INTRODUCTION

The mammalian immune system has evolved to efficiently ward off a panoply of external threats while minimizing, in most cases, self-inflicted damage. Many infective organisms, however, have themselves evolved sophisticated strategies to circumvent and overcome the immune response of the host. It is in this fascinating interplay that we have come to recognize that some parasites can directly manipulate and suppress inflammatory responses to an extent that actually protects the host from immunological disorders such as allergy, autoimmune and the metabolic syndrome.1-4 A major question then arises as whether the disappearance of parasites from most of the industrialized countries is causally responsible for the relentless rise in inflammatory disorders such as asthma,5 inflammatory bowel disease 6 and type 1 diabetes 7 over the course of the 20th century.8

The phenomenon of parasite-mediated immune suppression was first noted in the 1960s by Greenwood as a notably low prevalence of autoimmune conditions in Nigerian hospital admission cohorts 9; this prompted him to study animal models in which malaria infection abated autoimmunity10; the "Hygiene Hypothesis" as such was independently postulated by Strachan reflecting on family data in which younger members of larger sibships exhibited lower allergy levels, attributed to greater exposure to micro-organisms in infancy.11,12 In this era, anecdotal reports also appeared in which, for example, infection with the hookworm helminth Necator americanus abolished hay fever in a British subject.13

Hookworms are among the highly prevalent group of helminth (metazoan, worm) parasites which will be the primary focus of this article. Helminths remain extraordinarily prevalent in lower-income countries, with over 2 billion people infected.14 Unlike most micro-organisms and unicellular protozoa, helminths cannot outrun the immune system by rapid growth and instead rely on down-modulation of host immunity. In some cases, infections are asymptomatic and the host appears to be immunologically tolerant of the parasite 15; in others, regulation is not so well-ordered and inflammatory responses to the parasite generate severe pathology of tissues such as the liver 16 or lymphatic system.17 Whether the "tolerant" state may confer benefits such as reduced allergy is a topic of current debate, but even

Abstract

There is increasing interest in helminth parasite modulation of the immune system, both from the fundamental perspective of the "arms race" between host and parasite, and equally importantly, to understand if parasites offer new pathways to abate and control untoward immune responses in humans. This article reviews the epidemiological and experimental evidence for parasite down-regulation of host immunity and immunopathology, in allergy and other immune disorders, and recent progress towards defining the mechanisms and molecular mediators which parasites exploit in order to modulate their host. Among these are novel products that interfere with epithelial cell alarmins, dendritic cell activation, macrophage function and T-cell responsiveness through the promotion of an immunoregulatory environment. These modulatory effects assist parasites to establish and survive, while dampening immune reactivity to allergens, autoantigens and microbiome determinants.

KEYWORDS

allergy treatment, basic mechanisms, parasites
if so there are clearly also disbenefits, in respect of compromised responses to vaccination \[^\text{18}\] and certain microbial infections.\[^\text{19,20}\]

## 2 | INSIGHTS FROM HUMAN PARASITE INFECTIONS

A long-standing theme in human helminth infections has been the paucity of parasite-specific immune responses, manifest, for example, as inability of effector T cells to proliferate or produce inflammatory cytokines when stimulated with parasite antigens, considered to be a form of immunological tolerance.\[^\text{21,22}\] Established helminth infections are also characterized by highly elevated IgG4 levels,\[^\text{23,24}\] as also observed in desensitized allergic patients outside parasite-endemic environments.\[^\text{25}\] Interestingly, IgG4 expression in human helminth infections is linked to the regulatory network, through IL-10 production and other down-modulatory signals.\[^\text{26}\]

Immunological tolerance to parasites has been more closely attributed to regulatory cells in a number of settings.\[^\text{27-30}\] Both parasite-specific and bystander immune responses can be restored in vitro by depletion of Tregs,\[^\text{29}\] and in vivo by anthelmintic chemotherapy.\[^\text{31,32}\] As discussed below, parasites are able to directly promote or induce Tregs.\[^\text{33}\] In addition, Bregs and immunosuppressive macrophages have been implicated in a number of studies on helminth parasite infections.\[^\text{34,35}\]

## 3 | HELMINTH PARASITES AND ALLERGY

A landmark study was published in 2000 by the Yazdanbakhsh group,\[^\text{36}\] measuring skin prick test (SPT) reactivity (atopy) to house dust mite allergen; Schistosoma-infected children were significantly less prone to allergy, while in the small proportion who retained demonstrable skin test reactivity, peripheral blood T cells failed to mount an IL-10 response to parasite antigens. Hence, the links were made firstly between helminths and diminished allergy, and secondly between the parasite infection and, in most children, an immunoregulatory cytokine.

A diversity of subsequent studies, in different settings of infection with a variety of helminth species, has broadly supported a negative association with allergic reactivity \[^\text{37-40}\], while there have also been reports that could not establish a significant influence of helminth infection,\[^\text{41}\] it has been argued that protection from allergy is likely to require a threshold intensity and duration of infection and may vary from parasite species to species.\[^\text{42,43}\] Most recently, the original observations have been confirmed in a much larger study of >2000 neonates over 3-5 years in Ecuador, in which one-third of the cohort contracted helminth infections but overall developed significantly less asthma and wheeze.\[^\text{44}\]

It is important to note that not all studies have reported negative associations between infection and allergy. Indeed, there are many instances of sensitization and allergic reactions to parasites, particularly where zoonotic transmission occurs and the human is not the definitive host.\[^\text{45,46}\] Examples are Toxocara canis, a canine nematode in which larval forms migrate through tissues of humans who have accidently ingested eggs.\[^\text{47}\] and Anisakis simplex, a marine nematode which can be acquired by eating undercooked fish.\[^\text{48}\] However, in both cases these are "dead-end" infections in which parasites are maladapted to the human and so fail either to complete their life cycle or down-modulate host immune reactivity.

In contrast, the prevalent human helminth parasites are very effective at ensuring both transmission and immune modulation. In further key studies, a causal link between parasitism and down-modulated allergy was established by evaluating the consequences of anthelmintic drug treatment to expel parasites. In another Gabon study, infants cleared of intestinal nematode parasites more frequently converted to an atopic state of SPT reactivity, than the comparator cohort of untreated children.\[^\text{49}\]

## 4 | BROAD SPECTRUM OF IMMUNE MODULATION BY HELMINTHS

Following work with allergy in helminth-infected children, a remarkable study was reported by Correale and colleagues on adult multiple sclerosis (MS) patients who had adventitiously acquired intestinal helminth infections; 12 such individuals were followed but remained in remission while uninfected subjects with similar disease scores at the initial time point experienced repeated relapses and exacerbations.\[^\text{50}\] The infected patients showed enhanced IL-10 and TGF-β production by peripheral blood mononuclear cells \[^\text{50}\] and increased regulatory B-cell numbers.\[^\text{34}\] In a subsequent follow-up, these authors treated 4 infected patients to clear the helminth parasites, but reported diminution in immunosuppressive cytokines together with an intensification of disease scores.\[^\text{51}\]

In a third setting, in India, a reciprocal relationship was found between intensity of infection with the mosquito-borne filarial nematode Wuchereria bancrofti and the incidence of type 1 diabetes,\[^\text{52}\] although in this case no causality could be established. Finally, in Zimbabwe the levels of anti-nuclear antibody (ANA) were measured in S haematobium-infected and S haematobium-uninfected individuals, as an early precursor (but not predictor) of autoimmune reactivity; anti-ANA titres were significantly lower in the infected cohort, but increased following treatment with the anti-schistosomal drug praziquantel.\[^\text{53}\]

## 5 | LEARNING FROM ANIMAL MODELS

Many animal models of helminth infection have echoed and expanded on the observations of immune modulation in humans. For example, type 1 diabetes in the NOD mouse model is potently inhibited by infections such as Schistosoma mansoni \[^\text{54}\] and Heligmosomoides polygyrus \[^\text{55-57}\] as also are other autoimmune disorders such as EAE in models of multiple sclerosis,\[^\text{58,59}\] as well as experimental colitis in animals.\[^\text{60}\] Moreover, there are multiple reports of helminth infections suppressing graft rejection and prolonging allograft survival,\[^\text{61}\] and emerging evidence is that these parasites counteract metabolic...
disorders in models of obesity. Some of these effects—for example, the ability of the liver fluke *Fasciola hepatica* and eggs from *S. mansoni* to suppress Th1/Th17-mediated autoimmunity—have been attributed to immune diversion towards a nonpathogenic Th2 response, however, in allergy and other models, a more subtle redirection of immunity to favour a regulatory environment has been demonstrated. Fuller accounts of these findings have been published recently in major review articles.

It is perhaps in the context of allergy that the principles and mechanisms of helminth down-modulation have been most clearly established and shown to operate at several levels against both innate and adaptive immunities. Multiple helminth species can, when introduced in to mice, forestall the development of allergic inflammation, including *H. polygyrus* and *S. mansoni* as well as the filarial parasite *Litomosoides sigmodontis*. Mechanistically, protection can be transferred from infected donors to uninfected recipients with CD4+ Tregs and abolished by Treg depletion with anti-CD25 antibody or genetic ablation. However, B-cell transfer experiments have also successfully conferred protection against allergy, consistent with a "Breg" population stimulated by helminth infections, albeit in 1 system functioning through activation of Treg counterparts.

**6 | THE HYGIENE HYPOTHESIS TODAY**

Many authors have elaborated, adapted and broadened Strachan's original postulate, in particular to encompass parasites as well as microbes, and to incorporate regulatory cell networks which were poorly defined in the 1980s. In addition, a gamut of environmental influences has been invoked, from the "old friends" of mycobacteria to specific commensal microbes, and through to farm dust and diet in a continuum, each of which can clearly exert major influences on development of immunity. Importantly, the immune system is conceived as an integrated whole in which all disorders including autoimmunity and inflammatory bowel diseases may be concomitantly regulated.

Two "hygiene hypotheses" have been formulated that are not mutually exclusive but involve conceptually distinct mechanisms (Figure 1). Firstly, there is the idea that in early life, the immune system is conditioned or imprinted by its environment, such that a higher infection experience will promote regulation; alternatively that the presence of parasites (or other modulatory organisms such as certain commensal bacteria) sufficiently inhibits the mature immune response to dampen autoimmunity etc. In related argument, observations on human allergies primarily reflect sensitization (through SPT) rather than clinical allergy, suggesting that the primary effect of helminths is in determining the tonal "set-point" of the immune system rather than the specific response to any 1 antigen.

The second interpretation of the hygiene hypothesis is that the fully formed immune system, in school-aged children and adults, can be recalibrated by exposure to infectious agents, whether common viral and bacterial microbes, or helminth parasites. This notion underpins the approach of using live organisms, or products from those organisms, as new therapies for inflammatory diseases, as discussed.
below, and is supported by nearly all studies in experimental animals, in which the effects of parasite infection are tested on the inflammatory reactions of adult mice.

7 | IMPRINTING IN EARLY LIFE

An important issue arising from the alternative formulations of the hygiene hypothesis is how early-life, and indeed prenatal, exposure to helminths and helminth antigens may influence the immunological “set-point” that may have lifelong consequences. For example, infection with the whipworm *Trichuris trichiura* during the first 5 years of life in Brazilian children was reported to significantly reduce incidence of allergy in their later years, even in children no longer carrying the parasite infection.83 Similarly, in the mouse model of *Schistosoma mansoni* infection, pups born to chronically infected dams in the “regulatory” phase of infection showed significantly reduced airway responses to ovalbumin challenge.84,85

The impact of gestational helminth exposure and immune development is also fascinating in the human setting.86 In Uganda, maternal hookworm infection resulted in reduced allergy (eczema) in infants for up to 5 years of age, as indeed did infection with either hookworm or *T trichiura* when analysing the children alone.87 In an earlier Ecuador study, maternal helminth infection appeared to have little influence on overt allergy, although SPT reactions were significantly reduced in the offspring of these mothers.88 More recently, a study from the same country reported that while maternal helminth infection increased risk of infants developing allergy (wheeze, skin reactivity), within the infant cohort itself, neonatal helminth infection reduced allergies.44

8 | HELMINTHS AND THE MICROBIOTA

Intestinal helminths share their niche with the commensal microbiome, principally bacteria but also fungi and viruses.89–91 In addition, there is microbial colonization of the airways which has major implications for the immune status of the respiratory tract.92 With increasing recognition of how microbial exposure first shapes the developing immune system, and then interacts with the host to develop a healthy homeostasis, many questions have been raised about helminth effects on the microbiome, and whether immunoregulation in parasite infection acts indirectly through changes in the microbial population.93,94 Helminth infections can clearly alter the microbiome in both humans and animals 95–97; for example in the murine model of *H polygyrus*, infection favoured expansion of small intestinal *Lactobacillus* 98,99; interestingly, mice pre-exposed to the same *Lactobacillus* were more susceptible to worm infection, both organisms expanding the regulatory T-cell compartment of the host.99 However, the same helminth can also allow a pathobiont, *Salmonella typhimurium*, to expand with deleterious effects.100 Hence, the influence of helminths on the microbiome is highly context-dependent with correspondingly varied outcomes.

A central question has been whether, in the model systems in which helminths down-modulate allergy to bystander antigens, parasites act indirectly by altering the intestinal microbiome.101 This was also addressed in the *H polygyrus* model, in which amelioration of airway allergic inflammation was attributed to the outgrowth of *Clostridium* species in the large intestine, as the source of short-chain fatty acids which promote regulatory T-cell activity through the GPR41 receptor.102 As these authors note, however, this study does not exclude the likelihood that helminths also directly suppress immune reactions independently of the microbiota, as evidenced by increasing definition of allergy-suppressing proteins released by many parasites, among them *H polygyrus* itself.67,103

In both the intestinal tract and the airways, barrier integrity can be physically compromised by helminth parasites, which can initiate a type 2 proto-allergic response (Figure 2). Studies on barrier function in helminth infections of the intestinal tract have documented increased epithelial permeability,104 which contributes to the “weep-and-sweep” mechanism for parasite clearance. Although this is in part dependent on type 2 cytokines, it is interesting to note that helminth products can themselves induce increased permeability,105 suggesting that parasite immunomodulatory molecules may thereby gain better access to host tissues, and providing a pathway through which intestinal helminths may exert systemic effects on the host immune system.

9 | WHAT ABOUT HELMINTH THERAPY?

Over the past decade, interest has developed in deliberate helminth parasite infection as a therapy for inflammatory disorders,106 sparked by promising trials in which Crohn’s disease and ulcerative colitis patients benefitted from infection with the pig whipworm, *Trichuris suis*.107–109 Other authors reported a case of a UC patient who deliberately self-infected with the whipworm *T trichiura* leading to reduction in inflammatory marker expression and overall remission of disease.110 In larger trials, however, neither the whipworm nor other tests with the human hookworm *N americanus* demonstrated significant protection in IBD or indeed in a number of other conditions including asthma,111 rhinitis,112 multiple sclerosis 113 and coeliac disease.114 Thus, despite accounts of benefits to some individual patients, and a general trend towards subtle improvements in patients, there is currently no compelling study that supports deliberate helminth infection as a standard counter-inflammatory therapy.115,116

10 | THE ALTERNATIVE—PARASITE MOLECULES AND MECHANISMS

With live helminth infections proving less than universally effective, there is increasing priority given to dissecting helminth-driven regulatory pathways and finding mediators from parasites that engage these pathways.69,117 Such helminth-derived molecules, in synthetic
FIGURE 2  Pathways of allergic inflammation and helminth immune modulation. Helminths may penetrate and damage epithelial tissue, releasing parasite PAMPs (pathogen-associated molecular patterns) and host DAMPs (damage-associated molecular patterns). Type 2 inflammation (coloured red) is initiated in response to DAMPs/PAMPs, together with antigen presentation by dendritic cells (DCs), to generate type 2 innate lymphoid cells (ILC2) and helper T cells (Th2). Type 2 lymphocytes induce allergic mediators including eosinophils and IgE from B cells. In the presence of an immunomodulatory helminth, a regulatory network is invoked (coloured green) and DCs may instead induce regulatory T cells (Tregs) that produce suppressive cytokines (IL-10 and TGF-beta). These act on B cells to switch to IgG4 production, on macrophages to assume an anti-inflammatory (M2) phenotype, and on effector Th2 cells to block activation and develop a state of tolerance. These pathways inhibit both helminth-specific and bystander (e.g., allergen-specific) reactivity, thereby creating a profound anti-inflammatory effect.

FIGURE 3  Illustration of pathways of immune interference by the model helminth parasite *H. polygyrus* mediated by the excretory-secretory products (HES) and 2 newly defined components. One, Hp-ARI, targets innate immunity by neutralizing IL-33, thereby forestalling activation of ILC2, eosinophils and M2 macrophages. A second, TGM, activates the TGF-β pathway to induce regulatory T cells; these suppress the adaptive Th2 arm of immunity, further inhibiting M2 macrophage induction and the differentiation of epithelial effector populations such as the goblet cells. In these ways, the parasite prevents both outcomes of the Th2 response, namely allergic inflammation and helminth expulsion.
form, could reproduce the anti-inflammatory properties of live parasites without exposing patients to the detrimental effects of infection. A growing number of studies have highlighted key parasite products that directly interact with the host immune system and uncovered new pathways by which immune modulation occurs in parasite infections 67,118–121 (Figure 3). A selection of parasite molecules of particular interest in control of inflammation is discussed below, and the reader is referred to recent more comprehensive reviews for further information. 67,122

Parasites interfere with each phase of the immune response from the initial recognition and activation signals, through to the final stage of effector cells attempting to resolve infection. Even the very first steps of the response through epithelial cell alarmins are directly targetted. This is well illustrated by recent work describing Hp-ARI (Alarmin Release Inhibitor) from H. polygyrus. It was first established that proteins secreted by this parasite were able to block the action of IL-33, the initiator of type 2 immunity in the tissues, thereby preventing ILC2 activation and subsequent airway eosinophilia in response to Alternaria fungal allergens. 123,124

Identification of the mediator involved revealed Hp-ARI as bi-functional protein which binds both active IL-33 in fluid phase, and also nuclear DNA. As IL-33 is normally held in the cell nucleus until cell stress or trauma triggers its release, Hp-ARI reverses the process, capturing the alarmin cytokine and sequestering it within the nucleus, thus neutralizing its biological function in immunity. 103 In vivo, Hp-ARI effectively blocks the airway allergic reaction to Alternaria even if given 24 hours in advance of the allergen challenge. 103

11 | MODULATION OF MYELOID CELLS BY HELMINTH PRODUCTS

A broader picture emerges from studies on the activation and modulation of dendritic cells (DCs), which are targeted by multiple parasite products, many of which inhibit IL-12 production and expression of co-stimulatory markers. 125–127 Schistosome eggs release the protein omega-1 which downgrades DC protein synthesis, particularly blocking IL-12 production, and promoting the induction of a Th2 response. 128,129 The same parasites secrete a small lipid molecule, lyso-phosphatidylserine, which drives a more regulatory DC phenotype through a TLR2 interaction. 130 Another major modulator of DCs is the ES-62 glycoprotein secreted by a rodent filarial parasite, Acanthocheilonema viteae, which acts at the intracellular level to bind and divert the MyD88 adapter protein required for TLR and IL-33 signalling. 131,132 The glycan moiety of ES-62 is further substituted with phosphorylcholine (PC) which is the active principle of the molecule; ES-62 devoid of PC is no longer immunomodulatory, while PC-substituted ovalbumin and small molecule mimics of PC are able to recapitulate its effects 133,134; hence, new drugs inspired by ES-62 may prove as effective as the whole glycoprotein in ameliorating conditions such as asthma 135 and rheumatoid arthritis. 136

Other myeloid cell populations are also profoundly modulated by helminth products. Macrophages in particular play an essential role in the immune response to helminths and can mediate both protective 137 and pathological consequences. 138,139 A family of cysteine protease inhibitors are produced by filarial parasites, with the ability to block both conventional cathepsins, and also the asparaginyl endopeptidase required for antigen processing by human cells in vitro. One of these (Av-Cystatin) has been further studied in mouse models and found to act through macrophages, resultig in them suppressing airway allergy in treated mice in an IL-10-dependent manner, 140 through the recruitment of IL-10+CD4+ T cells. 141 As with DCs, interference with TLR activation is found by parasite products, for example the Fasciola hepatica cathepsin L1 enzyme which breaks down TLR3 in macrophages and prevents downstream signalling through TRIF 142 while another protein from the same parasite, FhHDM-1, is able to interfere with both surface interactions with LPS, and internal antigen processing and inflammasome activation. 143,144

Macrophages in helminth infection adopt a characteristic alternatively activated (or M2) phenotype. 145 expressing high levels of arginase-1 which by converting the amino acid substrate into polyamines and proline strongly favour tissue repair and wound healing. M2 macrophage differentiation is stimulated by the cytokines IL-4 and IL-13, but can be further promoted in synergy with certain helminth products such as the macrophage migration inhibitory factor (MIF) homologues from the filarial parasite Brugia malayi 146. Furthermore, M2 macrophages play an essential role in metabolic homeostasis; hence, infection with Nippostrongylus brasiliensis indirectly counteracts obesity, stimulating eosinophils which release IL-4 and induce M2 differentiation. 147 In a parallel development, the schistosome protein omega-1 has been found to ameliorate insulin resistance in mice through the IL-33-dependent activation of M2 macrophages. 148

12 | HELMINTH-INDUCED REGULATORY T CELLS

Arguably, the most central feature of helminth infection is the promotion of regulatory T-cell activity. 33,149 and as discussed above, Treg expansion can also account for the inhibition of allergic responses in mouse models. 71,150 Parasites have evolved multiple strategies to exploit the Treg pathway, including modulating DCs to drive Treg induction 151,152 and IL-10 production. 130 In one recently reported example, hookworm Anti-Inflammatory Protein (AIP)-2 protein acts in mouse models through CD103+ DCs to expand Tregs; as a result, AIP-2 administration can abate airway allergic inflammation 152 as well as colitis induced by TNBS administration. 153

While products such as AIP-2 act indirectly on the host to generate Tregs, some parasite molecules can do so directly without the need for intermediary DC populations. 154 In this respect, the most remarkable is the TGF-β mimic (TGM) from H. polygyrus, which bearing no sequence similarity to mammalian TGF-β, has convergently evolved to bind the same family of TGF-β receptors, driving Smad phosphorylation and, in T cells, Foxp3 expression. 155 While TGF-β requires proteolytic processing from a longer preprotein, and release
from the extracellular integrin matrix before it gains activity, TGM is active as a newly synthesized full-length protein. A further contrast is that TGFβ binds directly to the TGFβRII chain, which recruits and phosphorylates TGFβRI, while TGM binds strongly and independently to both receptor chains. As a consequence, TGM is a potent ligand for the TGFβ signalling pathway which can induce a higher level of Foxp3 expression in naïve T cells.155 Thus, TGM represents a molecular pathway, which explains and underpins the observed ability of *H. polygyrus* to induce and recruit Tregs in vivo, which are known to be required for parasite survival in the immunocompetent host.156 In mouse models, TGM proved to confer extended survival of fully allogeneic skin grafts in mice, to a similar degree to infection with the parasite itself.155

A further illustration of how helminth interferes with the host cytokine network has recently been described through p43, the major secreted protein of *Trichuris muris* whipworms from mice. This product is able to bind host IL-13, and through a separate thrombospondin-like binding site can sequester the cytokine within host extracellular matrix, preventing it from activating the type 2 immune response.157 As IL-13 is a central player in allergic asthma158 and closely homologous proteins are also elaborated by the human whipworm *T. trichiura*, this pathway is also likely to be important in alleviation of allergy by helminths.

13 | CONCLUSION

Helminth parasites have co-evolved with our immune system and are being revealed as storehouses of extraordinary immunological tools that manipulate every facet of immunity. The study of the immune response to helminths has illuminated many areas of common ground with allergy and other inflammatory settings. In particular, the cellular immunology of the response to helminth infection has revealed critical new populations such as the type 2 innate lymphoid cell159 and the intestinal epithelial tuft cell,160,161 while reinterpreting the functions of subsets such as M2 macrophages,162 mast cells and basophils.163,164

With our growing understanding of the molecular strategies of helminth parasites, we can now begin to see how they may inspire future therapies against inflammatory diseases. Defined parasite products target specific pathways, receptors and cell populations which require to be controlled in particular disease conditions, as in the examples of an inhibitor of IL-33, the alarmin which is closely linked to asthma in humans. In addition, broadly acting mediators such as those driving regulatory cell populations hold promise for recalibrating the over-active immune system in allergic disease.

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CONFLICT OF INTEREST

The author has no conflict of interest in relation to this work.

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