Immunity to gastrointestinal nematode infections

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Numerous species of nematodes have evolved to inhabit the gastrointestinal tract of animals and humans, with over a billion of the world's population infected with at least one species. These large multicellular pathogens present a considerable and complex challenge to the host immune system given that individuals are continually exposed to infective stages, as well as the high prevalence in endemic areas. This review summarizes our current understanding of host–parasite interactions, detailing induction of protective immunity, mechanisms of resistance, and resolution of the response. It is clear from studies of well-defined laboratory model systems that these responses are dominated by innate and adaptive type 2 cytokine responses, regulating cellular and soluble effectors that serve to disrupt the niche in which the parasites live by strengthening the physical mucosal barrier and ultimately promoting tissue repair.

HELMINTHS AND HUMANS

Nature is rife with parasitism, and it has been estimated that one fifth of all humans are hosting one or more species of gastrointestinal nematode.[1] As with many other pathogens, parasitic worm infections are prevalent among children in developing countries where hygienic conditions are poor, with symptoms ranging from abdominal pain and mild anemia to diarrhea, stunted growth, and impaired cognitive development; a tragedy given that most nematodes are easily avoided by improvements in basic hygiene, such as access to clean drinking water. Efforts to treat infected individuals with antihelminthic drugs are thus rendered relatively ineffective in the long term because of continued exposure to infective eggs and larvae in the immediate environment, frequently resulting in reinfection.

With that being said, some parasites might incur benefits as well. Epidemiological data demonstrate that over the past decades there has been a steady rise in both the prevalence and incidence of various immune-associated disorders,[2–4] whereas the occurrence of parasite infections has decreased dramatically.[5] This inverse correlation has given rise to the hygiene hypothesis that, as the name implies, proposes that excessive cleanliness alters the balance of the immune system (in part because of the lack of parasite exposure), thus resulting in aberrant reactions to harmless environmental molecules, food antigens, or the body itself. Given that our species evolved in close contact with a diverse array of pathogens, this explanation is certainly plausible,[6,7] so much so that some have considered using worm infections as treatment, notably for inflammatory bowel disease.[8,9] Regardless, it is clear that parasites have had, and will continue to have, a significant impact on our species in the foreseeable future. Hence, understanding the complex interaction between gastrointestinal parasites and the mucosal immune system is of crucial importance, not just for the development of improved antihelminthic therapies, but also for potential treatments targeting inflammatory and autoimmune disorders.

Here we describe the cellular and molecular mechanisms that promote protective immunity to enteric roundworm infection. Much of our current understanding comes from wild rodent parasites that have been adopted for laboratory use, including *Heligmosomoides polygyrus*,[10] *Nippostrongylus brasiliensis*,[11] *Trichinella spiralis*,[12] and *Trichuris muris*,[13] that closely mimic human helminth infections. Although the life cycles of these nematodes vary greatly, a crucial part of their lifespans is spent in the intestinal tract where a distinct form of protective immunity is elicited, namely type 2 immunity.

TYPE 2 IMMUNITY

Nematode infections are fundamentally different from other pathogen encounters. Whereas the average bacterium is ~2 μm in length, adult worms can be several hundred times larger than the typical immune cell. As a consequence, the essential physiological and immunological mechanisms required for the expulsion of parasitic worms are altogether

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different from those elicited in response to bacterial, fungal, or viral infections. The type 2 response entails several biological processes that serve to disrupt the parasite niche by strengthening the physical barrier and promoting tissue repair. These mechanisms are highly coordinated and involve several different cell types and effector molecules that have been implicated at various stages of the response (**Figure 1**).

DETECTION

Although the early events after gastrointestinal nematode infection are poorly understood, epithelial cells are clearly the first host cells to come in contact with parasite larvae once the mucus barrier has been breached (**Figure 1a**). Whether or not these cells survive the assault and are capable of responding to infection is unknown. Alternatively, healthy epithelial cells adjacent to infected ones might sense secreted parasite-derived molecules and/or tissue-derived damage-associated molecules to initiate the inflammatory cascade. Regardless, mice in which nuclear factor-κB signaling is abrogated specifically in epithelial cells are incapable of generating protective immunity upon *T. muris* infection and thus cannot expel the worms,[14] strongly indicating that there is need for epithelial activation before immune engagement. Indeed, recent evidence from *H. polygyrus*, *N. brasiliensis*, and *T. spiralis* infections demonstrates that specialized chemosensory epithelial cells called tuft cells expand upon infection and are critical for providing the early signals that drive type 2 immunity.[15–17] It is unclear whether the larvae are sensed directly by tuft cells or indirectly via signals from other epithelial cell subsets before activation. Nevertheless, mice that lack intestinal tuft cells do not expel *N. brasiliensis*,[15] thus implicating the epithelium in the generation of protective immunity.

The precise parasite-derived antigens being recognized by epithelial cells are largely unknown. A possible candidate is the polysaccharide chitin; one of the main components of the nematode egg, and expressed in the secretory apparatus of larvae and during molting. Chitin elicits strong type 2 immunity in the lung mucosa,[18,19] and acidic mammalian

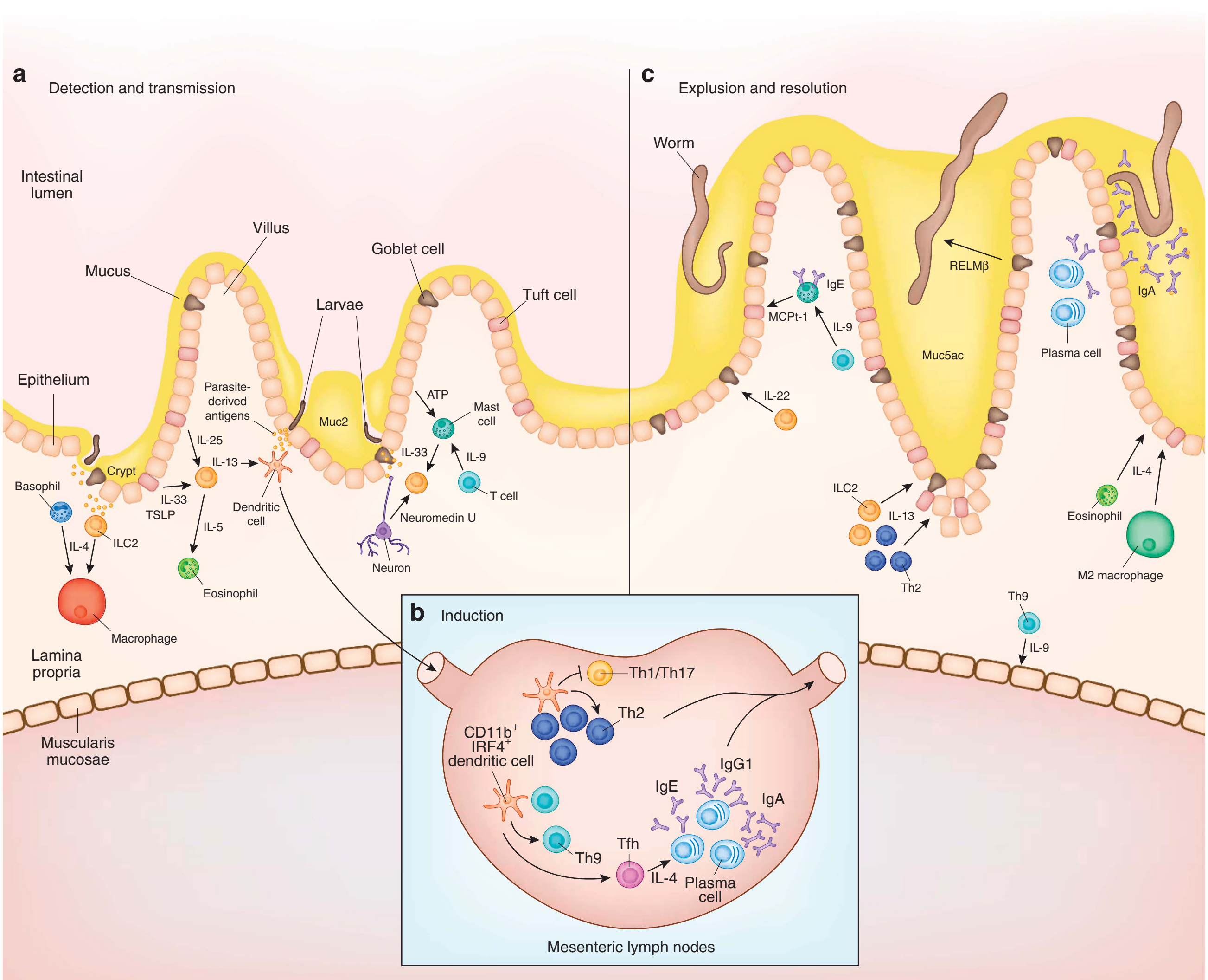

Figure 1 Immunity to gastrointestinal nematode infections. (**a**) Detection and transmission phase in the intestinal tissue. (**b**) Induction of immunity in the draining lymphoid tissue. (**c**) Expulsion of the parasites from the intestine and resolution of the response.

chitinase, which is predominantly expressed by certain pulmonary[20] and gastrointestinal[21] epithelial cells, is required for optimal protection against both *N. brasiliensis* and *H. polygyrus* infections.[22] However, as chitin is also a major part of the fungal cell wall, it alone is an insufficient explanation for the induction of antiparasitic immunity. Given that intestinal nematodes tend to cause more tissue destruction than other pathogens (because of their sheer size and invasiveness), it is perhaps more plausible that type 2 immunity results from combined recognition of both endogenous damage-associated alarmins and worm-derived molecules that become available for uptake after larval molting (including chitin), as well as parasite-derived antigens that are continuously secreted throughout infection. Cholinergic neurons, which innervate the mucosal tissue, were recently shown to promote type 2 immunity in response to secreted products from *N. brasiliensis*,[23] lending credence to this hypothesis. However, the exact mechanisms of detection remain to be elucidated.

TRANSMISSION

Once a parasite has been detected by the epithelium and/or other nonhematopoietic cells, the signal is transmitted to cells of the innate immune system so that an appropriate inflammatory cascade can be initiated (**Figure 1a**). Whereas neurons relay their signals via the neurotransmitter neuromedin U,[23,24] the main epithelial-derived cytokines implicated in the early generation of type 2 immunity are interleukin (IL)-25,[25–28] IL-33,[29–31] and thymic stromal lymphopoietin (TSLP)[14,32,33] that strongly synergize and prompt the release of IL-4, IL-5, IL-9, and IL-13 from various sources, notably type 2 innate lymphoid cells (ILC2).[15–17,25,34–38] Epithelium-derived IL-25 and IL-33, in particular, are important for driving IL-5 and IL-13 production from ILC2, the latter of which induces a number of responses, including goblet and tuft cell expansion, resulting in a strong positive feedback loop with increased production of IL-25 by epithelial cells.[15–17,31,34–37] As a consequence, mice lacking IL-25 have less efficient expulsion of *T. muris*,[26] *T. spiralis*,[39] *N. brasiliensis*,[25,27,40] and *H. polygyrus*[28] worms. Furthermore, exogenous administration of IL-25 fails to restore expulsion in *il13*$^{-/-}$ mice,[25,27] whereas the reverse is true,[15,17] illustrating that IL-25 acts upstream of IL-13 rather than directly on expulsion. Strikingly, exogenous administration of IL-25 in the early stages of *N. brasiliensis* infection results in worm clearance in both wild-type and *rag1*$^{-/-}$ mice,[25] strongly suggesting that at high enough concentrations of IL-25, ILC2 activation can overcome T- and B-cell deficiency (which normally is associated with chronicity). It should also be noted that although epithelial tuft cells appear to be the main producers of IL-25 in mice,[15,17] human eosinophils and basophils are capable of secreting this cytokine as well.[41] Nevertheless, mice that lack the IL-25-regulating protein Act1 specifically in epithelial cells cannot expel *N. brasiliensis*,[42] further emphasizing the importance of epithelial-derived IL-25 in mediating type 2 immunity.

Whereas IL-25 is predominantly tuft cell derived, IL-33 is expressed by several epithelial cell subsets,[17] as well as some hematopoietic cell types.[43,44] It belongs to the IL-1 family of cytokines and is thus translated in a proform that can be further processed. However, in contrast to IL-1β and IL-18, IL-33 is biologically active before cleavage and can localize to the nucleus where it binds chromatin, which is augmented upon *T. spiralis* infection.[45] Its precise role is unclear[46] but it appears to be inactivated rather than activated upon cleavage by caspase-1,[47] thus preventing its function as an epithelial-derived alarmin under normal conditions. In contrast, once IL-33 is released in the setting of tissue damage, it can be further activated by granulocyte-derived proteases to exert its function.[48,49] Much like IL-25, it is important for driving IL-13 production by ILC2 during infection[31,35] and can also be recognized by other cell types.[50–53] Furthermore, whereas exogenous administration of IL-33 at early time points after *T. muris* infection promotes worm clearance, injection at later stages of infection does not induce expulsion,[29] suggesting that there is an early window of opportunity in which it exerts its effects. The relative importance of IL-33 as compared with IL-25 is not clear, as there is some functional redundancy between the two, and it thus remains to be determined whether both are equally important upon parasite infection.

Another function of IL-33 is to induce the expression of TSLP in the epithelium.[29] The data on TSLP during parasite infections are sparse, but unlike IL-25 and IL-33, which are critical for the expulsion of multiple parasites, TSLP appears to be involved only during *T. muris* but not *N. brasiliensis* or *H. polygyrus* infections,[14,32,33] and this is understandable given that TSLP is mainly expressed in the large intestine.[33] TSLP can be directly recognized by dendritic cells[54] as well as basophils,[55] again suggesting that epithelial-derived cytokines can bypass ILC2. Indeed, although the main target of IL-25, IL-33, and TSLP appear to be ILC2, it should be noted that both murine and human memory T cells are strongly activated by IL-25,[41,53] IL-33,[53,56,57] and TSLP,[53,58] without the need for T-cell receptor engagement,[57,59] thus being able to respond to antigen nonspecifically. Hence, it remains to be determined what the target cells are for these cytokines, and whether ILCs are truly critical for antiparasitic immunity in previously challenged hosts.

In contrast to epithelial-derived alarmins, the hematopoietic-derived cytokines are involved during both early and late stages of infection, making it difficult to distinguish between their effects on transmission, induction, and expulsion. Nevertheless, IL-13 is by all accounts the most pivotal, being required for protection against most parasitic nematodes,[60–63] perhaps for its role in supporting the migration of dendritic cells that subsequently drive adaptive immunity.[64,65] IL-13 is also critical for inducing many of the expulsion mechanisms in the intestine that will be discussed further on. Although IL-4, IL-5, IL-9, and IL-13 have distinct functions, there is considerable redundancy between them. For instance, although IL-4 deficiency strongly affects the expulsion of *T. spiralis* in C57BL/6 mice, BALB/c mice are not affected by the lack of this cytokine, whereas IL-13 deficiency is equally debilitating in both strains.[63] Similarly, female mice are resistant to *T. muris* infection in the absence of IL-4 (in contrast to their male counterparts) mostly because of a stronger propensity for IL-13 production.[66] Furthermore, with the exception of IL-4 in the skin,[67] IL-4 appears to be dispensable for *N. brasiliensis* expulsion.[61,68] The redundancy between IL-4 and IL-13 likely stems from their shared usage of the IL-4Rα subunit,[69–71] although interestingly, IL-4Rα deficiency in T cells has no impact on worm expulsion during either *T. spiralis*,[72] *H. polygyrus*,[73] or *N. brasiliensis*[61,62] infections, in contrast to total IL-4Rα ablation.[63,73–75] Instead, IL-4 might need to be produced rather than recognized by T cells, as it is mostly secreted by follicular helper T cells to promote IgG1 class switching of B cells.[68] Nonetheless, IL-4 production by ILC2 has recently been implicated in the generation of protective T cell immunity to *H. polygyrus*, and interestingly was dependent on leukotriene D4.[76] Leukotriene D4 did not induce IL-13 or IL-5 expression that as mentioned is mainly promoted by IL-25 and IL-33, illustrating a compartmentalized activation mechanism. IL-4 is also produced by basophils[68,77,78] that also is more likely to be important for humoral immunity and thus play a role during challenge infections.

IL-5 has a complicated and context-dependent role in type 2 immunity. As with IL-13, it is secreted mainly by ILC2, but functions predominantly as an eosinophil recruitment and growth factor.[79–81] Eosinophils, which make up only a fraction of circulating leukocytes, are relatively abundant in the intestinal tract[82] and have traditionally been associated with combating parasites. There are little data, however, to suggest that deficiency in either IL-5 or eosinophils affects the polarization of protective immunity or by extension the outcome of infection, despite that eosinophil-derived mediators can skew dendritic cells to promote type 2 immunity.[83,84] Thus, eosinophils do not appear to be critical for the generation of T helper cell type 2 (Th2) immunity or clearance of *T. muris*,[85] and blocking IL-5 does not affect *H. polygyrus* expulsion despite significantly decreasing eosinophil numbers.[86] If anything, eosinophils act positively on the fecundity of *H. polygyrus* worms.[87] However, mice that overexpress IL-5 have massive systemic eosinophilia and are less susceptible to *N. brasiliensis*,[88] whereas eosinophil-deficient mice are unimpaired in their ability to expel,[89] illustrating that IL-5 has additional unknown functions beyond those associated with eosinophils.

As with the role of IL-5 in promoting eosinophil responses, IL-9 acts mainly as a maturation factor for mucosal mast cells,[90–92] and is largely T cell derived,[93–95] although it can be secreted by ILC2,[96] as well as by mast cells themselves[97,98] that in turn promote enhanced secretion of IL-25, IL-33, and TSLP from epithelial cells.[99] As a result, *T. muris* and *H. polygyrus* expulsion are impaired in mast cell-deficient mice[99,100] as well as upon administration of neutralizing IL-9 antibodies,[101,102] although it should be noted that studies using mast cell-deficient mice (c-kit mutants) suffer from possible confounding factors given the role for c-kit on many other cell types, and thus remain to be clarified. Interestingly, a recent study also found that mast cells not only can respond to IL-33 but might also enhance the transmission of type 2 signals by the production of IL-33 in response to adenosine triphosphate release by dying epithelial cells.[44]

INDUCTION

Once the innate immune system has been alerted to the presence of intestinal parasites, it must propagate the signal to the mesenteric lymph nodes and engage the adaptive immune system, a task mainly accomplished by conventional dendritic cells (**Figure 1b**). Intestinal dendritic cells can be classified into at least three distinct subsets based on their sole or combined expression of CD11b and CD103, as well as the dependence on either interferon regulatory factor 4 or 8 (IRF4 or IRF8) for their development and/or survival.[103] All three subsets are capable of processing antigens, migrating to mesenteric lymph nodes upon activation, and priming naive T cells.[103] However, recent evidence across various infection and allergy models demonstrates a dominant role for IRF4-dependent CD11b$^+$ dendritic cells in the induction of Th2 immunity,[52,104–111] notably during infection with *N. brasiliensis*,[104,105] *T. muris*,[106,107] and the parasitic trematode *Schistosoma mansoni*.[106,108,109] Conversely, IRF8-dependent CD103$^+$ dendritic cells are important for the generation of type 1 responses of both helper[112,113] and cytotoxic[114,115] T cells, thus promoting *T. muris*[113] and *H. polygyrus*[116] chronicity. Together, these studies demonstrate that specialized subsets of dendritic cells are responsible for the induction of distinct types of adaptive immunity. Although the precise mechanisms behind this compartmentalization are unclear, they likely involve both cell-intrinsic signals and external factors that actively promote the generation of protective immunity and vice versa. One such example is the phosphatase SHIP-1 that, if specifically deleted from dendritic cells, results in impaired *T. muris* expulsion, likely because of enhanced production of IL-12.[117] Similarly, the expression of CD40,[118] OX40 ligand,[119] and nuclear factor-κB[120] have all been implicated in the ability of dendritic cells to generate optimal Th2 immunity in response to *S. mansoni* egg-derived antigens, suggesting that levels of costimulation might be a critical factor in determining the outcome of priming. In contrast, expression of the transforming growth factor-β-activating integrin $\alpha_v\beta_8$ promotes chronicity, with mice becoming resistant to *T. muris* infection when $\alpha_v\beta_8$ is lacking on dendritic cells.[121] Similarly, the MAP3 (mitogen-activated protein kinase kinase kinase) kinase TPL-2 was also shown to modulate immunity to *H. polygyrus*, as its deletion in dendritic cells resulted in enhanced resistance to infection that was attributed to its downstream influence on the homing of leukocytes.[122] Indeed, different dendritic cell subsets have divergent expression of certain cytokine and pattern-recognition receptors,[123–126] and might thus be inherently more or less prone to respond to specific pathogens and cytokines to begin with. These types of signals, in combination with cell-extrinsic cues from epithelial and innate immune cells, could determine which type of dendritic cell that gets activated upon parasite infection. Moreover, the nature of the initial stimulus is also likely to have an impact on the resulting response.[127] For instance, dendritic cells in the skin of mice that are exposed to

N. brasiliensis larvae or the contact sensitizer dibutyl phthalate (both of which induce type 2 immunity) acquire distinct transcriptional profiles, revealing a previously unappreciated role for type I interferons during parasite infection,[128] and highlighting the complicated nature of pathogen recognition by the innate immune system.

Interestingly, some studies suggest that ILC,[129–131] basophils,[132–134] and eosinophils[135,136] can express major histocompatibility complex class II and directly prime Th2 responses, notably upon *N. brasiliensis*[131] and *T. muris*[132] infections, with each cell type having been shown to migrate to the mesenteric lymph nodes during infection.[85,87,137,138] However, given that protective immunity is abolished in mice where all[139,140] or specific subsets[104–106,108,109] of dendritic cells have been depleted, it is perhaps more likely that these other innate cells contribute to local tissue immunity by promoting dendritic cell activation, or by further enhancing the cytokine response of mature T cells that have migrated to the infected tissue.[53] Moreover, dendritic cells are responsive not only to cytokines produced by other innate cells, but also to epithelium-derived cytokines, including TSLP,[54,141–143] IL-25,[144] and IL-33,[52,145] thus potentially bypassing ILC2 and granulocytes entirely.

The induction of adaptive immunity is paramount for protection against gastrointestinal nematodes, with T cells no doubt playing a critical role in worm expulsion, as is evident in athymic or lymphopenic mice infected with *T. spiralis*,[146,147] *N. brasiliensis*,[148,149] *T. muris*[150,151] and *H. polygyrus*.[149,152] Immunity is mediated by helper T cells rather than cytotoxic T cells, as shown by the neutralization of $CD4^+$ but not $CD8^+$ cells[153,154] and by adoptive transfer of $CD4^+$ T cells from previously infected mice that confers protection in normally susceptible lymphopenic mice.[155,156] In contrast, the role of B cells in the immune response to nematode infection is more context dependent. For instance, mice that lack mature B cells appear to have less efficient expulsion of *T. muris*.[157] However, adoptive transfer of B cells alone from previously infected mice is insufficient to confer resistance to *T. muris* infection,[158] whereas transfer of IgA[159] or IgG1 (refs. 160, 161) antibodies from resistant mice confers partial resistance to various nematodes, most likely because of their neutralizing effect on secreted parasite antigens, or by trapping larvae.[162–165] Given that adoptive transfer of helper T cells from previously infected mice to lymphopenic mice can confer resistance, these findings suggest that B cells might play a role in promoting the generation and/or polarization of the T-cell response, either by cytokine secretion or antigen presentation[166,167] rather than directly affecting worm expulsion. Antibodies might instead play a role upon secondary challenge, if not during primary infections, as was shown for *H. polygyrus*.[165,168]

Resistance to intestinal nematode infections is clearly dependent on the induction of adaptive immunity, particularly T cells. However, some data suggest that T cell-derived IL-4 and IL-13 are dispensable for parasite expulsion, at least in the case of *N. brasiliensis* infection,[38,169] and can be provided by innate sources instead. T cells might on the other hand be the more important source of IL-9. As such, Th9 cells have been suggested to be distinct from Th2 cells and mediate expulsion of *N. brasiliensis*[95] and *T. spiralis*.[39] Given that T cells represent a much larger pool of effector cells in most infectious contexts, and can respond in a similar way to innate cells the relative importance of innate and adaptive immunity remains to be established. It is also worth emphasizing that these questions relate to primary infections only, most often given as a large bolus of infectious stages. It must be remembered that naturally occurring infections by these parasites will be through repeated challenge with low numbers of eggs or larvae throughout life, and this may well influence the dynamics of the host response and the relative contributions of the different immune components to the partial resistance that is usually generated.

EXPULSION

Once adaptive immunity has been induced in the local lymph nodes, activated effector cells must home back to the site of infection where expulsion can take place. Ejection of gastrointestinal nematodes relies on a combination of physiological mechanisms that include enhanced mucus secretion by goblet cells, release of neutralizing proteins by granulocytes and epithelial cells, epithelial hyperproliferation, and increased intestinal peristalsis (**Figure 1c**), perhaps the most important of which is augmented production of mucins. Mucins trap worms by impeding motility, and hence mice lacking mucin 2 (the predominant glycoprotein of the mucus layer) are rendered susceptible to *T. muris* infection and show delayed worm expulsion,[170] illustrating the importance of this barrier. Nonetheless, *T. muris* and other nematode larvae are still able to penetrate the mucus layer of mucin-proficient mice upon infection, indicating that they have evolved strategies to circumvent this barrier. Indeed, one of the main secreted proteins of *T. muris* is a serine protease with the capacity to degrade Muc 2.[171] The type 2 immune response, however, acts not only to increase goblet cell proliferation and mucus production, but also by modifying existing mucins by sulphation[172] and switching to secretion of Muc5ac that is resistant to degradation.[171] In addition, the host can produce serine-protease inhibitors that prevent further loss of mucin 2.[171] Consistent with these data, Muc5ac is only upregulated in resistant mouse strains[170] and Muc5ac-deficient mice have impaired expulsion of *T. muris*, *N. brasiliensis*, and *T. spiralis*.[173] Increased mucus production and the mucin switch are largely driven by IL-13,[173] IL-4,[174] and IL-22,[175] but the principle of physical obstruction provided by mucus layers can also be extended to other mucosal sites such as the lungs where the lectin surfactant protein-D, which acts as a lubricant, is needed for optimal protection against the pulmonary stage of *N. brasiliensis* infection.[176]

Another expulsion mechanism is the release of various proteins by activated granulocytes and epithelial cells, most of which are toxic to parasites. The relative contribution of each molecule is highly context dependent. For instance, although eosinophils release a plethora of proteins that are potent in killing worms *in vitro*,[177,178] eosinophils appear to be dispensable during most worm infections given that eosinophil-deficient mice are resistant seemingly despite their thinner mucus layer.[179] Mast cells on the other hand contribute to worm expulsion through the release of various proteases that serve to loosen tight junctions between epithelial cells, thus aiding in the shedding of embedded worms, notably during *T. spiralis* infection.[180–182] However, mast cells appear to be unessential for the expulsion of *N. brasiliensis* infection,[183–185] illustrating the context-specific nature of these responses. Goblet cells also secrete several molecules in addition to mucins that contribute to expulsion.[186–188] Resistin-like molecule-β (RELMβ), in particular, prevents lumen-dwelling worms from feeding by effectively coating their cuticle, thus hampering growth as well as blocking motility and attachment to the host epithelium.[186,188] RELMβ expression is highly increased in the intestinal epithelium during several parasite infections[186] (likely induced by ILC2) and is involved in the expulsion of *H. polygyrus*.[188] It might also be required for efficient expulsion of *N. brasiliensis*, although the data are conflicting.[188,189] In contrast, there seems to be no role for RELMβ in the expulsion of *T. spiralis* or *T. muris*.[187,188] RELMα, on the other hand, is mainly expressed in the pulmonary epithelium and might be important for combating the pulmonary stage of *N. brasiliensis*.[189] RELMα is further implicated in the function of alternatively activated macrophages, highlighting its role in type 2 immune responses.

After being trapped in mucus and coated by various toxic proteins and neutralizing antibodies, worms are expelled by a combination of increased epithelial proliferation and intestinal peristalsis. The precise contribution of each mechanism likely depends on the parasite in question. For instance, accelerated epithelial turnover might be more important for expulsion of *T. muris* worms that preferentially infect epithelial cells. Because of its rapid turnover, *T. muris* worms thus need to continuously burrow through the epithelium in order to remain within their niche. Accordingly, epithelial hyperproliferation serves to shift the epithelium outward from the crypts. In contrast, peristalsis might be of more relevance during *H. polygyrus* infection, given that the worms enter the lamina propria and resurface to wrap around the villi rather than specifically infecting the epithelium, as is the case for *T. muris*. Peristalsis could therefore aid in shedding infected cells that the parasite is attached to. Increased epithelial turnover in response to *T. muris* infection seems to occur mainly in resistant mouse strains, largely driven by IL-13,[190] and as such, signaling pathways that regulate the proliferation of epithelial stem cells such as the lysine methyltransferase Setd7 affect the outcome of *T. muris* infection, but not *H. polygyrus* infection.[191] Intestinal peristalsis is mediated by contraction of smooth muscle cells, and is induced by both IL-9 (ref. 102), IL-4 and IL-13,[27,73,192] and seems to be controlled mainly by T cells. Thus, the responsiveness of smooth muscle cells to neurotransmitters that control contraction via muscarinic receptors are important for *N. brasiliensis* expulsion.[193] Most of the available data on gut peristalsis during nematode infection are however highly correlative[73,102] and its importance remains to be established. Nevertheless, together these mechanisms effectively expel the invading parasite.

RESOLUTION

When a worm infection has been cleared, inflammation is resolved and the damaged tissue must be repaired. This process is partly orchestrated by type 2 cytokines and involves several cell types, notably macrophages and eosinophils (**Figure 1c**). Thus, despite being redundant for the expulsion of most nematodes, eosinophils might be important for wound healing and tissue regeneration in which they have been implicated in nonmucosal tissues.[194–196] Eosinophils have also been shown to promote the survival of long-lived plasma cells in the bone marrow[197] as well as the generation of IgA-secreting plasma cells in the gastrointestinal tract[179,198] (at least in the small intestine[199]) via the production of IL-1β, suggesting that they might affect secondary challenge infections where antibodies presumably play a larger role. Indeed, both IL-5 and eosinophil-deficient mice harbor increased numbers of *N. brasiliensis* larvae after secondary infection,[89] with similar results during secondary *T. spiralis* infection.[200] Furthermore, eosinophils negatively regulate Th17 cells[201] and promote the expansion of regulatory T cells in the steady state[198,202] that might affect overall inflammation, illustrating their complex contribution to tissue homeostasis. Similarly, whereas resident intestinal macrophages are mostly suppressive in nature and do not act inflammatory to pathogen stimulation, type 2 cytokines give rise to alternatively activated macrophages that might contribute to the expulsion of certain parasites.[75,192,203,204] Furthermore, macrophages in the intestinal mucosa are also likely to play an important role in tissue repair, as has been shown in various settings of inflammation.[205–210]

Whereas most research on host–parasite interactions has focused on the underlying factors that govern resistance and susceptibility, the long-term consequences of both acute and chronic worm infections are largely unexplored. Given the inverse correlation between parasite exposure and the occurrence of immune-associated disorders, it is quite surprising that so little attention has been devoted to this subject, particularly in the case of *Trichuris* infections that have been in clinical trial for the treatment of various inflammatory disorders.[9,211] Chronically infected mice do not display any overt symptoms of disease, but are by no means unaffected considering that persistent *T. muris* infections are lethal in the absence of IL-10,[212] indicating that there is ongoing inflammation beyond the spontaneous inflammation inherent to *il10*$^{-/-}$ mice. Indeed, chronic *T. muris* infection results in the accumulation of interferon-γ^+ T cells in the bone marrow,[213] and does not appear to protect against the development of colitis.[214,215] Furthermore, depending on the strain, chronically infected mice gain less weight than their uninfected counterparts,[216] and in some cases even acquire colitis-like symptoms, thus losing weight,[217] mirroring the malnutrition and wasting of some infected humans. In contrast, lung pathology appears to be decreased in response to papain challenge,[218] illustrating that worm-induced protection against inflammatory disorders is highly context specific. Data on the long-term effects of acute *T. muris* infection are even sparser. Alternatively activated macrophages seem to increase in number after expulsion,[219] perhaps contributing to tissue repair, and there are dramatic changes to the epithelial niche, with increased numbers of mucosal mast cells that persist in the epithelium for months after expulsion and appear to affect epithelial barrier integrity.[220] However, other potential long-lasting consequences of acute *T. muris* infection remain unexplored. In contrast, *H. polygyrus* appears to be protective in several inflammatory models,[221,222] and this has been attributed to its ability to dampen inflammation by promoting the generation and function of regulatory T cells via some of its secreted proteins.[223,224] Hence, the hygiene hypothesis might apply only to a narrow group of nematodes and it is important that we distinguish between general phenomena of parasite infection (such as the importance of IL-13) and more specific ones (such as the contribution of eosinophils) if we are to apply our knowledge to patients in the clinic.

CONCLUSIONS AND FUTURE CHALLENGES

Parasitic nematodes are an integral part of the mucosal milieu and have played an important role in the evolution of the intestinal immune system. Their presence leads to the induction of type 2 immunity that involves a vast array of cell types and molecules that work in concert to protect against a wide range of extracellular parasites at mucosal surfaces. Although some worm infections might be beneficial to human health, the long-term effects of infection remain poorly understood and there are many unresolved questions as follows. (i) To what extent are parasites able to directly manipulate the immune system, and with what consequences on subsequent infections? Nematodes clearly have the ability to influence the host as they are often able to survive for extended periods of time without causing pronounced inflammation. Identifying the pathways that are regulated upon infection thus might prove valuable for the development of new anti-inflammatory drugs. (ii) How does early parasite exposure affect the developing immune system? Given that nematode infections mainly afflict children it is not unlikely that their immune system is permanently altered as a consequence. (iii) What is the contribution of the microbiota in regulating immune responses to extracellular parasites? Some, or even many of the observed effects on the host upon nematode infection might be due to changes in bacterial composition. Establishing the causal links in the cross-talk between intestinal bacteria, parasites, and the immune system is notoriously difficult and remains to be resolved. (iv) Can parasite-derived molecules be harnessed for treating immune-associated disorders, and are they sufficient? Answering these and other questions will be important as more and more people are afflicted with various diseases partly attributed to the absence of nematode infections.

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DISCLOSURE

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