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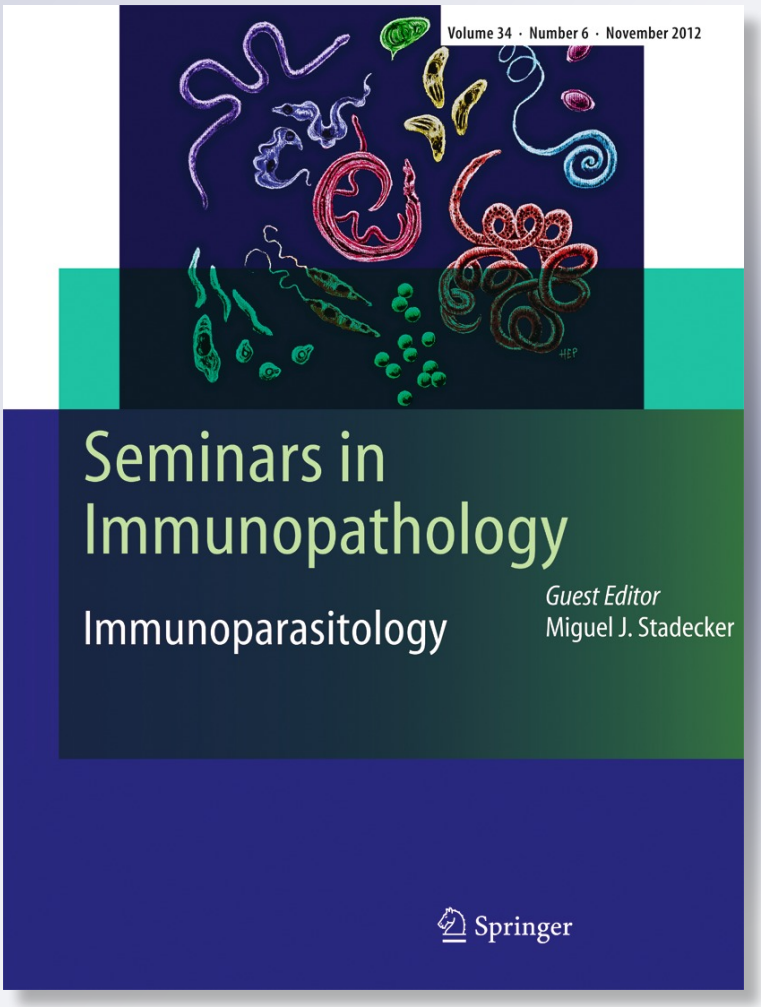

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REVIEW

Helminth infection in populations undergoing epidemiological transition: a friend or foe?

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Abstract Helminth infections are highly prevalent in developing countries, especially in rural areas. With gradual development, there is a transition from living conditions that are dominated by infection, poor sanitation, manual labor, and traditional diet to a situation where burden of infections is reduced, infrastructure is improved, sedentary lifestyle dominates, and processed food forms a large proportion of the calorie intake. The combinations of some of the changes in lifestyle and environment are expected to result in alteration of the landscape of diseases, which will become dominated by non-communicable disorders. Here we review how the major helminth infections affect a large proportion of the population in the developing world and discuss their impact on the immune system and the consequences of this for other infections which are co-endemic in the same areas. Furthermore, we address the issue of decreasing helminth infections in many parts of the world within the context of increasing inflammatory, metabolic, and cardiovascular diseases.

Keywords Helminths · Co-infection · Allergy · Metabolic syndrome · Cardiovascular diseases · Epidemiological transition · Immune responses

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The burden of helminth infections

A diverse range of helminth parasites, differing in terms of their size, life cycle, and clinical impact, can lead to chronic infections in humans. Soil-transmitted helminth (STH) infections, together with schistosomiasis and filariasis, form a major proportion of a group of neglected tropical diseases and together affect about one third of the world population [1]. Helminth infections, the ancient companions of poverty, together with the major infectious diseases are the targets of millennium development goals to improve global public health outcomes.

There are more than 20 helminth species infecting humans, of which the majority of infections are light, asymptomatic, and rarely cause attendance to health centers [1, 2]. However, children with heavy and chronic STH (*Ascaris lumbricoides*, hookworms [*Necator americanus*, *Ancylostoma duodenale*], and *Trichuris trichiura*) infections can suffer from malnutrition, growth stunting, intellectual retardation, as well as cognitive and educational deficits [2]. In addition, it is known that a proportion of individuals with intestinal schistosomiasis (caused by *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma mekongi*, and *Schistosoma intercalatum*) can present with intestinal and hepatosplenic symptoms, while those with *Schistosoma haematobium* infection can suffer from urogenital symptoms [3]. A more serious condition has been seen when eggs get dislodged in the spinal cord or the brain, leading to neurological damage, such as myelopathy (acute transverse myelitis and sub-acute myeloradiculopathy) in *S. mansoni*- or in *S. haematobium*-infected subjects and acute encephalitis of the cortex, sub-cortical white matter, or basal ganglia in *S. japonicum*-infected subjects [4]. In schistosome-naïve travelers, acute infection can result in systemic hyper-reactive symptoms, commonly referred to as Katayama fever [5]. The range of pathologies seen with a third group of major helminth infections, the filarial

nematodes, are lymphatic oedemas caused by *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, blindness caused by *Onchocerca volvulus*, and calabar swellings caused by *Loa loa* [6, 7]. In lymphatic filariasis, the lymphatic vessels at the site where the adult worms nest are dilated (lymphangiectasia), most commonly seen in the extremities and male genitalia [6]. Individuals with chronic onchocerciasis can develop depigmentation and loss of skin structure and elasticity that can lead to premature skin aging, while ocular lesions resulting from the migration of microfilariae to the eye can lead to severe visual impairment and blindness [6]. The calabar swelling in loaiasis is the typical clinical sign of this infection which is presented as a regional fugitive/episodical angioedema around the migrating adult worms, mostly in the arms and the legs [6, 7]. Although these outcomes of helminth infections are not the norm, their severity can form a strong basis for the urgent calls to control helminth infections worldwide.

It remains interesting that the majority of helminth infections have no outward clinical signs. It is thought that these infections often co-exist in harmony with their human host as a result of long evolutionary co-adaptation. To this end, helminths are able to influence their host to ensure their long-term survival, while this same adaptation might be beneficial to the host if it restricts damage to tissues and organs. The current view is that, although in the majority of infected populations these parasites can manipulate the immune system, in a small proportion of subjects, this manipulation seems to fail and leads to pathologies as described earlier.

The immunological consequences of helminth infections

Helminths are known to skew the immune system towards type-2 immunity characterized by T helper (Th) 2 cells and their cytokines (interleukin (IL)-4, IL-5, IL-9, IL-13), high level of tissue eosinophilia, mucosal mastocytosis, and production of immunoglobulin (Ig) E. Another hallmark of helminth infections is their ability to induce regulatory responses via regulatory T cells (Treg) that express molecules involved in the inhibition of immune responses such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or glucocorticoid-induced TNF receptor [8] and secrete suppressory cytokines (IL-10 and transforming growth factor (TGF) ß) [9]. Helminth infections have also been associated with regulatory B cells (Breg), which can release IL-10 and restrain hyper-inflammatory responses [10]. These parasites seem to also affect the expansion of innate immune cells with the ability to dampen immune response. Among these are the suppressor macrophages [11] as well as the induction of regulatory dendritic cells (DCreg) which are characterized by the expression of IL-10, TGF-β, indoleamine 2,3-dioxygenase, and cyclooxygenase-2 [12, 13]. Moreover, helminth infections result in the skewing of macrophage development away from classically activated macrophages to alternatively activated macrophages (AAM) (which can be induced by IL-4, IL-13, and IL-10) [14]. This army of regulatory cells can modulate immune responses in antigen (Ag)-specific and non-specific manner and can lead to restriction of inflammation. In terms of pro-inflammatory responses, several studies in humans as well as in animal models have indicated that Th1 and Th17 cells can be part of the immune response induced by helminth infections and might play an important role in pathological outcomes.

In schistosomiasis, immunoepidemiological studies have indicated that Th2 responses are associated with resistance to reinfection [15, 16]. However, in animal models, Th1 cells have been shown to also contribute to immunity against these parasites [17, 18]. With respect to pathology, pro-inflammatory responses, represented by high TNF and by the type-1 associated cytokine, interferon (IFN)-γ, were shown to be elevated in the circulation of Kenyan patients with hepatosplenomegaly [19], yet in a study in Brazil schistosome-related pathology was reported to be associated with higher IL-13 production [20]. Notwithstanding the experimental details, these apparently conflicting outcomes might reflect the fact that pathology is a complex process and immunological responses would be expected to be different during the different phases of the development of pathology. With respect to other cytokines, recent studies that have focused on examining the role of Th17 cells have shown these cells to be associated with schistosome-induced pathology in animal models [21, 22] and in humans [23]. In terms of control of the immune responses in schistosomiasis, several mechanisms seem to be involved, most prominent being the down-modulation of effector responses by IL-10 and TGF-ß, which prevent schistosome-induced pathology [24–26]. The exact mechanisms are not fully understood but could involve, in addition to Treg, IL-10 production B cells which have been shown to be present in murine and in human chronic schistosomiasis [27]. Moreover, in a recent review, the role of AAM as key players in controlling the development of immune pathology in schistosomiasis was highlighted [28]. To what extent Treg, B cells, or AAM play a role in the control of immune responses and pathology in human schistosomiasis needs to be determined in well-designed studies.

In STH infections which are mainly restricted to the gastrointestinal tract, acute or early infections, as shown in animal models with *Trichuris muris*, are often thought to be associated with pro-inflammatory cytokines, such as TNF [29, 30]. Th2 responses have been shown to be needed to expel these helminths from the gut [31, 32]. One of the mechanisms involved in the Th2-induced expulsion is the stimulation of higher intestinal epithelial cell turnover [33] and, as recently shown, the alteration of the composition of

the mucus layer [34]. Whereas work in experimental models has elegantly shown how different arms of the type-2 immune system are involved in intestinal worm expulsion [35] and how gut helminths try to avoid expulsion by up-regulation of IFN-γ to combat Th2 responses [36], relatively little is known about the situation in humans. One of the first human studies examining immune response to STH showed that stronger Th2 cytokines were associated with lower infection burden, suggesting that in humans type-2 responses may also be associated with protection from STH [31]. A few studies have reported the up-regulation of suppressory cytokines such as IL-10 and/or TGF-ß [37]. In Cameroon, children living in areas hyperendemic for helminths produce more IL-10 and TGF-ß than children living in mesoendemic areas [38], whereas in a study in Brazil, increased spontaneous IL-10 production was seen in a larger proportion of children infected with STH [37]. The higher production of these cytokines was related to hyporesponsiveness to helminth or bystander antigens [39] and presumably allows worm survival. A more comprehensive analysis of the response to STH infection was undertaken in chronically infected children whose peripheral blood gene expression patterns were studied extensively by using microarrays. The results indicated that chronic STH infection was associated with altered gene expression profiles that suggest these infections to be associated with modified Th2 responses (i.e., up-regulation of IL-5 and IL-10), with down-regulation of neutrophil activation and function and up-regulation of mediators associated with eosinophils [40]. Interestingly, microRNA (miRNA) was also studied using a specific array [40], and the results showed that a single miRNA, hsa-let-7d, was down-regulated during chronic STH infection. This miRNA, already reported to affect iron metabolism [41], is part of the let-7 miRNA family, found to be abundant in the alveolae of normal lungs but almost absent in the lungs of mice with idiopathic pulmonary fibrosis [42], suggesting its possible role in preventing lung fibrosis. Although these studies need to be linked to extensive target identification and functional studies, they indicate the potential for gaining a full picture of how these parasites might affect not only the immune system but also target organs.

In lymphatic filariasis, inflammatory responses occur when the adult worms die, either drug-induced or spontaneously. Granulomas arise around the worms, characterized by macrophages which develop into giant cells as well as plasma cells, eosinophils, and neutrophils [43]. Peripheral Th1 and Th17 cells as well as antibody responses are reported to be up-regulated in patients with chronic pathology [44]. The immune regulatory responses that are up-regulated during microfilaremic state without any signs of pathology are characterized by production of IL-10 and TGF-β [45] as well as with increased Treg. Metenou et al. [46] have shown that individuals infected with *W. bancrofti* and/or *Mansonella perstans* have increased frequency of natural Treg as well as IL-10 producing effector cells. A study in a *B. timori* endemic area, conducted by Wammes et al. [47], showed that the Treg of microfilaremic subjects has stronger suppressory activity than the Treg of endemic amicrofilaremic controls or subjects with chronic pathology. In onchocerciasis, hyper-reactivity has been shown to be correlated with pathology of the skin and lymph nodes [48]. A possible role for IL-13 in the pathogenesis of onchocerciasis was found in an immunogenetic study, which showed that Th2-dominated sowda form of hyper-reactive onchocerciasis was associated with a mutation in the IL-13 gene, a gene known to be linked to allergic hyper-reactivity [49]. As in lymphatic filariasis, Treg has been described in subjects with onchocerciasis [50, 51] and thought to keep the development of pathology at bay.

Taken together, it seems that the pro-inflammatory responses typified by Th1 and Th17 and also by hyperactive Th2 responses might underlie the immunopathology in helminth infections. However, most helminth infections appear to be associated with regulatory mechanisms [52] that try to keep pathological responses under control. These regulatory responses can be helminth Ag-specific or exert non-specific spill over suppressory effects on unrelated Ags.

Helminths and their spillover effects on health outcomes

Various helminth infections seem to have profound effects on the immune reactions against other infections and bystander Ags, be it vaccines, environmental allergens, or self-Ags. However, this is an area full of controversy and clearly needs more research.

Co-infection

It is common that helminth infections are co-endemic with malaria, tuberculosis (TB), and human immunodeficiency virus (HIV) [1]. This situation raises the question of what impact helminth infections may have on the co-endemic infections as they are believed to be able to suppress effector T cell responses. In filaria-infected individuals, the magnitude of inflammatory cytokines, IFN-γ and IFN-γ inducible protein 10, in response to malaria Ag was shown to be affected by filaria-induced IL-10 [53]. Moreover, in malaria-infected individuals, concomitant filarial infection has been shown to decrease the frequencies of malaria-specific Th1 and Th17 cells [54]. The same seems to be the case for mycobacteria Ag-specific responses, which appear to be down-regulated in filaria-infected subjects via increased expression of the negative co-stimulatory molecules CTLA-4 and inhibitory receptor programmed death 1 [55]. Interestingly, although chronic mycobacteria [56] and plasmodia infections [57, 58] on their

own are associated with increased Treg, a study on Flores island, Indonesia, using in vitro Treg depletion has shown that Treg from STH-infected subjects have stronger functional activity than Treg from those free of STH in immune responses to bystander mycobacteria and plasmodia Ag [59].

Although at the immunological level helminths seem to be able to influence responses to co-infections, it is far from clear whether this is translated into clinical and epidemiological outcomes. Epidemiological studies on the relationship between helminths and malaria, TB, or HIV have shown conflicting results [60, 61] as have studies in animal models [62–67].

In some studies, a positive association has been reported between helminths and malarial parasitemia, while in others this has been refuted or even a negative association has been found with clinical outcomes [68–70]. For example, there is evidence that helminth co-infection with malaria is associated with increased risk of anemia [71], but there is also evidence for a protective role against developing anemia [72] or no association [73]. A recent review by Nacher [60] suggests that there are different malaria outcomes with different species of helminths. This is supported by a recent case–control study in Colombia that showed an example of how different helminth species vary in their association with *Plasmodium falciparum* [74]. It showed that whereas *A. lumbricoides* infection had a protective effect, hookworm infection seemed to be a risk factor. In line with this unclear situation on the effect that helminths have on malaria parasites or outcomes are the inconsistent results of the deworming trials [75–77], which might be due to the differences in the characteristics of the populations studied, species of helminths prevalent, and the study designs.

Regarding the relationship between helminth infections and mycobacteria, there is still limited evidence for any significant interaction. In helminth-infected individuals, a higher risk to develop pulmonary TB has been reported [78], as well as IFN-γ production in response to purified protein derivative upon Bacillus Calmette Guerin vaccination [79]. However, in an area highly endemic for helminths in the Amazon, where it was expected that high helminth infection pressure would attenuate the tuberculin skin test (TST), there was no significant suppressive effect of helminth infection on the TST size [80].

The same inconclusiveness applies to the relationship between helminths and HIV. Concerning HIV acquisition and progression, Webb and colleagues [81] have reviewed this subject and indicate that there are inconsistent findings with regard to whether helminth–HIV co-infection can have a more detrimental effect on the host compared to a single HIV infection or the beneficial effect of anthelminthic treatment on HIV. A Cochrane review in 2009 demonstrated a beneficial effect of deworming on both plasma HIV-1 RNA and CD4 counts [82], but a recent report on anthelminthic treatment with albendazole and praziquantel during pregnancy in Uganda indicated that there was no effect of treatment on vertical HIV transmission [75]. However, in this study, the authors acknowledge that the data were generated on a small number of infants born to HIV-infected mothers. For the mothers, anthelminthic treatments resulted in a modest reduction in HIV virus load in the albendazole (to treat hookworm and *T. trichiura*)-treated mothers, but no difference was seen in praziquantel (to treat *S. mansoni*)-treated subjects compared to placebo at 6 weeks after administration of the drug [83]. These results might again be in line with what has been discussed in a meta-analysis of the effect of anthelminthic treatments on HIV that suggests that different helminth species might have different outcomes [84].

It has to be concluded that in order to be able to draw firm conclusions regarding the effect of helminths on malaria, TB, or HIV, well-powered placebo-controlled anthelminthic trials are needed with a streamlined design that will also take care of the issue that different helminth species might have a distinct modulatory role.

Non-communicable diseases

Allergy and asthma

Allergic diseases (allergic asthma, eczema, and rhinitis) are dominated by type-2 responses [85]. The prevalence of these diseases are thought to be relatively low in developing countries especially in rural areas [86–88], which has often been put into the context of the hygiene hypothesis and the high prevalence of helminth infections (Fig. 1). It has been argued that in rural areas of low-to-middle-income countries (LMIC), the exposure to microorganisms and parasites is high and therefore the immune system is educated in a way that it no longer reacts to innocuous substances such as environmental allergens. Although helminth infections skew immune responses toward Th2, they have been reported to be inversely associated with allergic disorders [89]. This has been argued to be due to the ability of chronic helminth infections to induce regulatory responses [90]. This means that helminth infections which have been associated with increased IL-10 or TGF-ß production by several regulatory cells might suppress the effector mechanisms that lead to the development of allergy. In a study in human schistosomiasis in Gabonese children more than a decade ago, it was shown that the anti-inflammatory cytokine, IL-10, in response to the helminth Ags, was associated inversely with skin prick test (SPT) reactivity to house dust mite allergen [89]. However, in a more recent study of Ecuadorian children, *A. lumbricoides* infection, although inversely associated with SPT reactivity to allergen [87], did not involve IL-10 production in response to *A. lumbricoides* Ag [91]. In contrast to the study in Ecuadorian children but in line with the Gabon study, in another study where hookworm-infected

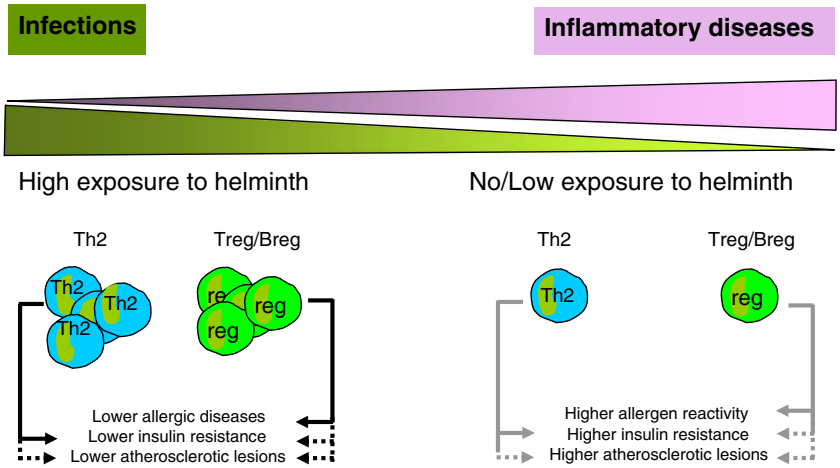

Fig. 1 A schematic representation of epidemiological transition and disease outcomes. Epidemiological transition is associated with changes in disease burden. With decreasing burden of infectious diseases, populations are facing increasing inflammatory non-communicable disorders. One hypothetical framework for these observed changes is that infections such as helminths which are associated with expansion of Th2 and regulatory T and B cells are disappearing and therefore leading to altered immune profiles. There is evidence, as discussed in this review, that Th2 responses are associated with lower insulin resistance while enhanced Treg and Breg can lead to suppression of allergic diseases in animal models. Therefore, when Th2 and regulatory cells decline, it follows that insulin resistance and allergic diseases become rampant. The *black lines* represent strong modulatory pathways in areas where infections are highly prevalent, while *gray lines* represent weak modulatory pathways in areas where infections are largely controlled. The *solid lines* represent associations based on data available, while *dotted lines* represent theoretical associations that are yet to be tested

schoolchildren were studied in Vietnam, IL-10 production in response to *N. americanus* excretory–secretory Ag was inversely associated with skin sensitization [92]. The discrepancy between these studies might be caused by infection intensity as shown in an animal model [93] or differences in helminth species. Another important aspect of the relationship between helminths and allergies is the issue of IgE cross-reactivity. There is evidence for IgE cross-reactivity between helminth Ags and allergens such as with cockroach [94] or mite [95]. It has been suggested that this cross-reactivity might influence allergy outcomes. Whereas in Europe, high total and specific IgE are associated with increased risk of SPT positivity [96] and allergic disease, this association is less clear in areas endemic for helminth infections [97, 98]. The reason may be that IgE cross-reactive between helminths and allergens has low biologic activity [90]. Thus, in areas where helminths are endemic, early sensitization to helminth Ag might lead to weak IgE binding to cross-reactive allergens, preventing strong allergic responses, and might explain in part the mechanisms whereby helminth infections lead to fewer allergic disorders.

With respect to deworming trials, 1 year of anthelminthic treatment in studies in Ecuador and in Vietnam showed inconsistent results, the former showing no effect, but the latter led to increased SPT reactivity to allergen [92, 99]. In addition, a study in Denmark analyzing records of children born between 1995 and 2008 showed that treatment with mebendazole of children infected with *Enterobius vermicularis* had a marginal effect on the incidence of asthma [100]. Interestingly, in a study of anthelminthic treatment of pregnant women in Uganda, an increased risk of infantile eczema was seen in mothers who received anthelminthics compared to those that received placebo [101]. This raises the issue regarding the timing of deworming; maybe exposure to worms in early life imprints on the immune system, affecting allergic outcomes more profoundly than when helminths are removed later in life [102]. Moreover, there is increasing evidence for the difference in risk factors associated with allergic and non-allergic asthma [103] or maybe even eczema.

The converse experiments have been attempted where patients were infected with helminths to treat allergic disorders. The outcomes of these trials did not show any beneficial effects [104–106]. Randomized placebo-controlled trial of treatment with hookworm in adult patients with allergic asthma [106] showed improvement of bronchial responsiveness in infected group, but this was not significantly different compared to the placebo-treated group. It might indicate that higher doses of hookworm infection are needed. It must be pointed immediately that not all helminth infections can be therapeutically equal; for example, in mouse models for experimental allergic inflammation, previous infections with *Strongyloides stercoralis* [107] or *Nippostrongylus brasiliensis* [108] resulted in suppression of allergic response to ova (as an allergen) challenge, while infection with *Toxocara canis* resulted in exacerbation of the allergic response [109]. Altogether the hypothesis that helminth infection might be beneficial against allergic disease or deworming might increase risk for the disease is still controversial and needs more convincing evidence [110–112]. There has been one very-long-term study where 15–17 years of ivermectin treatment to control

onchocerciasis in Ecuador has resulted in increased SPT reactivity to allergens [113]. Understandably, such studies are difficult to perform and the question remains whether these can be repeated. A recent Cochrane review [104] also acknowledged insufficient evidence on the efficacy, tolerability, and likely costs of using helminth infection as therapy to support their use in the routine management of allergic rhinitis.

Autoimmune diseases and inflammatory bowel disease

There are very few epidemiological studies of autoimmune diseases in LMIC; however, geographical differences have been reported. The conclusion of ecological studies is that the situation of autoimmune diseases is mirroring that seen in the field of allergy. It is suspected that there might be an inverse association between the prevalence of autoimmune diseases and the prevalence of infections including helminths [114]. One of the first studies showing the association between helminth and autoimmune diseases was in an animal model of multiple sclerosis (MS), where injection of mice with *S. mansoni* eggs led to reduced severity of the disease and delayed development of clinical symptoms [115]. Recently, several studies have demonstrated that the course of autoimmunity is determined by a mixture of pathological Th1 and Th17 responses [116, 117], and in the light of immune regulation, the potential role of helminths to reduce the severity of disease in MS patients [118–120] and inflammatory bowel disease (IBD) [121–123] has been shown in a number of trials. A clinical trial using repeated *Trichuris suis* ova treatment resulted in reduced relapses in MS patients [123]. In another study of MS patients, B cells isolated from patients who were infected with helminths produced higher levels of IL-10 than B cells from uninfected patients [120]. These B cells could also produce high levels of brain-derived neurotrophic factor and nerve growth factor which are thought to have a neuroprotective effect. The most detailed cellular and molecular information on changes that take place in the intestinal mucosa has been gathered on one ulcerative colitis patient who self-treated himself with eggs of *T. trichiura* [124]. Ingestion of two doses of helminth eggs (500 and 1,000 eggs) led to nearly 3 years of complete disease remission [124]. As the symptoms began to deteriorate paralleling a decline in egg counts, a third dose (2,000 eggs) was taken and resulted in both symptom and histopathological improvement, the latter seen in biopsies following colonoscopy [124]. Detailed immunological studies showed that active colitis was associated with cytokine-producing CD4+ IL-17+ Th cells, whereas helminth colonization and disease remission were characterized by the presence of IL-22+ Th cells in the colonic mucosa. Moreover, the helminth-colonized ascending colon had higher expression of IL-4, IL-25, and RELMβ [124], while the rectum with active symptoms had elevated IL-17 and TNF as well as reduced expression of RELMβ [124]. With respect to IL-22, gene delivery of this cytokine to a local inflamed colon in a colitis model led to attenuation of colitis, which was shown to be due to the enhancement of intestinal mucus production by goblet cells [125]. The role of other cells such as macrophages is not as clear. The macrophages of the gastrointestinal tract, which are distinct from blood macrophages [14], seem to be essential for keeping the balance of commensal microbiota such that pathology is avoided [126]. There is however still controversy about whether AAM are beneficial or detrimental in this aspect. In a murine model of bacterial colitis, infection with *Heligmosomoides polygyrus*, which was associated with increased AAM, seemed to lead to severer colitis [127]. Yet in another chemically induced colitis model, *Hymenolepis diminuta* infection induced an increase of FIZZ1/RELMα and argininase-1 expression as markers of AAM and attenuated colitis [128]. The discrepancy on the role of macrophages could be the result of the use of different species of helminths in the two studies or the type of colitis model used. Nevertheless, Wolff and colleagues recently summarized that helminthic therapy for autoimmune diseases such as IBD is relatively safe [129] and might provide new therapeutic possibilities for inflammatory diseases such as MS and IBD. It is again important to note that large-scale trials are essential before any firm conclusion can be drawn.

Cardiovascular disease

Cardiovascular disease (CVD) involves the heart and the blood vessels. Atherosclerosis is an important risk factor for developing CVD [130] and is now believed to involve inflammation. Part of the inflammatory process is thought to be mediated by the infiltration and retention of low-density lipoprotein (LDL) in the arterial intima. The transformation of these lipids into oxidized lipids can initiate an inflammatory response that can accelerate CVD progression [131]. The oxidized lipids can stimulate innate immune responses and lead to the recruitment of inflammatory cells, such as monocytes, into the vessel wall that when activated can attract other cells and aggravate the growing plaque (reviewed by Hansson [132]). However, currently available therapeutics against CVD are largely restricted to alleviating hypertension and hyperlipidemia [133, 134], while drugs targeting inflammatory mediators are not yet available. Interestingly, the lipid-lowering drug statin, one of the most frequently used medication, has been shown to have anti-inflammatory effects [135, 136]. Moreover, studies on the role of anti-inflammatory mechanism in atherogenesis have suggested that Treg [137] might be involved to limit inflammation and attenuate atherogenesis. In an experimental model of hypertensive mice, Kassan et al. [138] showed that IL-10 released by Treg could improve microvascular endothelial function by reducing the nicotinamide adenine dinucleotide phosphate oxidase activity and increasing endothelial NOS activity. These data suggest

that indeed the balance between pro- and anti-inflammatory cytokines might be an important element in the regulation of vascular endothelial function.

CVD prevalence is increasing in Asian countries [139]. In this region, rapid socioeconomic development has led to a shift in infrastructure, technology, and food supply that promotes over-nutrition and sedentary lifestyles [140]. Also, in Asia, despite large geographical differences, infectious disease control such as deworming program is underway [141]. Hypothetically, helminths might protect against CVD by reducing risk factors such as nutritional status. Helminths are known to reduce energy intake and to be associated with poor nutritional status, which in turn is associated with beneficial effects on traditional CVD risk factors such as reduced serum lipid levels [142]. Using apolipoprotein deficient (apoE−/−) mice, a transgenic mice that has impaired plasma lipoprotein clearance and develops atherosclerosis in a short time [143], the development of atherosclerotic lesions was reduced by approximately 50 % in mice infected with *S. mansoni* [144]. The same group showed that the cholesterol-lowering effects were mediated by soluble factors released from *S. mansoni* live eggs. A similar experiment, but using frozen eggs, showed a reduction in total cholesterol and LDL in mice injected with schistosome egg compared to those not injected with eggs. However, in the latter study, no difference in atherosclerotic lesion formation was observed [145]. Taken together, these data suggest that helminth infections or their products might be able to act as lipid-lowering agents.

Recently, a number of studies have shown a higher risk of death from CVD among patients with rheumatoid arthritis (RA) [146–148], which would be in line with the notion that increased inflammation such as higher TNF and IL17 in RA would lead to a higher risk of CVD [149]. A meta-analysis by Micha et al. [150] summarized that methotrexate, an anti-RA drug which is also used for the treatment of chronic inflammatory disorders, has a beneficial effect on CVD. Interestingly, the reported immune-modulatory capacity of statins is based on their ability to induce Treg recruitment [151] and to inhibit the pro-inflammatory action of IL-17 and TNF on human endothelial cells [152]. A similar immune suppression by Treg, decreasing pro-inflammatory cytokines such TNF and IL-17, has been shown in helminth-infected subjects [47, 54]. Moreover, a family of antioxidant proteins, the peroxiredoxins (PRDX), essential for the enzymatic scavenging of hydrogen peroxide [153], has been shown to play a role as immune modulators [154]. There is evidence that PRDX-1 and -2 are able to interfere with endothelial activation and to regulate pro-inflammatory responses in apoE−/− mice, respectively [155, 156]. Another PRDX family, PRDX-4 seems to protect against the formation of unstable atherosclerotic plaques [157]. Interestingly, PRDX is also one of the molecules secreted by several helminth parasites and is thought to help the parasites to get through the defense barriers and avoid attack mounted by the host [158–160]. Therefore, an interesting area of research would be to test the role of helminth-secreted PRDX and possibly other helminth-derived products on CVD as potential anti-atherogenic therapy (Fig. 1).

Diabetes

Obesity, DM2, and CVD share a metabolic profile characterized by insulin resistance (IR) and chronic sub-acute inflammation [161]. It has been shown that the pro-inflammatory cytokine TNF is able to induce IR [162, 163]. This was shown in murine models where a lack of TNF function results in improved insulin sensitivity and glucose homeostasis, while administration of TNF leads to IR [164]. As already discussed in earlier sections, helminth infections seem to affect inflammation. In this regard, cross-sectional studies in southern India showed an inverse association between DM1 [165] and DM2 [166] with lymphatic filariasis. In our study in an area endemic for STH on Flores Island, Indonesia, individuals infected with STH showed lower IR (Wiria et al., unpublished data). The influence of helminth infections has been shown in animal models of DM1 [167] and DM2 [168]. Inhibition of DM1 development by helminth infections appeared to be due to the ability of helminths and their products to induce IL-10 production by DC, B cells, AAM, and Treg. Likewise in an experimental model of DM2, Ricardo-Gonzales et al. [169] demonstrated an improvement of glucose metabolism mediated by the IL-4/STAT6 immune axis, a key pathway in helminth immunity and Th2 response. They showed that IL-4 administration improved insulin action, lowered levels of insulin, total cholesterol, and triglyceride, and protected the mice from diet-induced obesity. Another study showed that helminth-induced eosinophilia forestalls obesity and IR [168]. Wu et al. [168] showed that in mice kept on high-fat diet, infection with *N. brasiliensis* induced sustained eosinophilia. Eoshinophils migrated into adipose tissue, secreted IL-4, and then induced AAM in the tissue; these cells are able to sustain insulin sensitivity [168]. Despite the extensive population studies on the role of helminths in allergy or autoimmune diseases, epidemiological or mechanistic data on the relationship between helminths and DM2 are still lacking, and even less is known about the effect of deworming programs on IR and emergence of DM2 (Fig. 1).

Helminth-derived molecules

Recent years have seen a surge in efforts to identify helminth-derived molecules with modulatory activity [170]. The characterization of such molecules would be beneficial on two fronts: (1) they can serve as vaccines if

used by parasites to enhance their survival—their neutralization would be expected to enhance worm expulsion [35] and (2) they have the potential to be used to tame hyper-inflammatory disorders. Early studies have shown that schistosomes carry lyso-phosphatidylserine that are able to modulate DC and induce Treg [171]. In addition, the ability of schistosomes to stimulate Th2 responses [172] was shown to be mediated via immune-modulatory molecules present in the extracts of eggs or in products secreted by eggs (omega-1, IPSE, PRDX). These molecules can work via modulating DC [173] and basophils [174] and via machrophages [158]. Other human helminth parasites are also known to release modulatory molecules, such as AvCystatine, which is derived from *O. volvulus* worms and stimulates the preferential production of IL-10 by macrophages [175]. Much work is underway to characterize molecules from worms that are used as models of human infection. For example, from *Fasciola hepatica*, a molecule which is called *F. hepatica* helminth defense molecule-1 [176] can prevent LPS-induced activation of innate immune responses in macrophages, and from *H. polygyrus* the excretory–secretory antigen (HES) is able to induce Foxp3+ Treg via a TGF-ß-like activity [177]. Interestingly, vaccination by HES resulted in antibody production and protection against infection with *H. polygyrus* [178]. Thus, the study of immune modulatory molecules may provide new candidates for treatment of inflammatory diseases on the one hand and vaccines against parasites on the other.

Conclusions

Studies of helminth infections which seem to be able to modulate the immune system have provided detailed information on cellular mechanisms involved in pathology, immunity, and tolerance. Of particular interest has been the ability of these parasites to exert anti-inflammatory responses. On the one hand, this could potentially have detrimental consequences for co-infections or vaccination programs, while on the other hand it could exert beneficial effects on diseases that stem from strong inflammatory reactions. The identification of helminth-specific molecules with immune modulatory activities holds great potential as new therapeutics. However, the clinical implications of these parasites and their immune modulatory activities have yet to be determined in well-designed population studies.

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Conflict of interest All authors declare that they have no conflict of interest.

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