Chronic Helminth Infections Protect Against Allergic Diseases by Active Regulatory Processes

Hermelijn H. Smits · Bart Everts · Franca C. Hartgers · Maria Yazdanbakhsh

Abstract Developed countries are suffering from an epidemic rise in immunologic disorders, such as allergy-related diseases and certain autoimmunities. Several studies have demonstrated a negative association between helminth infections and inflammatory diseases (eg, allergy), providing a strong case for the involvement of helminth infections in this respect. However, some studies point in the opposite direction. The discrepancy may be explained by differences in frequency, dose, time, and type of helminth. In this review, new studies are discussed that may support the concept that chronic helminth infections in particular—but not acute infections—are associated with the expression of regulatory networks necessary for downmodulating allergic immune responses to harmless antigens. Furthermore, different components of regulatory networks are highlighted, such as the role of regulatory T and B cells, modulation of dendritic cells, early innate signals from structural cells (eg, epithelial cells), and their individual contributions to protection against allergic diseases. It is of great interest to define and characterize specific helminth molecules that have profound immunomodulatory capacities as targets for therapeutic application in the treatment or prophylaxis of allergic manifestations.

Keywords Helminth · Allergy · Dendritic cell · Treg cell · IL-10 · B cells

Introduction

The human immune system has evolved to mount appropriate defensive responses to various dangerous pathogens while tolerating or ignoring the innocent ones. The constant presence of chronic helminth, microbial, and protozoan infections and the daily risk of acquiring food-, water-, and vector-borne infections is still present in developing countries, whereas this was largely controlled in economically developed and Westernized countries during the 20th century. In contrast, Westernized countries now face very different problems: the epidemic rise in obesity, cardiovascular diseases, metabolic disorders, and hyperinflammatory diseases. As such, alarming increases have been observed in childhood allergy (eg, rhinitis, atopic dermatitis, and allergic and nonallergic asthma [1]), inflammatory bowel diseases (eg, Crohn's disease and ulcerative colitis), and autoimmune disorders (eg, type 1 diabetes and multiple sclerosis) [2]. It has been proposed that education of the immune system by certain microbes and parasites can prevent in part the development of inflammatory diseases [3]. Reduced infections due to improved health care and personal hygiene and decreased exposure to microorganisms and their products in our immediate environment as a result of urbanization may lead to insufficient stimulation of the immune system. This would result in an altered programming of the immune system and allow uncontrolled expression of inflammatory molecules, thus explaining the rise of inflammatory diseases in Westernized countries. Indeed, a large body of epidemiologic data indicates that some infectious agents tend to control inflammatory diseases, in which parasitic worms form an important group. In particular, the interplay between helminth infections and allergic disorders has been studied in great detail. In the current review, we focus on this interaction and highlight the importance of the infection dynamics and regulatory network. Helminth-induced mechanisms not only regulate host immunity to the worms, resulting in a mutually beneficial environment for survival of both parasite and host, but may also control the development

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of allergic diseases. Finally, we focus on the benefit of these new insights for the development of novel future therapies.

Do Helminths Protect Against Allergic Disease? Evidence from Population Studies

The number of studies on associations between allergic disorders and parasitic infections is still growing. One approach that is frequently used to determine the relationship between helminths and allergy is to study general parameters for allergic reactions, such as allergen skin prick provocation tests and questionnaires (clinician assessed or self-reported). However, this does not apply to all types/ aspects of allergic disease, as physician diagnosis is required at least for (allergic or nonallergic) asthma, eczema, or rhinitis in conjunction with clinical symptoms. A systematic meta-analysis of published findings attempted to compare a large number of studies related to intestinal helminth infection and different aspects of allergic disease [4]. However, sufficient conclusions could not always be drawn because of the relatively few studies that addressed physician-diagnosed clinical symptoms. As such, studies involving intestinal helminth infections did not yield a general consensus regarding protection against different forms of allergic disease.

However, caution should be taken in not overinterpreting the general conclusions because several crucial factors that are likely to influence the relationship between helminth and allergic disease need to be taken into account [5].

Timing

The time of first infection and duration of infection are likely to be important; early and/or long-lasting (chronic) infections are more efficient in downmodulating allergic disease, whereas later infections and/or sporadic, transient infections may enhance allergic clinical symptoms [6]. For example, the effect of geohelminths on the suppression of atopy is more important early in life and may cause a fixed deviated immune phenotype that is not changed later in life, after elimination of the infection [7]. Indeed, recent studies show that maternal geohelminth infections could affect infant immunity [8, 9], raising the possibility that the immunologic effects of infection start in the fetus.

Intensity

Heavy parasite burden may induce immune suppression, whereas mild infections may promote allergic disease. In the meta-analysis, all published studies were included that reported parasitic infection in at least 1% of the available study population [4]. This led to an enormous variation in

helminth intensities and species of parasitic helminths. In some endemic areas, close to 100% of the inhabitants may be infected, representing intense and chronic helminth infections, whereas in others, helminth infections can occur occasionally and in a small percentage of the population, with an intensity that is often mild. In areas with at least moderate endemicity for different species of helminth parasites, a considerable number of studies have demonstrated an inverse association between helminth infections and allergic disorders. For example, chronic infections with intestinal helminths (*Ascaris*, *Trichuris*, and hookworms) were reported to protect against allergic reactivity in populations in Venezuela, Gambia, Ethiopia, Taiwan, and Ecuador [10]. However, in areas endemic for other helminthes (eg, schistosomes or filarial), the presence of infections also seems to be associated with lower prevalences of allergies, as shown in studies in Gabon, Brazil, and Indonesia [10]. Similarly, chronic and intense *Schistosoma heamatobium* infections in Ghana were negatively correlated with the prevalence of atopic disease, whereas mild infections were not [11, 12]. Population studies in areas in which helminth infection intensities are low are conducted only sporadically [13, 14]; nevertheless, these low-intensity helminth infections seem to potentiate atopic disorders. In addition, some of the travelers to endemic areas who become infected with schistosomes develop acute schistosomiasis and can suffer from fever, lung eosinophilia, and pulmonary symptoms such as cough and shortness of breath [10].

Host Genetics

The ability to induce specific host immune regulatory mechanisms may be partially determined by host genetics. Individuals who are genetically susceptible to atopic disease may be more likely to develop allergic responses to helminth and allergens and may be genetically more resistant to infection [15]. On the other hand, people in rural Africa seem to suffer less from allergies, whereas people of African ancestry who live in affluent countries have a higher prevalence and greater severity of allergic symptoms than natives of these host countries, pointing to the involvement of genetic control in allergic diseases [12].

Different Helminth Parasites

Meta-analyses showed that infections with *Trichuris*, hookworm, or schistosomes were primarily negatively associated with allergen skin test reactivity, whereas hookworm infections were also associated with a reduced prevalence of allergic asthma [4, 16]. Although the sample size was too small for the meta-analysis, a similar association was found for schistosome infections and

asthma in individual studies [17]. In contrast, in some studies, *Ascaris lumbricoides* infection was associated with an increased prevalence of asthma, pointing toward the importance of the species of helminths in the relationship between allergies and helminths. In addition, helminth species for which humans are not the definitive host, such as *Toxocara* spp, and for which chronic infection cannot be established [18, 19] also seem to potentiate atopic disorders rather than protect against them.

Important lessons can be learned from intervention studies: short-term application of antihelminth drugs (<12 months) in Ecuador did not change the prevalence of atopy or clinical signs of allergy (wheeze) compared with the untreated group [20]. Deworming for 12 months in a large cohort of Vietnamese schoolchildren resulted in increased allergen sensitization, but not in clinical allergies such as eczema, wheeze, or rhinitis. However, long-term treatment for intestinal helminths (>22 months) in Venezuelan or Gabonese children resulted in increased allergen sensitization and skin prick test reactivity to house dust mite [21–23], supporting a direct link between chronic and intense helminth exposure and protection from allergy. To gain a better understanding of early immunologic influence and its interplay with genetic risk factors, this needs to be further addressed in large birth cohort intervention studies in helminth-endemic areas.

The Helminth Paradox

Helminths are master regulators of the host immune response, effectively minimizing immune attacks meant to expel the worms and thereby ensuring their survival in the host for years and limiting host tissue damage. They strongly induce polarized T-helper type 2 (Th2) responses, elevated serum IgE titers, and eosinophil-rich inflammation infiltrates in the tissue. However, despite this strong Th2 polarization, chronic infections do not induce clinical symptoms of allergic disease. This presents a paradox; however, further characterization of helminth-induced immune responses shows a strong regulatory network that is discussed in the context of disordered immunoregulation, as explained below.

Immune Suppression

It is postulated that chronic helminth infections can protect against allergic disease because of their profound suppression of the host immune system, leading to a general T-cell hyporesponsiveness that is facilitated by the induction of a regulatory network. Thus far, this network has been described to include the activity of regulatory T (Treg) and B cells and modulation of innate immune cells, such as macrophages, dendritic cells (DCs), and local stromal cells, resulting in an anti-inflammatory environment characterized by increased levels of interleukin (IL)-10 and transforming growth factor (TGF)-β [24]. This hyporesponsiveness is not only directed toward parasite antigens but seems to extend to bystander antigens, such as vaccine antigens or other pathogens. For example, impaired Th1 responses were reported to tetanus toxoid immunization [25] or against influenza virus in *Schistosoma*- or *Onchocerca*-infected patients [25, 26], and reduced immune responses to *Bacille Calmette-Guérin* (BCG) vaccination and to the cholera vaccine during intestinal helminth infection [27].

Several studies have described interactions between helminths and malarial parasites. Although the findings on malaria–parasite loads are controversial, data on malaria pathology seem more uniform, showing that helminth infection protects against renal failure and cerebral malaria [28]. Furthermore, a recent study showed higher IL-10 responses to malaria antigens in children infected with *S. haematobium* and/or different geohelminth species [29].

It is hypothesized that bystander immunoregulation by helminth infection can also control allergen-specific inflammatory responses and thereby lead to lower prevalence of allergies in helminth-infected individuals. However, control of bystander T-cell responses may depend on particular life cycle stages or the severity/intensity of an infection. Animal models offer great opportunities to dissect the interplay between pathogens such as helminths and allergic diseases. Several studies have been reported recently.

Lessons from Animal Models of Helminth–Allergy Interaction

To study the causal relationship between helminth infections and the development of allergic diseases, several groups have developed combined murine models of allergic inflammation, acute asthma, atopic dermatitis, and several different helminth species. For example, studies with rodent nematodes (eg, *Heligmosomoides polygyrus*) have demonstrated that infection leads to strongly reduced ovalbumin-driven eosinophilic airway inflammation and immune responses to food allergens, but not decreased symptoms of atopic dermatitis [30–32]. In part of these studies, the effect was dependent on Treg cells, whereas in others, it was reversed by treatment with blocking IL-10 antibodies [30, 33]. A similar inhibition of lung inflammation and airway hyperresponsiveness was demonstrated by *Ascaris suum* eggs, *A. suum* extract implants, or *Ascaris* worm products (eg, PAS-1) in an IL-10–dependent manner [34, 35] and correspondingly by infections with *Nippostrongylus brasiliensis* [36] or *Schistosoma mansoni* [37–39]. In
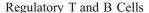
part of these studies, the suppressive effect was dependent on the activity of IL-10 [36–38] or on the activity of forkhead box P3 (FoxP3)[+] Treg cells [39].

However, a few studies showed no effect or a partial effect on airway inflammation, whereas some even found an exacerbation of allergic disease. For example, early infections with helminths such as *A. suum* [40] or *Toxocara canis* [41] potentiated airway inflammation, and infection with *Trichinella spiralis* increased anaphylaxis in mice [42]. The opposing effects of different parasitic helminths in murine models may suggest variations in the immune modulating capacity of distinct species. However, this paradox could also very well reflect the difference between acute and chronic stages of infection. Indeed, by exploring acute and chronic infections with *S. mansoni*, we have observed a clear dose-dependent reduction in ovalbumin-specific eosinophilic airway inflammation and airway hyperresponsiveness that was mediated by IL-10 during chronic, but not acute, infection [37].

All together, it seems that helminth infections at chronic stages are associated with general immunosuppression, which can have protective effects in different allergic disease models. The exact mechanisms by which these parasites dampen allergic responses are probably multiple. The next challenge is to find out which part of the regulatory network provides the strongest and most long-lasting allergen-specific inhibitory response, including the identification of the parasite antigens that are responsible for inducing this.

How Helminths Modulate Immune Responses

It is clear from a wealth of literature that both the worms and eggs of different helminths can modulate immune responses by affecting different types of innate and adaptive immune cells. Based on the evidence, a model can be put forth to explain how helminths suppress the host immune system and guarantee their own survival. In recent years, a great deal of new information has become available that explains the immune hyperresponsiveness by a complete regulatory network in which different cell types are involved. Next to polarized Th2 responses, the development of regulatory T and B cells and immune modulation of myeloid cells, such as DCs, or alternatively activated macrophages and early innate signals from epithelial cells seems to be an important element of a chronic helminth infection and could harbor putative targets that are important for inhibition of allergic diseases. The role of alternatively activated macrophages was recently discussed elsewhere [43] and is not addressed further here.

Regulatory T and B Cells

Several studies have shown that Treg cell activity (both by natural CD4^{+}CD25^{+}FoxP3^{+} and adaptive CD4^{+}IL10^{+} Tr1 cells) protects against allergic disease [44]. In contrast, patients with mutations in the *FOXP3* gene leading to a loss in the natural Treg compartment show several immune-mediated pathologies, including allergy, whereas the activity of allergen-specific Treg cells from asthmatic patients seems to be impaired [45]. Importantly, successful allergen-specific immunotherapy in humans—that which leads to a reduction in allergic symptoms—is associated with the emergence of IL-10–producing Treg cells. Simultaneously, the B-cell compartment is affected, which is evident from an increase in IgG$_4$ and IgA responses and a simultaneous decrease in IgE [46]. Central to helminth-induced immune regulation of allergic responses in humans is the cytokine IL-10, which may be produced by several different cell types, including helminth-induced regulatory T cells [47] and B cells [48], of which the Treg cells are clearly the most studied players.

For example, in patients suffering from onchocerciasis, antigen-specific IL-10 and/or TGF-β–secreting Treg cells were found [49, 50], whereas in patients infected with *Brugia malayi*, increased expression of FoxP3 (specific transcription factor of natural Treg cells) was demonstrated, as was the involvement of regulatory molecules such as TGF-β and cytotoxic T-lymphocyte antigen 4 [51]. Likewise, schistosome-infected individuals in Kenya and Gabon had higher CD4^{+}CD25^{hi} and CD4^{+}CD25^{hi}FoxP3 T-cell levels compared with uninfected individuals [52]. Importantly, CD4^{+}CD25^{hi}FoxP3 Treg cells have a clear immunologic impact on host immunity, as in vitro removal of CD4^{+}FoxP3 T cells from peripheral blood mononuclear cells of either geohelminth- or schistosome-infected schoolchildren restored BCG-specific proliferation and interferon-γ production [53], a phenomenon that was not observed in endemic controls.

In animal models, chronic nematode infection increased the number of FoxP3^{+} T cells [24], while in chronic schistosome infections, some studies noted increases in FoxP3^{+} T cells [24], whereas others did not [54]. Nevertheless, the frequency of CD103 on Treg cells increased during disease progression [54], suggesting that these cells become more active during chronic schistosomiasis [55].

Elevated IL-10 has been reported in many human and murine studies in the context of helminth infections, but the source and role of IL-10 seem to vary in response to different helminth species. In some experimental models, the high IL-10 levels were attributed to adaptive Treg cells [30, 31, 56, 57], whereas in others, IL-10 has been linked to non-Treg populations [38, 54, 58]. By using IL-10–deficient mice and by adoptive transfer of different cell subsets, it was shown that both T-cell and non-T-cell-

derived IL-10 play an essential part in helminth-induced immune modulation [56, 58, 59]. One important alternative source of IL-10 could be the B cell.

B cells possess a variety of immune functions, including production of antibodies, presentation of antigens, and production of cytokines. A large body of literature—in particular on models of autoimmunity, but also on transplantation and cancer—shows that IL-10-producing B cells have great potential to regulate T-cell-mediated inflammatory responses and therefore are named *regulatory B cells* [60, 61]. For example, IL-10-producing regulatory B cells were shown to downmodulate experimental autoimmune encephalomyelitis, collagen-induced arthritis, and inflammatory bowel disease [60]. In addition, in models of chronic parasitic inflammation, such as chronic schistosomiasis and filariasis, IL-10-producing B cells were reported [37, 62, 63] and associated with reduced pathology and modulation of T-cell responses [64, 65].

Thus far, most evidence comes from murine models and needs to be confirmed in humans. Nevertheless, a few studies have focused on B cells in human populations. For example, helminth infection in multiple sclerosis patients was associated with reduced disease activity; the B cells from these patients displayed enhanced production of IL-10, in particular a CD1d^{hi} subset that was correlated with in vitro inhibition of T-cell proliferation [66]. Similarly, we found increased circulating IL-10-producing CD1d^{hi} B cells in *S. haematobium*-infected Gabonese patients.

Although the concept that regulatory B cells can dampen allergic inflammation still needs to be established in particular in humans, a small number of allergy studies in murine models have already provided supportive evidence. For example, B cells were responsible for the induction of local inhalation tolerance by inducing Treg cells during continuous allergen exposure [67]. In addition, transfer of schistosome-induced, IL-10-producing B cells strongly reduced inflammation in different models of allergic inflammation [37, 38, 63]. Interestingly, in *H. polygyrus*-infected, allergen-sensitized mice, mesenteric lymph node CD23^{hi} B cells transferred protection against allergic airway inflammation in an IL-10-independent manner [68]. Future studies must dissect the role of the different (regulatory) B-cell subsets in immune suppression and protection against allergic disease.

Immune Modulation of Dendritic Cells by Helminth Products

DCs residing in the mucosal lining of various peripheral tissues are central to the generation and polarization of adaptive immune responses. The main functions of DCs are to patrol the environment for possible danger signals, immediately activate local innate immune cells, and subsequently initiate appropriate adaptive immune responses in which the function and cytokine production of lymphocytes are completely determined by instructions from the DCs. DCs—but also other innate immune or resident tissue cells—are ultimately equipped to recognize a great variety of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns by means of various families of pattern-recognition receptors, of which the families of the Toll-like receptors (TLRs), NOD-like receptors, RIG-like receptors, and the C-type lectin receptors (CLRs) are presently the best known. As a consequence of ligation of different pattern-recognition receptors, DCs will receive signals that are subsequently translated into different sets of Th1-, Th2-, Th17- or Treg-polarizing molecules [69].

Thus far, a few signature molecules of various helminths have been identified that can modulate DCs to drive strong Th2 or Treg cell responses, a hallmark of helminth infections. The most prominent example is omega-1, a glycoprotein derived from schistosome eggs that specifically primes DCs to drive polarized Th2 responses [70, 71]. Its target receptor or signaling route is currently unknown, although it has been suggested that its ribonuclease activity is involved in its capacity to condition Th2-priming DCs [71]. Another clear example is ES-62, a secreted phosphorylcholine-containing glycoprotein of the filarial nematode *Acanthocheilonema viteae*, as it conditions DCs to induce Th2 responses via activation of TLR4, as it is primarily mediated by its phosphorylcholine moiety [72]. Also, lacto-N-fucopentaose III (LNFPIII)/Le[x], a glycoconjugate carrying a carbohydrate structure found in schistosomes, has been implicated in TLR4-dependent priming of Th2 responses via DCs [73]. However, the significance of this latter finding remains controversial, as schistosome-soluble egg antigens (SEAs) harboring this same Le[x] motif have been shown not to bind to TLR4 [74, 75] and are quite capable of modulating DCs for Th2 priming in the absence of TLR signaling [76]. Ligation of TLR2 by helminth molecules seems to be more important for the conditioning of DCs to drive regulatory responses. Monoacetylated phosphatidyl serine lipids from schistosomes specifically instructed DCs to preferentially induce IL-10-producing Treg in a TLR2-dependent fashion [77], and although less potent, phosphatidylserine lipids derived from *Ascaris* worms had a similar effect [75]. Likewise, a recent report described the induction of Treg cells by *Schistosoma japonicum* HSP60-derived, peptide-treated APC in a TLR2-dependent manner [78]. Recent reports even cite a clear link between Treg cells and TLR2, as TLR2-deficient mice showed a reduced number of CD4^{+}CD25^{+} Treg cells and immunopathology during schistosomiasis that was controlled by TLR2-primed Treg cells [79]. Interesting in this respect is the observation that Treg cells can respond

directly to TLR2 ligands, such as Pam3Cys, but not to ligands of other TLR receptors, and this augments Treg cell proliferation [80, 81].

Apart from TLRs, a growing body of evidence indicates that CLRs—recognizing sugar moieties—also play an important role in the sensing of helminth glycans by DCs. The glycoproteins from SEAs are recognized and internalized by human DCs in a DC-SIGN (specific intercellular adhesion molecule-3-grabbing nonintegrin)-, mannose receptor-, and macrophage galactose-type lection-dependent manner [74, 82]. The binding of SEAs to DC-SIGN was found to be dependent on sugar motifs Le[x] and LDN-F, while chemical modification of the glycans present in SEAs abolished the Th2-driving capacity of SEAs [83]. This, together with the observation that Le[x]-containing LNFPIII favors Th2-biased responses [84] strongly suggests that CLRs play a dominant role in conditioning DCs for induction of Th2 responses by schistosomal antigens. Moreover, antigens from *T. canis* have been recognized by DC-SIGN expressed on DCs [85], whereas the induction of a Th2 response in vivo by antigens of the parasitic nematode *B. malayi* as well as the free-living nematode *Caenorhabditis elegans* was found to be dependent on intact glycans [86]. This suggests that Th2 biasing by helminth glycans is a general phenomenon and that helminth glycans may serve as a conserved molecular pattern that instructs DCs via CLRs to drive Th2-polarized responses.

Many helminth products show the inability to classically activate DCs, as exemplified by a mixture of high molecular weight components from *A. suum* that reduced the expression of major histocompatibility complex (MHC)-II, CD80, CD86, and CD40 molecules on mouse CD11c^{+} DC, leaving the cells hampered to support strong T-cell proliferative responses in vitro. The inhibitory effect was abolished in IL-10-deficient mice [87]. Similarly, SEAs also lack the capacity to classically activate DCs [88]. As such, the concept has been put forth that helminth products actually potently suppress TLR-mediated DC activation by other microbial PAMPs. This was confirmed by many studies showing the inhibitory effects of helminth-derived components on TLR-induced activation as determined by inhibition of proinflammatory cytokine production and expression of MHC-II/costimulatory molecules [89]. The pathways underlying this suppression are still poorly understood. Interestingly, the suppression of TLR-mediated responses by helminth antigens has striking similarities to the effects induced by several microbial pathogens that target DC-SIGN [90].

Overall there is a consistent picture that helminth products, regardless of whether they interact with TLRs or CLRs, fail to induce conventional DC maturation [91] and inhibit DC activation induced by proinflammatory PAMPs, which could impair Th1 development and bias the immune response toward Th2 or regulatory responses.

Early Innate Signals from Neighboring Cells

Recent studies in mice with repeated airway delivery of native allergens or respiratory viruses have highlighted the critical role of innate signaling in the generation of allergic pulmonary inflammation, which shows that the complex immunologic response not only includes Th2 cell-driven inflammation, but also the participation of Th1, Th2, Th17, natural killer T cells, and airway epithelial cells (ECs). ECs in particular can influence the functions of local immune cells via the expression of a wide range of molecules, including MHC-I and MHC-II, costimulatory molecules, chemokines, cytokines, and prostaglandins. During the past few years, a particular interest has been growing in three novel EC-derived cytokines, thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, and their ability to influence innate and adaptive immunity associated with Th2 cytokine-mediated inflammation at mucosal sites [92, 93]. TSLP affects DCs, T cells, natural killer T cells, and mast cells. IL-25 primarily influences macrophages, Th2 cells, eosinophils, and mast cells. IL-33 acts on T cells, mast cells, eosinophils, and basophils, illustrating the broad role of these cytokines in the regulation of inflammatory/allergic processes [93]. However, these cytokines seem to have dual functions, as they are involved in the development of protective Th2 cytokine responses in the context of helminth infections and strongly promote pathologic responses in cases of allergic inflammation [94]. In view of the hypothesis that certain helminth infections may protect against allergic diseases, it seems contradictory that helminths also induce these strong allergic inflammation-inducing cytokines. However, the location and timing may be important factors. For example, TSLP expression in the skin and lung has been linked to pathologic Th2 cytokine-mediated responses, whereas TSLP expression in the intestine seems to play an important role in host protective immunity, as TSLPR-deficient mice challenged with *Trichuris* failed to clear worms after infection [95]. However, TSLP does not seem to be essential to every intestinal helminth because the development of protective Th2 immune responses after infection with *H. polygyrus* and *N. brasiliensis* was still intact in TSLPR^{−/−} mice [96]. Similarly, using the same knockout mice, it was found that TSLPR signaling played only a minor role in the development of Th2-dependent pathology in the lung, liver, and intestine against *S. mansoni* eggs [97]. Collectively, these findings suggest that although TSLPR signaling serves a key role in allergen-driven Th2 responses, it exerts only restricted regulatory activity during certain chronic helminth infections. Similar to TSLP, IL-25 is required for the development of a Th2 cytokine-mediated response and protective immunity following *Trichuris* or *Nippostrongylus* infection, as IL-25-deficient mice could not clear the

infection or showed a delayed expulsion [98, 99]. At this stage, it is unclear whether IL-25 is induced only at the beginning—during the acute phase of infection—and how its activity is influenced by the immunoregulatory processes that take place during chronic and severe helminth infections. Little is known about IL-33 induction by helminths; thus far, its presence has only been described following infection with *Trichuris*, in which the expression peaked early during infection, indicating that IL-33 acts primarily during the initiation of these responses [100]. More studies must be carried out to evaluate the role of IL-33 in helminth infection, although initial studies favor a model in which IL-33 is induced early during infection and not so much during chronic—allergy-protective—stages.

In helminth-infected or nonallergic, healthy individuals, T cells remain nonresponsive to harmless allergens, likely by actively created mucosal tolerance. New concepts are being introduced that suggest that mucosal tolerance to allergens may result from "tolerant" cross-talk between lung ECs and mucosal DCs. In this respect, lessons can be learned from the gut, in which intestinal ECs were found to drive the differentiation of Treg-promoting DCs via the expression of TGF-β and retinoic acid [101]. Likewise, a similar role in homeostasis is suggested for lung ECs via promotion of anti-inflammatory and prophagocytic cells (eg, primary bronchial ECs induced macrophage differentiation from monocytes [102], whereas a lung epithelial cell line inhibited IL-12 and tumor necrosis factor-α production from antigen-presenting cells) [103]. Tolerance induction in the gut is strongly dependent on steady-state recognition of normal microbiota, as demonstrated in germ-free or knockout mice for specific TLRs, which recognize conserved microbial motifs [104]. Interestingly, molecules from several microorganisms could also induce IL-10 production in lung epithelial cell lines [105, 106]. These recent findings point toward a novel and exciting concept that microbial organisms can influence tolerance under homeostatic conditions by influencing cross-talk between ECs and other immune cells and pose the question of in which respect helminth species could interfere in the cross-talk of ECs and other immune cells.

Therapeutic Application

The case is now building that the epidemic rise in immunologic disorders in Westernized countries—for allergic diseases in particular—can be explained by a dysfunctional immune regulation resulting from decreased parasitic infections (eg, helminth infections). The question remains as to how this newly gained insight can help to stop the allergic March or to treat patients once they have become allergic. In search of novel therapies, it would be ideal to exploit the ability of chronic helminth infections to modulate the immune system. Promising results have been obtained by treating colitis patients with *Trichuris suis*, a whipworm that naturally infects pigs, and worm-based therapies are under development at several pharmaceutical companies [2]. Nevertheless, it would be more practical to focus on individual helminth-derived immunomodulatory molecules to selectively induce regulatory immune responses and avoid any possible side effects of natural worm infections. Some laboratories are isolating agents from helminths that could prove useful as therapeutic agents. These immunomodulatory parasite-derived compounds (detailed above) would form an ideal basis for therapeutic application in the treatment of hyperinflammatory disorders. However, one caveat in this immunoregulatory scenario is the possible interference with essential responses to other antigens, such as those contained in vaccinations, or to life-threatening pathogens. Therefore, serious efforts should be made to generate antigen-specific immunoregulation in order to circumvent dangerous side effects.

Conclusions

There is evidence that chronic, but not acute, helminth infection is driving responses that protect against allergic disorders. It is hypothesized that particularly during the course of chronic diseases, immunoregulatory processes are switched on (eg, the development of regulatory T and B cells, possibly via their priming by DCs, or innate signals from epithelial cells that have been in contact with certain signature immunomodulatory molecules). In view of these conclusions, it would make sense to focus on molecules that are expressed during the chronic phase of infection. A few molecules have been identified (detailed previously) that would make suitable candidates for therapy. It is important that efforts be made to bring these molecules to the clinic, preferably coupled to allergens to target allergen-specific changes and allow low concentrations to be effective.

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