether an immune response will contribute to host protection or pathological inflammation. Exposure to interleukin-12 (IL-12) produced by antigen-presenting dendritic cells (DCs) induces T-bet expression, driving T helper 1 (T_H1)-cell differentiation. These cells produce interferon-γ (IFNγ), and are unable to clear helminth parasites. The circumstances leading to T_H2-cell differentiation are not as clear but recently, IL-2, IL-25 and thymic stromal lymphopoietin (TSLP), and associated transcription factors, have been implicated. T_H2 cells produce a panel of cytokines that contribute to antihelminth immunity by instructing innate bone-marrow- and non-bone-marrow-derived cells, which in turn can instruct and amplify T_H2 cells. Strong T_H2-type responses often lead to increased resistance to parasites, as seen in *Heligmosomoides polygyrus* infection, or control of harmful inflammation mediated by T_H1 cells and T_H17 cells, as in schistosomiasis. However, chronic potent T_H2-cell responses can also lead to harmful T_H2-type inflammatory responses including fibrosis. Expression of the transcription factor forkhead box P3 (FOXP3) along with the cytokines transforming growth factor-β (TGFβ) and IL-2, leads to differentiation of regulatory T cells (T_{Reg} cells), which can inhibit the immune response. Several factors, including retinoic-acid-receptor-related orphan receptor-γ (RORγ), TGFβ, IL-6, IL-21 and IL-23, have been shown to promote T_H17-cell differentiation, and these effector cells can mediate harmful inflammation. IL-10, which is no longer considered to be exclusively a T_H2-type cytokine, can be produced by T_H1, T_H2, and T_{Reg}cells and downregulates both T_H1- and T_H2-type responses. TNF, tumour-necrosis factor.

Table 1

Cellular composition of helminth-induced granulomas

Cell type Present in the granuloma	*Heligmosomoides polygyrus*		*Schistosoma mansoni*	
	Day 4 after primary innoculation	Day 4 after secondary innoculation	Mild pathology	Severe pathology
AAM	−	+++	++	−
CAM	−	−	−	++
Neutrophil	++	++	−	++
Dendritic cell	+	++	++	++
Eosinophil	++	++	+++	+++
T_H1 cell	−	−	−	++
T_H2 cell	−	++	++	−/++
T_H17 cell	−	−	−	++
$CD8^+$ T cell	−	−	++	+
B cell and/or plasma cell	−	−	++	+

AAM, alternatively activated macrophage; CAM, classically activated macrophage; T_H, T helper.