Immunity to Helminths: Resistance, Regulation, and Susceptibility to Gastrointestinal Nematodes

Richard K. Grencis

Faculty of Life Sciences, University of Manchester, Manchester M13 9PT, United Kingdom; email: Richard.K.Grencis@manchester.ac.uk

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Abstract

Helminth parasites are a highly successful group of pathogens that challenge the immune system in a manner distinct from rapidly replicating infectious agents. Of this group, roundworms (nematodes) that dwell in the intestines of humans and other animals are prevalent worldwide. Currently, more than one billion people are infected by at least one species, often for extended periods of time. Thus, host-protective immunity is rarely complete. The reasons for this are complex, but laboratory investigation of tractable model systems in which protective immunity is effective has provided a mechanistic understanding of resistance that is characterized almost universally by a type 2/T helper 2 response. Greater understanding of the mechanisms of susceptibility has also provided the basis for defining host immunoregulation and parasite-evasion strategies, helping place in context the changing patterns of immunological disease observed worldwide.

INTRODUCTION

Helminths are part of a polyphyletic group of invertebrate parasites, of which nematodes (roundworms) are one of the most successful, ranging in length from a few millimeters to several meters. Recent estimates have suggested that there may be close to one million different species of nematodes (1)—a testament to their adaptive capacity—although only approximately 23,000 species have been described to date (2). Parasitism is a successful and prevalent life-cycle strategy that has been adapted by more than half of the documented nematode species. The evolution from free-living nematodes to parasitic species has led parasitic nematodes to adopt the gastrointestinal (GI) tract as a major habitat in all vertebrate host species, with those species that infect humans recognized as important but neglected tropical diseases (3). The fact that infection of livestock by GI-dwelling nematodes also causes considerable ill health and loss of productivity (4) has further spurred interest in developing control methodologies, including vaccine development, selective breeding for host resistance in animals, and anthelmintic drug development (5). Indeed, the alarming rise in drug resistance among GI nematodes (6) and the importance of host immunity in underpinning other approaches of GI nematode control have generated intense interest in understanding innate and adaptive immune responses to this group of parasitic helminths. Moreover, the availability of good laboratory systems—including GI nematode species that naturally infect rodents and, therefore, obviate adapting human- or large animal–infecting species to mice or rats—is a major research advantage for investigating host–parasite relationships that have evolved together (see **Table 1**). Furthermore, these model systems are now widely used in many fundamental studies of the immune response as ways of generating tractable immune infectious challenges at epithelial surfaces, mainly in the mucosa of the gut but also in the lung and skin (dependent upon nematode species and life cycle).

The present review concentrates, therefore, upon immunity to GI nematodes, but immunity to tissue-dwelling nematodes of parenteral tissues such as the filariae (7), the trematodes such as schistosomes and liver flukes (8, 9), and the cestodes such as the taeniids (10) are also areas of fertile immunological investigation. In-depth coverage of all these is simply outside the scope of the present review, although many of the features described herein are common to, or mirrored by, these other helminth infections.

As highlighted above, most of our mechanistic understanding of immune responses to GI nematodes has come from laboratory model systems. Numerous species have been extensively studied over the years, with a current emphasis on those that infect mice. This simply reflects the power and utility of modern genetic and immunological techniques that allow precise dissection of the host response. However, studies carried out before the advent of murine genetic manipulation did provide the foundation for our more recent studies and in many cases were particularly insightful. This review focuses on current studies, but I direct the reader to further reading of key publications where appropriate.

THE NATURE OF THE ANTIGENIC CHALLENGE

Implicit to defining immune responses to GI nematodes is an appreciation of the nature of the infectious/antigenic challenge, i.e., where, how much, how often, and for how long. Moreover, there is almost always an element of damage associated with at least some aspect of the parasite's life cycle. Although many species share common infection strategies, there are also important differences that we should appreciate when putting the host response into precise context. Several recent reviews have detailed these aspects (11, 12). Briefly, all nematodes progress through four larval (L) stages (L1–L4) separated by molting events, leading to adult parasites, most often of

Table 1 Major gastrointestinal nematode infections of human together with the most commonly used laboratory model systems and life-cycle comparison

Species	Host	Infection route	Infection stage	Systemic migration	Intestinal niche	Transmission
Ascaris lumbricoides	Human	Oral ingestion	Eggs	Via lungs	Small intestine, lumen	Eggs via feces
Necator americanus	Human	Skin penetration	L3 larvae	Via lungs	Small intestine, lumen	Eggs via feces
Ancylostoma duodenale	Human	Oral ingestion or skin penetration	L3 larvae	Via lungs	Small intestine, lumen	Eggs via feces
Trichuris trichiura	Human	Oral ingestion	Eggs	None	Large intestine, epithelium	Eggs via feces
Strongyloides stercoralis	Human	Skin penetration	L3 larvae	Via lungs	Small intestine, sub-mucosa	L1 larvae via feces[a]
Nippostrongylus brasiliensis	Rat/mouse	Skin penetration	L3 larvae	Via lungs	Small intestine, lumen	Eggs via feces
Heligmosomoides polygyrus bakeri	Mouse	Oral ingestion	L3 larvae	None	Small intestine, sub-mucosa then lumen	Eggs via feces
Trichinella spiralis	Rat/mouse/ cosmopolitan	Oral ingestion	L1 larvae	Via blood and lymph	Small intestine, epithelium	L1 larvae encapsulated within striated muscle of host[b]
Trichuris muris	Mouse	Oral ingestion	Eggs	None	Large intestine, epithelium	Eggs via feces
Strongyloides spp.	Rat/mouse	Skin penetration	L3 larvae	Via lungs	Small intestine, sub-mucosa	Eggs or L1 larvae via feces

[a] *S. stercoralis* can exhibit autoinfection where L3 stages precociously develop in the intestine.
[b] *T. spiralis*, unusually, has a direct life cycle in which L1 larvae are released from the adult parasites living within the intestinal epithelium. They migrate via the blood circulation and lymphatic system to striated muscle, where they invade and develop a "nurse cell" complex. They grow and remain here until the host is eaten and the L1 larvae are released within the intestine.

separate sexes. Infection by GI nematodes tends to occur either by ingestion of the infectious stage (egg: *Trichuris* sp., *Ascaris* sp.; L1: *Trichinella spiralis*; L3: *Heligmosomoides polygyrus bakeri*) or by penetration through the skin by L3 (*Nippostrongylus brasiliensis*, *Necator americanus*, *Strongyloides* sp.). In the latter, following skin penetration the parasites migrate via the blood to the lung, then disrupt the tissue into the airways and migrate up the trachea, only to be swallowed prior to establishment in their preferred location within the GI tract. Depending upon the species, GI-dwelling nematodes inhabit various niches within the intestine. Some inhabit the lumen of the gut (*N. brasiliensis*, *N. americanus*, *Ascaris* sp.); some are found within the mucus layer; and some invade the intestinal tissues, including the epithelium (*Trichuris* sp., *T. spiralis*) and submucosa (*H. polygyrus bakeri*), and may occupy different sites at different stages of their life cycle. Also, some prefer different regions of the GI tract (small versus large intestine and different locations within each). Some species undergo a systemic migration via the blood and lung even though they are initially ingested, with larvae burrowing through the gut wall to gain access to the circulation (*Ascaris* sp.). Given that all infections occur via immature stages of the parasites, establishment within the host is also accompanied by maturation into the sexually mature adult stages. Following

mating, the female parasites release eggs (most commonly but not exclusively), which pass out of the host into the external environment where they develop into the infective stages. As a general rule (*T. spiralis* is a notable exception), GI nematodes do not multiply within the host, with the number of parasites reflecting the number of infectious stages encountered.

Under natural conditions, infection occurs most often through repeated low doses. Infection by GI nematodes is generally chronic, so most infected individuals have parasites within their intestines for most of their lives and are challenged by infectious stages via skin and/or gut many times. This presents a repeated and varied antigenic challenge to the host over protracted time periods. Commonly, a host harbors more than one species of GI nematode (and indeed helminth group) simultaneously. Experimentally, however, most studies have used one or more infectious events to study underlying immune mechanisms, with the infectious dose consisting of a moderate to large bolus of the infective stage. This is rarely encountered naturally, but it does often generate a strong host-protective response, with parasites being expelled from the intestine. This approach has been extremely useful in defining protective immunity to these parasites and forms a platform on which to explore the mechanisms of chronic parasite infection where protective immunity does not operate effectively.

Interestingly, regardless of parasite species, investigators observe a commonality in terms of the nature of the immune response generated against GI nematodes, which is broadly characterized by a type 2 cytokine or T helper 2 (Th2) response. This has been well established using many experimental systems as well as analysis of both human and large animal studies (4, 13, 14).

As detailed above regarding the difficulties in studying naturally infected humans and large animals, most of our mechanistic understanding of immunity to GI nematodes comes from laboratory model systems, and the present review reflects this fact. However, many insightful studies have been carried out in humans following natural and experimental infection, together with studies in naturally or experimentally infected domesticated stock, which are discussed below. It is beyond the scope of this review to cover the literature comprehensively, but I direct the reader to appropriate studies and informative reviews below, as necessary.

SETTING THE SCENE

The first comprehensive experimental studies of immunity to GI nematode infection were carried out in the 1930s in the rat with the parasite *Nippostrongylus brasiliensis* infection. The papers by Africa (15), Taliaferro and Sarles (16–18), and Chandler (19, 20) were particularly insightful, with excellent descriptions of pathology and infection progression together with some of the first passive transfer studies using sera from heavily infected rats. These studies also described the presence of peripheral and intestinal eosinophilia, a characteristic feature of almost all helminth infections in both animals and humans (21). These early studies noted that serum-derived antibody was able to protect against reinfection and suggested that it mediated its protective effects by forming precipitates at the oral opening and within the parasite intestine. There was also a suggestion that a cellular compartment may be involved in protection, although exactly what cells were important and how they contributed were unclear (16). This idea was extended several decades later through a series of papers from Ogilvie and colleagues (22–24), again working with *N. brasiliensis* in the rat, together with studies from Dineen and colleagues (25–27) using the ovine parasite *Trichostrongylus colubriformis*, in this case a sheep parasite adapted to the guinea pig. Ogilvie and coworkers developed the idea in the 1960s and 1970s of protective immunity operating through antibody and cells—lymphocytes—and also identified (alongside other groups, e.g., Jarrett) the highly elevated IgE levels that were associated with worm infection (28, 29). The idea of host-protective immunity to GI nematodes was also highlighted by the description of the so-called spontaneous cure seen

in domestic sheep when animals were exposed to large numbers of infectious stages of GI nematodes such as *Haemonchus contortus*. Following exposure, the animals expelled the parasites from the gut and were relatively resistant to further challenge infections (30). In subsequent research, investigators found that thymectomy impairs worm expulsion in the *Trichostrongylus colubriformis* model, demonstrating for the first time the importance of T cells in expulsion of GI nematodes (31). The concept of worms being damaged via immunity (24, 32) was also identified, raising the possibility that the parasites were not necessarily killed by the host-protective response but rather were damaged and unable to maintain their intestinal niche. Indeed, several studies conducted in the 1960s and 1970s also demonstrated a profound inflammation associated with intestinal worm expulsion in some model systems (e.g., *T. spiralis*), including fluid leakage into the intestine and changes in intestinal muscle contraction. These combined changes were believed to aid removal of the worms from the intestine and are now considered part of the so-called weep and sweep phenomenon.

Development of the concept of resistance further consolidated the view that although the induction of protective immunity may be specific in nature, many of the effector mechanisms were mediating their effects in a nonspecific manner (33). This hypothesis was supported by studies associating many pathological and physiological changes with the loss of intestinal stages of the parasites from the gut (34). For the *T. spiralis* system, differences in effector responses between experimental hosts (rats and mice) following primary and secondary infections were also observed. For example, in the rat a secondary challenge infection was always expelled very rapidly (within 24–48 h) (35), with some studies supporting a possible role for antibody, including IgE (35, 36). In mice, a challenge infection was faster, and the accelerated expulsion appeared to be associated with a typical anamnestic response (37). Among the pathological changes observed, an intense intestinal mast cell hyperplasia was observed in many systems (38, 39), and mucosal goblet cell hyperplasia was also associated with protection against GI nematode infection (40–42).

Most of these studies were carried out in the 1980s and 1990s, in the pre–flow cytometry era, indeed also before the cell subset and cytokine era. However, this led to a focus on other aspects of host immunity to GI nematodes. A continuing theme was the role of antibody, and many studies sought to explore whether antibody was host protective or merely a reflection of infection. The early work based on passive transfer of sera taken from immune or hyperimmune (e.g., repeatedly challenged) animals suggested that antibody did reduce both intestinal worm burdens (and/or egg output from female worms), with precipitates forming around and within parasites. These findings suggested that blocking or neutralizing key functions of the parasite contributed to worm damage (23, 24, 43–45). Few studies examined the class of antibody that mediated protection, although work from the *H. polygyrus bakeri* system (formally *Nematospiroides dubius*) identified IgG1 as the class of antibody involved (46, 47). Notably, more recent studies have confirmed and extended these observations using transgenic mice with deletions in various genes involved in antibody production, class switching, and interaction with cells or complement (48). The data revealed that antibody does not need to interact with cells via Fc receptors or complement to mediate protection (48, 49). More recently, a role for antibody in controlling *H. polygyrus bakeri* during its brief intestinal phase has been described (50, 51), as discussed below. Antibody is not necessarily required for host protection against all GI nematodes in all settings (52); e.g., host protection to *T. muris* can operate in the absence of antibody (53).

INNATE IMMUNITY

The early studies did not evaluate the innate response to GI-dwelling nematodes other than to describe the goblet cell responses responsible for production of mucus, which was regarded in

broad terms as a secreted physical barrier (54). Recently, however, our understanding of innate immunity to GI nematodes has expanded dramatically.

The recent description and reclassification of several distinct innate cell populations (55) were driven in part by the identification of novel cell populations—innate lymphoid cells (ILCs) that produce type 2 cytokines (e.g., IL-5, IL-9, and IL-13) and hence are called ILC2s (56–60)—following infection of mice with GI nematodes. Although numerous studies had identified contributions of other innate or innate-like cell populations such as natural killer cells (61) and γδ T cells (62), we now know that ILC2s play a key role in responses to GI nematodes (63, 64). On a per-cell basis, they appear to secrete more cytokines than $CD4^+$ T cells (57, 63, 65) and can be the major cell population producing these cytokines following helminth infection (56). Moreover, ILC2s generated from bone marrow can adoptively transfer protection effectively (56, 59). Identification of RORα as the controlling transcription factor in ILC2s enabled GI nematode infection studies in *Rora*$^{sg/sg}$ mice that showed diminished IL-13 and reduced goblet cell responses, together with a delayed expulsion of parasites (*N. brasiliensis*) from the gut, despite having normal levels of $CD4^+$ T cells in the draining lymph node (66). Elevation of ILC2 numbers in lymphoid tissue and the intestine upon infection by other nematodes has also been described [*H. polygyrus bakeri*, *T. spiralis*, and *T. muris* (11, 51, 67)]. A protective role for these cells is further supported by studies of *H. polygyrus bakeri*, which demonstrated that IL-1β induced upon infection was able to downregulate the production of ILC2s and that this was associated with a reduction in protective immunity (67).

As a consequence of these studies, the factors governing the generation of ILC2s have also received a great deal of attention. Current views support the idea that bone marrow–derived precursors differentiate locally under the influence of factors such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) released predominately from the intestinal epithelium (55, 68, 69). Other signals such as epithelial act1 (an NF-κB-activating protein) in the gut (68) and trefoil factor 2 in the lung (70) are also involved in initiation of ILC2 responses following GI nematode infection. All the ILC subsets differentiate under the influence of IL-7 (71, 72), and evidence suggests that ILC2 survival at some barrier surfaces (e.g., lung and intestine) is controlled by IL-9 (60), a cytokine long known for an enhancing role in type 2 immunity (73, 74).

In vivo administration of IL-33 is a potent inducer of type 2 cytokine responses (75, 76) and can promote expulsion of GI nematodes (76–78), although this does not appear to be universally true (11, 77, 79). Moreover, GI nematode infection studies in IL-33R-deficient (ST2-null) mice indicate that IL-33 may not need to operate through its membrane receptor to exert its effects, which is in keeping with its capacity to function via other routes, e.g., as a direct nuclear transcription factor (78). IL-33 plays a protective role in *N. brasiliensis* infection, as IL-33-null mice have defective protection after both primary and secondary infection (80). The biology of IL-33 during helminth infection, therefore, is complex and not yet fully defined.

The absence of IL-25 impairs host-protective immunity in various GI nematode systems (57, 81, 82), but IL-25 administration does not induce protective responses in immunodeficient animals such as SCID mice (82), suggesting that components of the adaptive response may be required to generate effective protection. Similar observations have also been made for IL-33 (76) and add to the growing evidence of functional interplay between innate and adaptive cells (83). Nevertheless, ILC2 responses can be elevated in immunodeficient animals and, indeed, in nutrient-deficient animals (84). It is tempting to speculate from such studies that the gut environment can play a key role in influencing the ILC baseline, perhaps via microflora and micronutrients. ILC2s have recently been shown to express MHC class II and could function as antigen-presenting cells (APCs) (83). An interplay between the adaptive $CD4^+$ T cell compartment and ILC2s can be inferred from several studies in which the effectiveness of protection is compromised when T cells—particularly $CD4^+$

T cells—are absent (53, 56). Recent work has now shown a dialogue between $CD4^+$ T cells and MHC class II by ILC2s as an important component of IL-13-dependent clearance of *N. brasiliensis* (85).

TSLP is also produced by epithelial cells, and the absence of it or its receptor can impair type 2 cytokine–mediated immunity (86), including the ability to expel some GI nematodes such as *T. muris* (87). Indeed, intestinal epithelial cell–intrinsic IκB kinase (IKK)-NF-κB-dependent gene expression plays a key role in the NF-κB pathway during *T. muris* infection through TSLP licensing of dendritic cells (DCs) to induce Th2 responses (69). However, for other systems (*N. brasiliensis*, *H. polygyrus bakeri*) TSLP is not an absolute requirement, and TSLPR-null mice do not show impaired immunity (88). Even in TSLPR-null mice infected with *T. muris*, impaired resistance could be reversed if IFN-γ were also neutralized, indicating that perhaps TSLP effects operate indirectly through downregulating Th1 and/or Th17 responses (87).

Thus, the available data suggest a common theme in terms of innate immune protection to GI nematodes and type 2 cytokine responses, although this may be context and nematode species dependent. For example, *T. muris* differs from the other nematodes discussed above in that it requires the activation of a Th1 response and IFN-γ production to progress to chronic infection (89, 90). The activation of these processes is not required for chronic infection by *H. polygyrus bakeri*, and *N. brasiliensis* is essentially studied as an acute-resolving infection in mice. Thus, mechanisms controlling chronic infection by this species remain undefined.

INDUCTION OF ACQUIRED IMMUNITY

The Dendritic Cell

Although a major role for ILC2s is the production of effector cytokines during GI nematode infection, their role as APCs and the contribution they make to this activity has yet to be fully defined. It is clear from many studies, however, that DCs as a potent and well-established population of APCs do influence resistance to GI nematodes. The definition of DC subsets in the intestine is complex and can vary with intestinal location. Based predominately on studies of the murine small intestine, the lamina propria is populated mainly by two populations, $CD103^+CD11b^+$ and $CD103^+CD11^-$, derived from a common committed DC precursor, and a more minor $CD103^-CD11b^+$ population whose origin is unknown (91, 92). GI nematode infections have not been comprehensively defined with these recently described phenotypes, but we do know that DC populations change following infection. Upon intestinal infection with *N. brasiliensis*, numbers of DCs in the draining mesenteric lymph node increase and the proportions of the $CD86^{hi}CD8\alpha^{int}CD11b^-$ DC subset decrease, with an accompanying decrease in expression of CD40, CD86, and CD103 by DCs (93). Additionally, the transcription factor IRF4 is important in DCs in inducing Th2 responses in both the lung- and gut-associated lymphoid tissue following *N. brasiliensis* infection (94). In chronic infection with *H. polygyrus bakeri*, $CD8\alpha^+$ DC numbers decrease markedly and appear to have altered cytokine production potential (93). Also, ex vivo experiments suggest that DCs from *H. polygyrus bakeri*–infected mice were poor inducers of $CD4^+$ T cell proliferation in vitro but could induce higher levels of $FoxP3^+$ T cells (regulatory T cells, or Tregs) than could DCs from noninfected animals (95). Studies have shown that, following *T. muris* infection, host immunity is influenced by the speed of movement of $CD103^+$ DCs via CCL5 and CCL20 to and from the epithelium in the large intestine, with rapid movement promoting resistance and slower movement associated with susceptibility and progression to chronic infection (96). The further importance of DCs in influencing the response phenotype is emphasized by the use of mice whose DCs cannot activate transforming growth factor (TGF)-β through lack of expression of

the integrin αvβ8 (97). Such mice infected with *T. muris* have enhanced type 2 immune responses, expelling their parasites rapidly, which demonstrates a key role for this cell type in resistance.

Although DCs are the canonical APC, GI nematode infections have shown that other cell populations, most notably the basophil (98, 99) and ILC (85), can play an important antigen-presenting role. In the intestine, goblet cells have been shown to transfer gut antigens to other APCs (100), and mucins secreted by goblet cells are taken up by DCs together with antigens found in the mucus and influence the subsequent immune response (101). Other type 2–associated innate cell populations also have regulatory influences on responses to GI nematodes, including mast cells and eosinophils (102–104), but probably not by exerting their potential to act as APCs.

The Macrophage

Although traditionally studied as a phagocyte and an APC, the macrophage also plays various roles during GI nematode infection. Again, the definition of the populations involved varies among studies, but in the gut, an accepted macrophage phenotype is a $CD11c^+$, $CD11b^+$, $F4/80^+$, $CD64^+CX3CR1^{hi}$ cell (105, 106). Helminth infections have been associated with the alternatively activated (AAM; M2) phenotype, correlating with type 2 cytokine dominance following these kinds of infection (107, 108). Recent work has highlighted the potent proliferative potential of this population at tissue sites, adding a new dimension to their activity (109, 110). The functions of these cells remain to be comprehensively defined but may include antiparasite effector functions (see below), immune regulation (111), and tissue repair (112) in addition to an APC function.

THE $CD4^+$ T CELL AND ACQUIRED IMMUNITY

Although ILC2s must clearly now be regarded as a major source of cytokines following GI nematode infection, numerous studies in T cell–depleted animals, animals lacking T cells, or animals with $CD4^+$ T cells that exhibit substantially impaired protective immunity make it clear that $CD4^+$ T cells play a critical role in resistance to GI nematodes (13, 113, 114). Moreover, adoptive transfer of $CD4^+$ T cells confers protective immunity by generating type 2–controlled effector mechanisms (115), and $CD4^+$ T cells must migrate to the intestine to mediate protection (116). As expected, there is little evidence to suggest a role for $CD8^+$ T cells, even though they can be a source of cytokines following GI nematode infection (117).

The relative importance of the T cell to the ILC2 has not been comprehensively defined and is likely to vary with context in terms of GI nematode species involved and experimental approach employed. It may certainly be the case that the most effective control of effector mechanisms relies on multiple cell types acting in concert. There may also be functional redundancy, e.g., in cell populations producing IL-13, with the relative importance of particular cells depending on multiple factors (61).

EFFECTOR MECHANISMS

Innate Effector Mechanisms

Many experimental studies concentrate on dissecting the mechanisms of host protection that operate after a primary infection with parasites, although some have examined immunity after multiple challenges more akin to infection exposure experienced naturally. Nevertheless, as is highlighted above, abundant evidence (both observational in the field and experimental) suggests

that protective immunity depends on type 2 cytokine–controlled effector mechanisms, although the effector mechanisms involved appear to vary in efficiency among different GI nematode species and after multiple infectious challenges.

The first host-protective mechanism most nematodes encounter in the intestine is the secreted mucus barrier. Although investigators have long noted that a goblet cell hyperplasia is associated with the expulsion of GI nematodes and that it may play a role in parasite expulsion (118), only recently have the mechanisms by which the mucus layer achieves this expulsion and the components involved begun to be investigated. The mucus barrier is highly dynamic and consists of a hydrated gel that is often present as multiple layers, and the gel layers differ among different parts of the intestines (119, 120). The main constituents of the secreted mucus gel are large, heavily glycosylated glycoproteins of high molecular weight, and the mucins with Muc2 are the predominant type found in the intestine in humans, mice, and domesticated animals (121). The mucus gel formed by different mucins physically and biochemically alters the nature of the matrix, and these alterations influence its inherent functional capabilities, including its ability to interact with antimicrobial compounds, antibodies, commensal metabolites, etc. (122).

Mucus production from goblet cells during GI nematode infection is under the immune control of type 2 cytokines, with IL-13 and IL-4 together playing the dominant role (40–42), although IL-22 is also involved (123). Thus, both $CD4^+$ T cells and ILCs can potentially regulate the goblet cell hyperplasia observed following infection. This has been confirmed for $CD4^+$ T cells (124) and for ILC2s (84), although their relative importance is not yet defined. Few studies have explored in detail the IL-13-mediated control of goblet cells during GI nematode infection. Studies with *T. muris*, however, have clearly shown that Muc2 plays a protective role by accelerating worm expulsion; these studies have also demonstrated that the biophysical properties of the mucus gel are different between mice that are resistant or susceptible to *T. muris* (41). Moreover, *T. muris* produces secretions that can degrade Muc2 (125), a finding supported by recent studies of *Trichuris* genomes (126, 127). Furthermore, subsequent studies identified the upregulation and production of Muc5Ac in the intestine of mice resistant to *T. muris*. This was unexpected, as Muc5Ac is not usually produced at this site. Muc5Ac is under the control of IL-13, and Muc5Ac-null mice are completely susceptible to infection (42). Interestingly, unlike Muc2, Muc5Ac is not degraded by secretions from *T. muris* (125). Rather, investigators found that this mucin plays a protective role following infection with *N. brasiliensis* and *T. spiralis*, suggesting that it is a broad-acting effector mechanism against GI nematodes. Precisely how the mucins affect GI nematodes is unknown, but in vitro data so far suggest direct interaction affects worm viability (42).

Other secreted host-protective components, under type 2 cytokine control from goblet cells, also exert antiparasitic effects. For example, the resistin-like molecule RELMβ is upregulated during the expulsion of several GI nematodes, but efficacy in terms of host protection varies among species. RELMβ is host protective against those parasites that spend at least part of their life cycle in the lumen of the intestine (*H. polygyrus bakeri*, *N. brasiliensis*) (128) but is not effective against species that invade the gut epithelium, such as *T. muris* and *T. spiralis* (128, 129). It has been suggested that RELMβ interferes with parasite feeding and development (128), again reducing parasite "fitness," allowing the so-called weep and sweep mechanism to become more effective. Notably, type 2 cytokines including IL-9 also enhance this response by promoting intestinal muscle contraction (130) in addition to enhancing goblet cell hyperplasia (73).

Indolamine is also secreted from goblet cells and, in the case of *T. muris* at least, during chronic infection when it likely inhibits worm expulsion through downregulation of intestinal epithelial turnover (131). Immune control of intestinal epithelial cell turnover occurs during expulsion of *T. muris* from the large intestine. This species lives embedded within the epithelial layer, and acceleration of its turnover (under the control of IL-13) is believed to physically remove

the parasite from its preferred intestinal niche (132). Interestingly, amphiregulin also influences intestinal epithelial turnover during *T. muris* infection (133) and is produced by ILC2s.

Adaptive Effector Mechanisms

Early studies explored the possible role of mucosal mast cells and IgE in potential classical immediate hypersensitivity responses in the intestine. Mucosal mast cells are known to express high-affinity IgE receptors during GI nematode infection (134), although confirming the importance of this antibody class in host protection has been difficult apart from a few specific examples. Much of the elevated peripheral IgE is nonparasite specific (135), and researchers have suggested that its function is as a parasite-evasion strategy (136). Paradoxically, this implies that IgE has a host-protective role. Certainly, there is growing evidence that many parasite antigens are allergens (137). However, mucosal mast cells in the parasitized gut are active in animals deficient in the high-affinity IgE receptor (13). In terms of worm expulsion, not all systems demonstrate a protective role for mucosal mast cells. Mast cells do not appear to be required for expulsion of *T. muris* (138) or *N. brasiliensis* (139), although they potentially play a role against the luminal stages of *H. polygyrus bakeri* (140) and do play a role in *T. spiralis* (141) and *Strongyloides venezuelensis* infections (142). With regard to *T. spiralis*, removal of mast cells via in vivo neutralization of stem cell factor/c-kit interactions abrogates the mucosal mast cell hyperplasia and delays worm expulsion (143). Moreover, worm expulsion depends on mouse mast cell protease 1 (mMCP1) production (144) and on the generation of a so-called leaky gut in which the paracellular permeability is altered within the small intestine epithelium (145). Infections of IgE-null mice with *T. spiralis* that had delayed worm expulsion also showed markedly reduced production of mMCP1. Taken together, the data suggest that both IgE-dependent and -independent events contribute to mast cell activation in the parasitized gut, with a further possible role for IgE in regulation of the mast cell response (146).

It is tempting to speculate that the role of IgE has evolved in part to be more important against helminths not in the gut but at barrier surfaces such as the skin. As mentioned above, many GI nematodes initiate infection via invasion through the skin [which is similar to the case of other helminths such as the schistosomes, where IgE has been implicated in IgE-mediated protection in the skin (137)]. Recent work with the *N. brasiliensis* system has highlighted that immunity to the skin-invasive stages of GI nematodes is controlled predominately during secondary infections at the skin site (147). Interestingly, these studies show that it is the basophil and not the mast cell that is the key FcεRI-bearing cell population responsible for protection and, through IL-4 release, promotes the activation of M2 macrophages that trap larvae in an arginase-dependent manner (147).

Many species of GI nematodes reach the intestine following a systemic migration that usually involves travelling through the blood circulation and the lung tissue into the airways, followed by swallowing by the host and subsequent establishment in the GI tract. Thus, antigen challenge can occur via the skin, blood, and lungs. There are data from several studies including those of *Strongyloides* (148) and *N. brasiliensis* (149) suggesting that host protection from reinfection can occur in the lungs. Indeed, following a primary *N. brasiliensis* infection, neutrophils acquire a modified transcriptional profile that can entrain macrophages to kill migrating larvae in the lungs during secondary infection. IL-13 from neutrophils is key to the arginase-dependent killing mechanism by macrophages (150). Following lung infection by *N. brasiliensis*, the macrophage-derived chitinase-like protein Ym-1 induces IL-17 production by γδ T cells to induce neutrophilia that can both impede parasite survival and cause lung pathology (151). Other data support the hypothesis that, following *N. brasiliensis* infection, lung function undergoes considerable change long after the worms have passed through the lung tissue (152). Several immune mechanisms have been

suggested as playing a role in systemic/tissue control under type 2 cytokine production, including eosinophils (153). Although eosinophilia is a hallmark of helminth infection, the functional role of eosinophils remains enigmatic. It may be protective, but depletion of elevated eosinophils in several systems has little effect on the levels of host protection observed (138, 153). Interestingly, during infection with *T. spiralis*, which has an extended tissue-dwelling stage in the muscle, the eosinophil appears to protect the encysted larval stages, and in the absence of eosinophils, these parasites are damaged by macrophages and neutrophils (154). Moreover, eosinophils respond directly to nematode products and migrate toward nematodes both in vitro and in vivo, with a key role for leukotrienes in this process (155). Investigators have known for many years that leukotrienes are produced during GI nematode infection (156).

The role of macrophages in host protection against GI nematodes also varies between different GI nematode species. They do not appear to be critical for protection against *T. muris* (157) but do play a role against *H. polygyrus bakeri* (158). M2-type macrophages are involved in trapping larval stages in tissue granulomas during secondary/challenge infections at the stage of the life cycle when the parasite burrows into the submucosa of the small intestine, where they undergo development prior to reemerging in the intestinal lumen. Investigators showed that trapping is a $CD4^+$ T cell–, STAT6-, and arginase-dependent activity (158), although the role of IgE was not specifically investigated in this study. A role for antibody in activating macrophages in this response has also been shown: Antibody appeared to influence the programming of the macrophages by upregulating arginase-1, and this was an IL-4Rα-independent event (50).

Thus, the available data suggest that numerous effector mechanisms operate against GI nematodes at different stages of their life cycle (see **Figure 1**). During initial infection, parasites tend to successfully establish in the intestine and reproduce. However, host-protective immunity can be generated, most often in situations in which an experimentally high dose of the infectious stage is given. The effector mechanisms involved are multifactorial, with a battery of responses generated by the dominant type 2 cytokine responses with both $CD4^+$ T cells and ILC2s (and other cell populations such as basophils, eosinophils, and mast cells) as sources of the requisite cytokines. Multiple effector mechanisms are commonly activated, presumably because the immune system makes little distinction between different GI nematodes at the level of species, although clearly there must be signatures that indicate challenge by a metazoan parasite. Canonical pattern-recognition receptors for helminths per se have yet to be identified. An alternative, and not mutually exclusive, hypothesis to explain the evolution of type 2 responses against helminths is that, because such infections are almost universally associated with tissue damage during at least part of their life cycle, tissue repair (that is controlled by type 2 cytokines) is key to host survival against a pathogen that essentially does not replicate in the host (unlike prokaryotic and protozoan pathogens) but does cause damage. Type 2 responses are evolutionarily ancient responses that predate vertebrates, and the IgE immediate hypersensitivity type of response evolved later in mammals as a mechanism of protection against barrier (e.g., skin) challenge by biting arthropods, skin-invading parasites, or indeed any venomous organism (159).

Different effector responses are maximally effective against certain species of GI nematodes and others are not. Presumably this reflects the particular site of challenge dictated by the life cycle and the host immune-evasion mechanisms evolved by the particular species.

IMMUNITY IN TARGET SPECIES: HUMAN

Studies of immunity to GI nematodes in humans present considerable challenges, not least because of host genetic heterogeneity, ill-defined infection exposure, and the fact that infection is long-lived and chronic. Nevertheless, immunoepidemiological studies for many, but not all, of the major GI

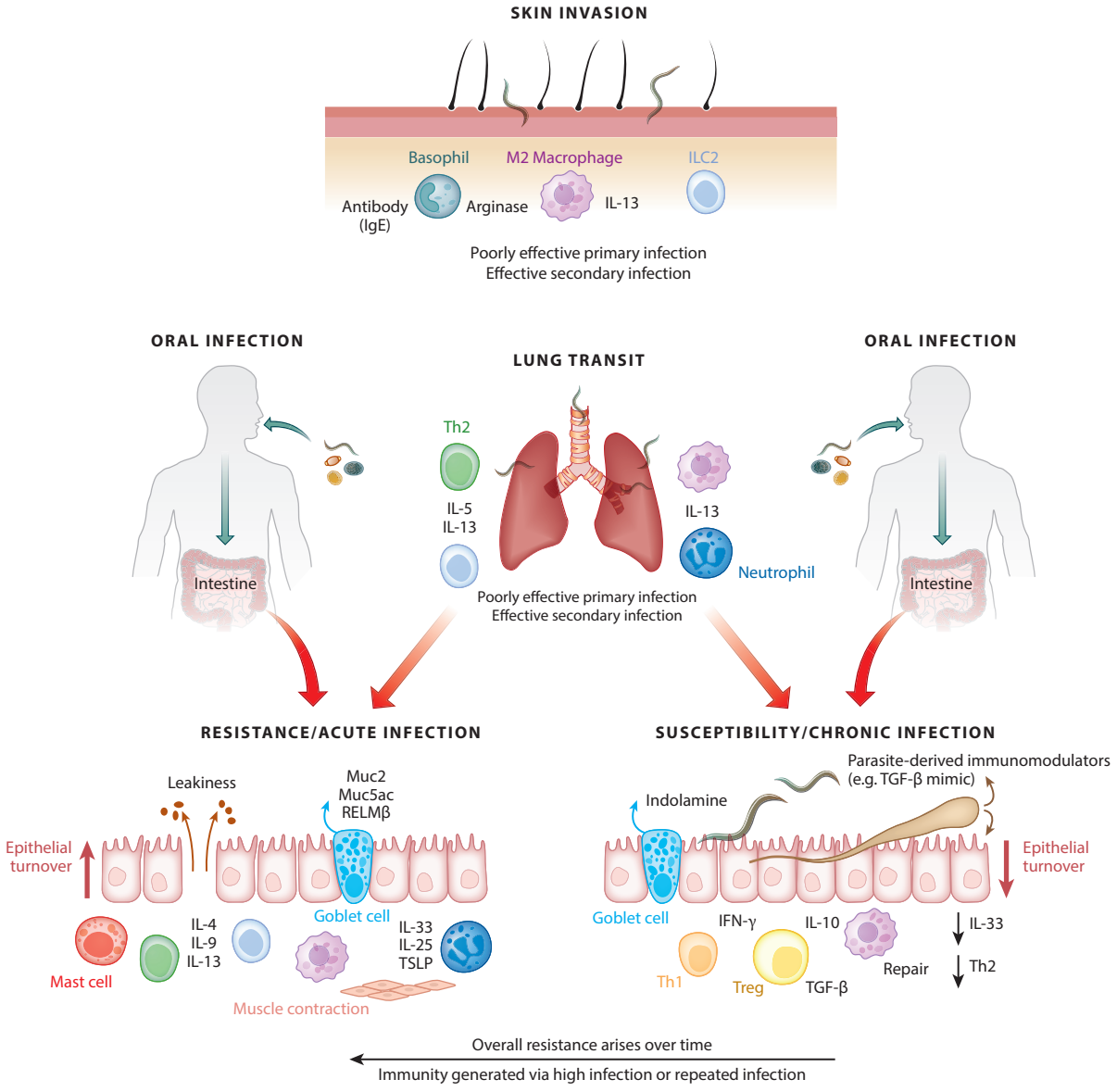

Figure 1

Schematic of the mechanisms of host protection and susceptibility to chronic infection to gastrointestinal-dwelling nematode parasites. Protective mechanisms against species that invade through the skin and/or transit through the lungs as part of their life cycle are also presented. The relative effectiveness of protection at the different anatomical sites after primary (single) or secondary (multiple) infections is presented, together with known players in the mechanisms that underlie susceptibility and chronic infection.

nematodes that infect humans suggest that over time humans acquire at least partial immunity to infection (160). This has been gleaned mainly from cross-sectional studies of infected populations, although reinfection studies have also been carried out for numerous systems, again supporting a role for acquired immunity (3). A wealth of serological data has been obtained that aimed to correlate particular antibody classes with protection. Certainly a robust antibody response is

mounted to natural GI nematode infection, but the correlates of protection, unlike those seen in other human helminth infections (161, 162), are not agreed upon, despite genetic studies that are supportive of type 2 immunity and resistance (163). More recently, cellular analyses of peripheral blood leukocyte populations together with cytokine analysis have been carried out to help define the ongoing responses (164). Broadly speaking, the data support the view of type 2 immunity and resistance and/or elevation of type 1 responses and susceptibility, indirectly supporting a role of type 2–mediated resistance (165, 166).

The notable exception to this is hookworm infection (*N. americanus* and *Ancylostoma duodenale*). Here, the epidemiological data to support the generation of acquired resistance are lacking (167), although some studies suggest that elevated IgE levels correlate with poor female worm growth/fecundity (168). Also, during the development of potential hookworm vaccines with an antigen derived from skin-invading stages of the parasite, preformed parasite-specific IgE in infected individuals could clearly mount a strong, immediate, hypersensitivity response (169). Whether this finding supports a protective role for an IgE-mediated skin response as seen in animal models remains to be seen. Following the recent definition of the *N. americanus* genome, a protein array based on 564 parasite proteins was probed with sera from an infected patient cohort, and although IgG responses to 22 significant target antigens varied by age group, there was no indication that these responses were linked to protection (170). Unusually, there have also been several experimental infections of humans who did not have prior exposure to infection with the hookworm *N. americanus*. These studies revealed an elevated type 2 cytokine response using peripheral and/or intestinal biopsy sampling, which demonstrates the regulation of proinflammatory cytokine responses and the upregulation of IL-22 (suggested to be involved in mucosal repair), IL-10, and TGF-β (171, 172). There was little evidence of a role for IL-17 responses, and this somewhat mirrors the situation observed with chronic *T. muris* infection in mice, in which in vivo neutralization of IL-17 appears to have few functional consequences (11). In the case of an ulcerative colitis patient who self-infected with a high dose of human whipworm (*Trichuris trichiura*) in an attempt to control ongoing inflammatory disease, the therapy reportedly led to remission of disease correlated with elevated type 2 cytokines and elevated IL-22 (173). Little can be drawn from the experiment regarding the protective immune response because there was no way of assessing immunity to challenge in any significant way. The naturally infected population studies show evidence of acquired immunity but no quantitative data on parasite exposure; thus, the immunological changes observed are varied and complex. Indeed, attempts to mimic multiple low-dose exposure in the laboratory, even in a very simplified way, generate a similar complex immunological profile, and identifying associations with resistance from these data alone is difficult (174).

IMMUNITY IN TARGET SPECIES: RUMINANTS

Experimental studies of immunity to GI nematode infection in domestic stock such as ruminants can offer an approach that more accurately reflects immunity resulting from naturally acquired infections. Although several studies do simply examine immune changes after single-dose infections, many use repeated doses of high numbers of infective parasites to stimulate resistance (175, 176). One could argue that this is more similar to the exposure that domestic livestock would experience naturally. Although this is overly simplistic and does not reflect seasonal changes in exposure, stocking level, and grazing strategies, the available data support the activation of type 2 immunity and elevation of parasite-specific antibody, characterized by IgG1, IgG2, and IgE, together with an elevation of the mucosal tissue cellular response, including eosinophilia and mastocytosis (4). Large-animal experiments present challenges in testing the functional importance of particular

cells or other factors, but some studies are consistent with the concept of type 2 responses and protection (177). For example, in vivo neutralization of IFN-γ in *T. colubriformis*–infected sheep enhanced acquired immunity to this parasite (178). Such studies have also highlighted that the outcome in terms of host protection is influenced by which life-cycle stage is the target of host immunity as well as by the timing of parasite challenge in relation to existing GI nematode infection. Data from numerous studies together with modeling suggest that these events have a major influence on the immune phenotype that is generated, although many of the effector mechanisms highlighted in rodent studies are thought to play protective roles (4).

PARASITE SURVIVAL, INEFFECTIVE IMMUNITY, AND IMMUNOREGULATION

Regulatory T Cells

A feature of natural infection by helminths including GI nematodes is that the parasites are long-lived. The life span of many species of helminth is years, even tens of years, and any immunity developed by the host is often partial at best. Thus, despite constant and repeated antigenic challenge, the parasite survives in the face of host immunity and mostly without inducing life-threatening pathology. This state is achieved in part through the induction of host immunity (even if only partial), the action of parasite immune-evasion strategies, and induction of host regulatory responses. These interrelated events have also been investigated in several experimental systems in addition to recent studies in humans from endemic areas.

In terms of immunoregulation, an intensive area of study of GI nematode infection has centered on regulatory T cell (Treg) populations (179), and indeed the basis of the modified hygiene hypothesis is built around the induction of Tregs during long-term infection by GI nematodes (180). Evidence of a role for FoxP3$^+$ Tregs following natural GI infection of human populations is given by numerous experimental laboratory studies showing elevations in the number of FoxP3$^+$ Tregs following helminth infection (179). *H. polygyrus bakeri* presents as a prolonged primary infection in many strains of inbred mice and is accompanied by an increase in numbers of FoxP3$^+$ Tregs (181–183). Their role in vivo has been assessed in this and other systems using two main approaches: (*a*) depleting anti-CD25/anti-GITR antibodies or (*b*) using the so-called DEREG mice in which FoxP3$^+$ Tregs are removed from conditional transgenic mice following injection of Diphtheria toxin (181, 184). The data vary between approaches, but there is evidence that they influence both resistance and pathology. A role for FoxP3$^+$ Tregs during *H. polygyrus bakeri* infection is also supported by the fact that adult parasites of this species produce a TGF-β mimic that can induce the production of Tregs in vitro (185). By extension, this could be a potential mechanism of immune evasion in vivo, perhaps by the generation of FoxP3$^+$ Tregs via the parasite-derived TGF-β mimic. The precise mechanisms by which FoxP3$^+$ Tregs regulate during *H. polygyrus bakeri* infection are unclear, however. Recent data indicate that IL-6 may also play a role in modifying the Treg population generated during *H. polygyrus bakeri* infection, which suggests functional capabilities distinct from the classical FoxP3$^+$ Treg (186).

T. muris infection in mice is also a model system in which chronic infection can readily be induced by low-dose infection or by using strains of inbred mice that allow progression of high infections to patency (90). Again, data are varied, although some studies indicate an elevation of FoxP3$^+$ Tregs following chronic infection (11) and a role in controlling worm expulsion following FoxP3$^+$ Treg depletion via antibody treatment (187) [this was not borne out using the DEREG mouse model, however (97)]. Certainly, TGF-β plays an important role in resistance to *T. muris*, given that in vivo neutralization of this cytokine during the early phases of infection promotes

resistance. Moreover, CD103$^+$ DCs in the large intestine of *T. muris*–infected mice express elevated levels of the TGF-β-activating αvβ8 integrin on their surface, and conditional DC-null mice for αvβ8 rapidly expel a low-dose infection that would normally progress to chronic infection (97). This may imply that Tregs are important or that the regulatory roles of TGF-β—in this system at least—are more complex. The normal resistance seen against *Strongyloides ratti* infection in mice is abrogated in DEREG mice and was associated with an enhanced type 2 cytokine response, suggesting that in this system FoxP3$^+$ Tregs do play an important role. Interestingly, however, this effect was only observed when FoxP3$^+$ Tregs were absent in the early phases of infection (188).

Mechanisms of Host Regulation

Although there is ample evidence that immunoregulation operates during helminth infection (via FoxP3$^+$ Tregs or other cell types), the mechanisms by which they do this are less clear. Following *H. polygyrus bakeri* infection, as discussed above, TGF-β may play a central role (185). In this system, TGF-β regulates both Th1 and Th2 cytokines and promotes the production of IL-10 (189). An extensive literature supports a role for IL-10 as a regulatory cytokine, including its production by FoxP3$^+$ Tregs (190). IL-10 is important both for induction of host protection against *T. muris* following acute infection and for control of IFN-γ-mediated intestinal pathology following chronic infection (191). Indeed, anti-IL-10R antibody treatment during the chronic stages of infection led to an increase in FoxP3$^+$ Tregs in the draining lymph node (11). Whether FoxP3$^+$ Tregs are the critical source of IL-10 in this system remains to be determined. The DEREG studies suggest that they are not, or at least that compensatory populations can come in and function in their absence. The CD4$^+$ T cell does appear to be the critical source required for controlling intestinal pathology, however (192). In terms of IL-10 control of pathology, chronic *T. muris* infection is associated with upregulation of IL-10R and SOCS3 in addition to IL-10 and IFN-γ in the intestine (126, 193). Interestingly, IL-10 drives the expression of IL-10R in the colon, and IL-10 action promotes SOCS3 activity, which is a key player in regulating inflammation (194).

From examining several systems, we know that the regulation promoted by GI nematode infection affects the host's capacity to deal with other infections and antigenic and inflammatory challenge. Indeed, this concept underpins helminth influence in the modified hygiene hypothesis (195). Certainly, *H. polygyrus bakeri* infection modulates responses to other antigens, as does chronic *T. muris* infection (11). The precise mechanisms of regulation of these responses remain to be defined, but they will affect the current interest in using helminths as therapeutic agents in the clinic for numerous inflammation-mediated conditions (196).

THE EXTENDED NICHE: THE INTESTINAL MICROBIOME

GI nematodes clearly perturb the intestinal niche, and their effect on host microflora is beginning to receive attention (197). Because the microflora are highly influential on the immunoregulatory system of the host (198), it would not be surprising if host immunity is influenced as a consequence of GI nematode infection. Studies have begun in this area in both experimental and natural GI nematode infections of humans and other animals. Primary *H. polygyrus bakeri* infection is associated with changes in gut microbiota of the terminal ileum, cecum, and colon despite occupying the small intestine with significantly increased Lactobacillaceae and Enterobacteria species (199, 200). Large infections (20,000 eggs) of *Trichuris suis* can generate different parasite loads in outbred pigs, and these different response phenotypes are associated with different colonic microflora, particularly those involved in digesting fiber (201, 202). In humans, the complexity is

multiplied by the various influences encountered in naturally infected host populations. A study of an Ecuadorian population infected with *Ascaris lumbricoides* and *T. trichiura* did not identify marked differences in fecal microflora populations (203), although a study of *T. trichiura* in Malaysia did suggest that infection influenced the fecal microbial community structure (204).

The impact of microflora upon host immunity to GI nematodes has been more difficult to define. A study of idiopathic chronic diarrhea in macaques suggested that infection by *T. trichiura* significantly ameliorated symptoms and was associated with upregulation of type 2 cytokine responses (205). On a more simplistic level, relatively mild antibiotic treatment of mice infected with *T. muris* during the early phases of infection decreased intestinal microflora load, enhanced type 2 responses, and led to expulsion of intestinal parasites (206).

Bearing in mind the complex and varied life cycles of GI nematodes, any dysbiosis of intestinal microflora may also be equally varied. As a consequence, direct or indirect effects of the microflora on immunoregulation during GI nematode infections may differ among species and influence infection. The mechanisms underlying any effects remain to be defined and could be multifactorial, not least in terms of changing host access to nutrients and metabolites. The now well-established role of metabolism in the development and function of multiple immune cell populations (207, 208) adds a further dimension to the complex intestinal niche of the helminth-parasitized gut that remains to be explored.

The observations that Th2 cells control satiety (209, 210) and that ILC2s act as nutrient sensors (84) during GI nematode infection make clear that the concept of GI nematodes as "silent serpents" is far from correct. Their influence on the physiology and health of the host via the immune system continues to offer significant and exciting challenges in understanding immune responses to infection.

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