



Helminth-induced regulatory T cells and suppression of allergic responses

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Infection with helminths has been associated with lower rates of asthma and other allergic diseases. This has been attributed, in part, to the ability of helminths to induce regulatory T cells that suppress inappropriate immune responses to allergens. Recent compelling evidence suggests that helminths may promote regulatory T cell expansion or effector functions through either direct (secretion of excretory/secretory molecules) or indirect mechanisms (regulation of the microbiome). This review will discuss key findings from human immunoepidemiological observations, studies using animal models of disease, and clinical trials with live worm infections, discussing the therapeutic potential for worms and their secreted products for treating allergic inflammation.

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Current Opinion in Immunology 2018, 54:xx–yy

This review comes from a themed issue on **Allergy and hypersensitivity**

Edited by **Onur Boyman, Mario Noti and Alexander Eggel**

<https://doi.org/10.1016/j.coi.2018.05.007>

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Allergy and parasitic infections

Allergic diseases, such as rhinitis and asthma, result from inappropriate immune responses to generally innocuous environmental stimuli. The reported incidence of allergy is increasing worldwide with 10–30% of people now suffering from allergic rhinitis [1]. This increase has been associated with many factors including improved diagnosis, progressive urbanisation, and a shift in environmental exposures [2,3]. Furthermore, increased prevalence of allergic diseases in urbanised communities has been associated with an altered microbiome [4,5]. This has highlighted the importance of a diverse and rich community of gut microorganisms to promote normal

development of the immune system. This priming is crucial not only to initiate appropriate immune responses against harmful pathogens, but also to maintain and induce tolerance to commensal microorganisms and harmless environmental stimuli [6].

In addition to microorganisms, correlations have been identified between the prevalence of parasitic helminths (worms) and allergic diseases, where increased worm prevalence is associated with reduced incidence of allergic conditions [7–9]. Approximately 2 billion people worldwide are infected with helminths [10]. Human epidemiological observations, and studies using animal models of disease suggest that worms may somehow protect against the onset of allergic conditions, potentially due to their potent immunoregulatory capabilities [8,11]. This review will explore the relationship between allergic disease and parasitic helminths, with a focus on exploring how worms regulate host immunity by promoting regulatory T cell (T_{reg}) immune responses.

Associations between worm infections and allergy

Many early life conditions, practices and resulting exposures have been highlighted for their role in limiting the development of allergy. Allergy is on the rise globally, while infectious disease burdens are decreasing [12]. This inverse correlation supports the “Hygiene” or “Old Friends” hypotheses, the notion that the 20th century boom in allergic diseases may be explained by lower exposure to infectious diseases in early childhood [13]. Most of human evolution has included co-existence with parasitic infections, but with improved sanitation, waste removal and the availability of screening and treatment tools, there has been a marked decrease in many of these parasites. Human epidemiological studies have suggested that infections with both soil-transmitted helminths and schistosomes are linked with lower rates of allergy and asthma [14–18]. Anthelmintic treatment of infected populations has been shown to increase allergen skin test reactivity in children, potentially indicating a causal role for helminths in allergy suppression [19,20]. In support of this, numerous animal studies have demonstrated that live worm infections can limit the development of experimental allergy [21–24]. Despite these findings, we’ve only just begun to discover the mechanisms by which worms regulate host immunity to achieve this suppression of allergy and inflammation at large.

Helminth infections induce a modified Type 2 immune response involving T_{regs}

Despite being the largest organisms that infect humans, most species of helminths are capable of surviving for years without provoking an immune response that is sufficient to eliminate the parasite. While the human immune system is often capable of expelling a parasite, the scale of the response required would likely be more detrimental to the host than tolerating light to moderate worm burdens. For this reason, regulatory mechanisms have evolved, either parasite or host-induced, which limit parasite expulsion while protecting the host from excessive immunopathology [25,26]. Indeed, it has been hypothesised that the Type 2 arm of the immune response evolved to combat helminth infections, as well as to limit and repair the damage they inflict during migration and feeding [27]. This immune response is characteristic of helminth infections and involves production of the cytokines IL-4, IL-5, IL-9, IL-13, IL-25 and IL-33 [28]. Through various signalling cascades, these cytokines coordinate T-helper type 2 (Th2) cell differentiation, B-cell class-switching to IgE, and inflammatory cell recruitment, all in an effort to kill or expel the parasite [11].

The Type 2 immune response to helminths and the immune response seen in allergy share significant similarities. Like a helminth infection, atopic asthma involves a Type 2 response, but results in mucus production in the lung, bronchoconstriction, smooth-muscle contraction and airway remodelling [29]. Logically, helminth infections — notably those where larval worms navigate through the pulmonary vasculature en route to the gut — should therefore augment asthmatic responses due to the similar nature of the immune responses they elicit; however, the opposite scenario may be true in some instances. This is likely because helminth infections promote a modified Type 2 response and concurrent regulatory immune responses that induce a state of hypo-responsiveness that prevents the development of allergic disease [11].

T_{regs} are an integral part of the immune system, responsible for regulating pro-inflammatory immune responses via the production of IL-10, IL-35 and TGF- β [30]. Studies have shown that T_{regs} from asthmatics are dysfunctional, which contributes to the exaggerated immune response to allergens (Figure 1) [31,32]. Helminths on the other hand, have been shown to increase the number and enhance the functional capacity of T_{regs} during infection. For example, in cross-sectional human studies, chronic infection with schistosomes and filarial nematodes were associated with higher levels of IL-10 and augmented T_{reg} activity [33,34]. Similarly, lymphocytes from children in areas hyperendemic for the intestinal parasites *Trichuris suum* and *Ascaris lumbricoides* were found to constitutively secrete more IL-10 and TGF- β [30]. The opposite effect has also been reported with anthelmintic treatment of humans, which resulted in a reduction in T_{reg} cell numbers [35]. Evidence

from animal models provides a similar picture. For example, frequencies and absolute numbers of Foxp3⁺ T_{regs} increase early in an infection with *Heligmosomoides polygyrus*, a rodent model of gastrointestinal human helminth infection, and this is associated with protection against lung inflammation [23,36,37]. This induction and persistence of T_{regs} is important for long-term parasite survival, as T_{reg} depletion leads to a protective immune response and parasite expulsion [25].

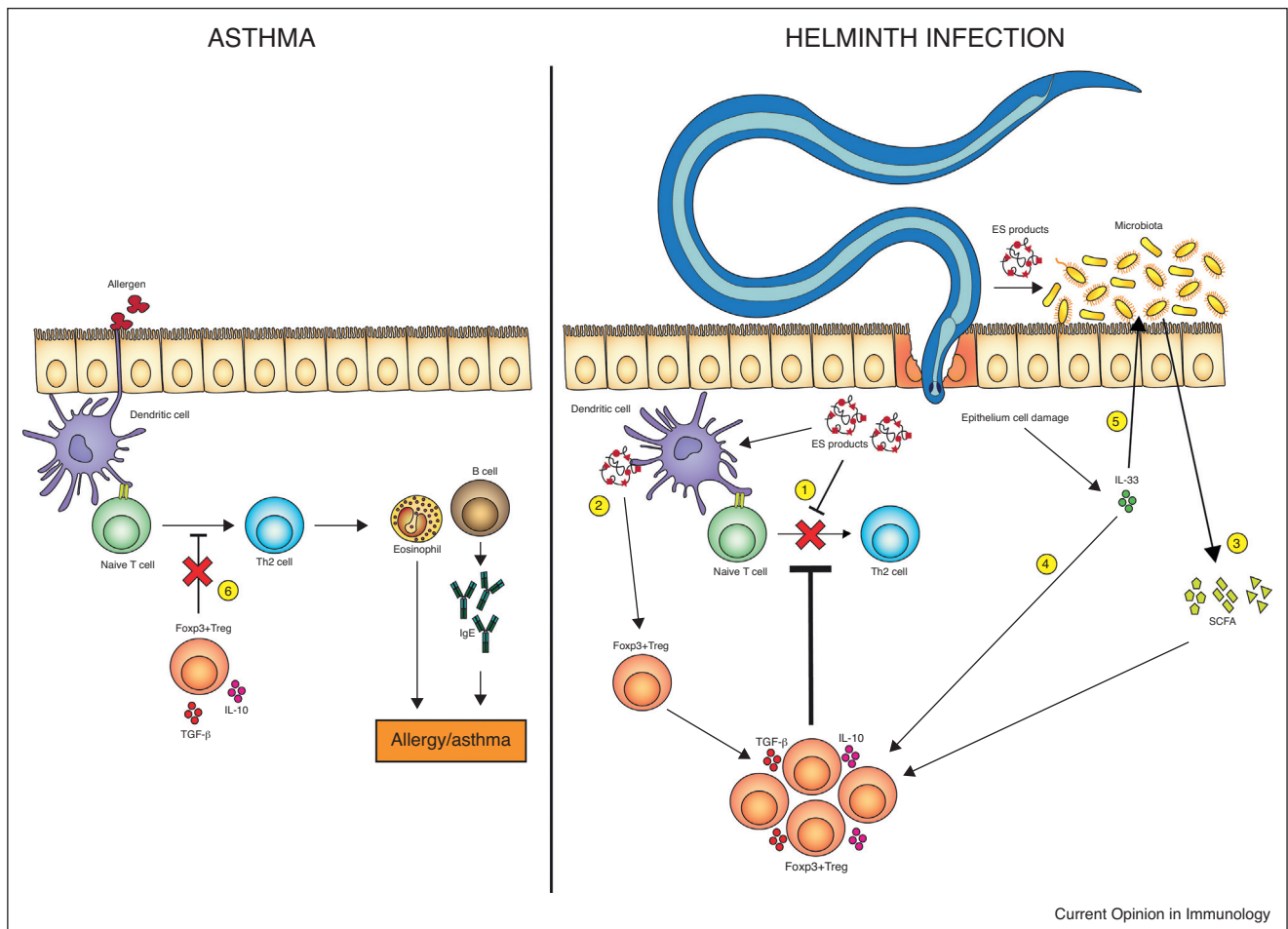
There have also been a number of clinical trials utilising experimental helminth infections to treat immune diseases. While few have looked specifically at T_{reg} responses specifically, the available data draws promising links between positive health outcomes and T_{regs}. A small trial of iatrogenic *N. americanus* infection to treat celiac disease showed a significant benefit across all tested gluten indices [38]. Duodenal biopsy post-infection revealed intra-epithelial upregulation of CD3⁺ CD4⁺ Foxp3⁺ T_{regs} with increasing gluten exposure. Upregulation of T_{regs} in combination with reductions in pro-inflammatory IL-17A- and IFN γ -expressing T cells provides a potential mechanism by which *N. americanus* parasites limit disease outcomes. Multiple sclerosis (MS) patients infected with gastrointestinal helminths were found to have fewer relapses, lower disability scores and reduced MRI activity compared with uninfected MS participants. Following anthelmintic treatment, absolute numbers of CD4⁺ CD25⁺ Foxp3⁺ T_{regs} markedly decreased as did the number of IL-10- and TGF- β -secreting cells; and MS outcomes worsened [39].

Mechanisms of helminth-induced regulatory T cell responses

Direct promotion of T_{regs} via secretion of parasite molecules

One of the most well studied mechanisms of how helminths may promote host T_{reg} responses is via the secretion of parasite excretory/secretory (ES) molecules (Figure 1). Native mixtures of ES products from *H. polygyrus* and the hookworm *Ancylostoma caninum* protected against asthma in mouse models of disease [40,41*,42]. ES products derived from *H. polygyrus* are able to induce *de novo* Foxp3 expression from mouse splenocytes [43]. Similarly, crude ES products from *A. caninum* suppress pathology in a mouse model of colitis through upregulation of IL-10⁺ CD4⁺ T cell responses [42]. One of the hypothesised mechanisms of how parasite ES proteins promote T_{reg} expansion is by acting on dendritic cells (DCs), where ES proteins may induce a tolerogenic phenotype in DCs (Figure 1) [41*,44,45*]. While many studies provide encouraging results for using ES products from helminths to treat diseases, it is important to note that the secretomes of *H. polygyrus* and *A. caninum* contain 374 and 315 proteins respectively [46,47]. It is therefore likely that multiple regulators of host immunity are present in the ES, each with potentially different functions.

Figure 1



Overview of potential helminth-induced regulatory mechanisms. **(1)** Helminths, through their secretions, directly limit naïve T cell differentiation to Th2 effector phenotypes. **(2)** These secretions may cause the upregulation of Foxp3⁺ T_{reg} cell responses through interactions with CD103⁺ dendritic cells and/or **(3)** Promote bacterial species which drive T_{reg} expansion through the production of SCFAs. This enhanced T_{reg} response is amplified by helminth derived epithelium damage inducing IL-33. **(4)** IL-33, through either direct binding to T_{regs} or **(5)** via the promotion of particular species in the microbiota, causes the expansion of this T_{reg} population. **(6)** Meanwhile, asthmatics have dysfunctional T_{regs}, hence therapeutic approaches that may boost their numbers or function may be beneficial.

A number of studies have identified specific worm-derived molecules that appear to promote T_{reg} responses. Filarial cystatin, a secreted protease inhibitor of filarial nematodes, prevented allergic airway reactivity and inhibited acute colitis [48]. The proportion of $FOXP3^+$ T_{reg} cells was significantly increased by the administration of cystatin as was the production of IL-10. Blocking IL-10 restored effector cell responses and the levels of OVA-specific IgE [48]. Interestingly, some parasites may directly augment T_{reg} -associated effector functions by the secretion of host TGF- β mimics. For example, a recombinant form of a secreted protein from *H. polygyrus* (*Hp*-TGM) possesses potent TGF- β -like function by binding to mammalian TGF- β receptors, resulting in expansion of murine and human $FOXP3^+$ T_{regs} [49^{••}]. Subsequently, a family of nine related *Hp*-TGMs were reported in the *H. polygyrus* secretome [50]. Similarly, the

initial proteomics analysis of *A. caninum* ES products revealed two Tissue Inhibitor of Metalloprotease (TIMP)-like proteins [51], which have since been named anti-inflammatory protein (AIP)-1 and AIP-2 [41[•],52]. In a mouse model of colitis, AIP-1 limited inflammatory cell infiltration, augmented IL-10 and TGF- β production, and promoted the recruitment of T_{reg} cells in the colon [52]. AIP-2 on the other hand, suppressed inflammation and limited pathology in a mouse model of asthma, which was dependent on the presence of both CD11c⁺ DCs and Foxp3⁺ T_{regs} [41[•]]. The finding that AIP-2 suppressed the proliferation of T cells from human allergic patients highlights the translational potential of this molecule [41[•]]. With hundreds of molecules of unknown function in helminth ES products, it follows that there are potentially an array of proteins and numerous mechanisms by which they regulate host immunity.

Other mechanisms of T_{reg} induction by helminths

While there is compelling evidence that helminths directly regulate host immunity through their secretions, increasing evidence suggests crosstalk with the local microbiota also plays a role. Several studies have shown that infection with *H. polygyrus* correlates positively with the abundance of *Lactobacillus* bacteria [53,54]. Elevating the abundance of *Lactobacillus* and other specific species in the microbiota may lead to an increase in short chain fatty acid (SCFA) production through the fermentation of resistant starches and dietary fibre [53,55]. SCFAs had a significant effect on the number of colonic T_{regs} and protected against inflammation in a mouse model of colitis [56[•]]. The transfer of an *H. polygyrus*-altered microbiota was able to confer protection against HDM-induced allergic asthma in mice [55]. While the mechanism by which SCFAs influence T_{reg} populations is still unclear, multiple SCFAs including acetate, propionate and butyrate were shown to promote naïve T cell differentiation to T_{reg} phenotypes (Figure 1) [57]. Furthermore, SCFAs, particularly butyrate, were shown to induce human CD4⁺ CD25⁺ T_{regs} [58]. It is however unclear whether the shift in commensal populations are the bacteria adapting to helminth infection or are in actuality driven by helminth-secretions. This notion of SCFA-induced regulation of immunity can be used in part to explain the significantly lower rates of allergy in developing nations. Poorer communities usually consume diets high in fermentable fibre, have greater incidence of intestinal helminths, and were found to excrete more SCFAs than their developed community counterparts [59].

The epithelia of the airway and gut express pattern recognition receptors to initiate Type 2 immune responses in the case of epithelial damage [60]. IL-33 is a key driver of this response and has been shown to be important in promoting Type 2-dominated phenotypes in allergy and in helminth infections. Conversely, in recent years, a role has also emerged for IL-33 in attenuating inflammatory responses. IL-33 has been found to be significantly upregulated by intestinal epithelial cells during inflammation [61,62]. IL-1RL1, the IL-33 receptor, is highly expressed on T_{regs} of the colon and promotes expansion of this population [61,63,64]. IL-33 was also found to promote lasting immunosuppression in a mouse model of septic peritonitis. In this study, IL-33 promoted M2 macrophage polarisation leading to IL-10 upregulation and T_{reg} expansion [65^{••}].

T_{reg}-independent mechanisms

With all of the evidence for helminth-driven T_{reg} immunomodulation, it is important to acknowledge support for T_{reg}-independent mechanisms. While evidence exists that IL-33 can induce a T_{reg} phenotype, it has also been demonstrated to be a potent regulator of the microbiome (Figure 1). IL-33 deficient mice are dysbiotic, with a greater population of pro-inflammatory bacteria compared to wild-type controls [66]. This effect was attributed to greater numbers of mucolytic and colitogenic

bacteria and the associated IL-1 α increase [66]. A *H. polygyrus* secreted protein, coined *H. polygyrus* Alarmin Release Inhibitor (HpARI), was shown to abrogate IL-33 by binding it directly. Through this mechanism, HpARI limited eosinophil responses and precluded type 2 immune responses [67[•]]. Additionally, metalloproteases in the ES products of *N. americanus* hookworms were shown to abrogate eotaxin function [68]. By inhibiting this potent eosinophil chemotactic protein, the worm limits eosinophilic inflammation and prolongs its survival.

Conclusion

Allergic diseases are on the rise globally as helminth infections decline. While helminths induce a Type 2 immune response with many of the features of allergic asthma, they have also evolved to regulate this response through the induction of T_{regs}. Evidence now suggests that helminths drive this regulation through a multifactorial approach. Specific ES molecules such as Hp-TGM from *H. polygyrus*, and AIP-2 from *A. caninum*, act to suppress Type 2 and/or Type 1 effector responses while promoting T_{reg} expansion. This effect may be boosted by a helminth-induced shift in gut microbiota towards species which also drive T_{reg} expansion (Figure 1). Interestingly, a role has also emerged for IL-33 in the expansion of T_{regs} following epithelial cell damage. These combined effects result in a state of hypo-responsiveness whereby exposure to allergens is less likely to result in the exaggerated immune response characteristic of allergy. All of these factors support the notion of helminths and their secretomes as a valuable resource for understanding immunoregulatory mechanisms and discovery of next generation immunotherapeutics guided by host-parasite coevolution.

Acknowledgements

This work was supported by the Australian National Health and Medical Research Council (NHMRC) grant 1037304 (to AL) and Senior Principal Research Fellowship 1117504 (AL), the Queensland Department of Science, Information Technology and Innovation (PG), a Children's Hospital Foundation Fellowship 50197 (SN) and an Australian Postgraduate Award and AITHM scholarship (JL).

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