

Helminth Infections: Protection from Atopic Disorders

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Westernized countries are suffering from an epidemic rise in immunologic disorders, such as childhood allergy. A popular explanation is that the increased prevalence in allergy is due to a diminished or altered exposure to gut-dwelling microbes, resulting in a disordered immunoregulation. Various population studies have provided a strong case for the involvement of helminth infections in this respect. Detailed analysis of helminth-induced immune responses showed that helminths not only prime for polarized Th2 responses but also potently induce T-cell hyporesponsiveness. Recently, it has been demonstrated that helminths induce suppressed host immune responses by the priming for regulatory T cells. It is proposed that this regulatory T cell-inducing activity accounts for the protection observed in the development of allergic disorders. It would be interesting to define and characterize particular helminth molecules that have profound immunomodulatory capacities as a target for therapeutic application in the treatment or prophylaxis of allergic manifestations.

Introduction

Since humans emerged as a species, they have had a constant battle with infectious agents. The immune system evolved to mount appropriate defensive responses to various pathogens, ranging from large multicellular intestinal helminths to intracellular viruses, bacteria, or protozoa, with the aim of expelling the invader with minimal host-tissue damage. The constant presence of chronic helminthic and protozoan infections and a daily risk for 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 course of the 20th century. In contrast, westernized countries now face very different problems related to the epidemic rise in several immunologic disorders. Alarming increases have been

observed in childhood allergy [1], such as rhinitis, atopic dermatitis and asthma, inflammatory bowel diseases (IBD; eg, Crohn's disease and ulcerative colitis), and autoimmunities, such as type 1 diabetes and multiple sclerosis (MS) [2,3]. The essential question is whether the increased incidence of these immunologic disorders is related to the rapid decrease in infectious burden, and, if so, whether this results from decreased stimulation of the immune system by particular infectious agents. In this review, we highlight the current understanding and latest findings supporting the popular "hygiene hypothesis," with emphasis on the role of helminth infections in the allergic march. Additionally, we focus on the benefit of these new insights for the development of novel future therapies.

Hygiene Hypothesis: Evidence from Population Studies

The hygiene hypothesis was initially proposed by Strachan [4] based on a study demonstrating that allergic rhinitis was more prevalent among first-borns and less frequent in children from large families. He suggested that frequent exchange of childhood infections among siblings in large families was responsible for the lower incidence of allergic diseases. Since then, many studies have examined the relationship between infections and allergy. Studies on the prevalence of allergy either in distinct geographic areas (developing versus westernized countries) or among populations with different lifestyles associated with a variable pathogen exposure often point toward a negative association between microbial exposure and allergy (Fig 1). For example, daycare attendance [5] or an anthroposophic lifestyle [6], both of which are expected to result in higher exposure to infectious agents, have a protective effect on the development of allergic disorders. Similar findings have been described for "traditional farming" by Riedler *et al.* [7], who showed that frequent visits to stables with livestock and poultry and intake of farm milk during the first year of life has a strong protective effect on the prevalence of allergic diseases. Again, it is assumed that the farming environment represents a microorganism-rich milieu. Indeed, more detailed studies comparing farmers' and non-farmers' children show an inverse correlation with the development of allergy and asthma and the concentration of particular microbial com-

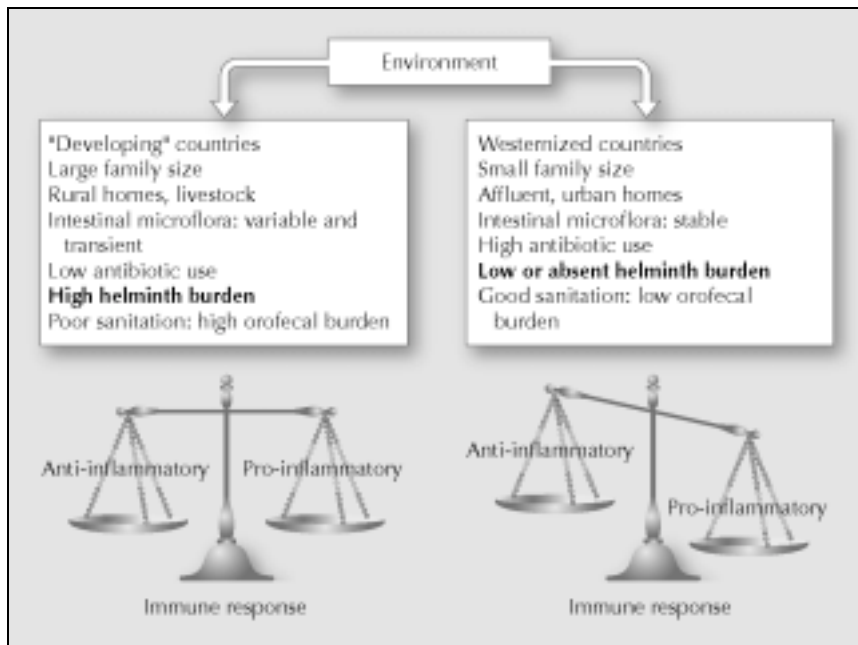


Figure 1. Schematic overview of risk factors associated with increased prevalence of immune disorders, such as allergic diseases or several organ-specific autoimmune diseases.

pounds measured in the children's mattresses, such as endotoxin or muramic acid [8,9].

Orofecal microorganisms

Results from the above-mentioned studies do not answer the question of which particular microorganisms are responsible for protection from allergic diseases. Important clues in this respect were initially presented by a study of Italian military recruits that showed an inverse relationship between the presence of antibodies to certain foodborne and orofecal infections, such as *Toxoplasma gondii*, *Helicobacter pylori*, and hepatitis A virus, and various manifestations of allergic diseases [10••]. Subsequently, similar findings were reported in large general US or Danish population samples [11,12]. Strikingly, this correlation was completely absent for several typical childhood diseases caused by airborne microbes, such as mumps, rubella, chickenpox, herpes simplex virus type I, and cytomegalovirus [10••]. It has been proposed that these findings merely provide examples of orofecal and foodborne microbes, a consequence of intake of contaminated food and water. The studies argue for a general role of orofecal microorganisms and the presence of particular microorganisms in the gastrointestinal tract to prevent allergic manifestations [13]. This is further underlined by the protective effect of mud-dwelling saprophytic mycobacteria, such as *Mycobacterium vaccae*, in an experimental asthma model [14]. In addition, large differences are observed in the composition of gut flora between westernized and developing countries, pointing at a larger diversity and higher turnover rate of colonized bacteria in developing countries [15,16]. This can be important with respect to the development of allergic disorders, as marked differences were found in the microflora composition of allergic versus nonallergic 2-

year-old children, such as less colonization of lactobacilli in the allergic subjects [17,18].

Some key studies in germ-free animals demonstrate the importance of the interaction among the gastrointestinal tract microorganisms for a normally functioning immune system. In these mice, it was not possible to establish oral tolerance, a condition that results in hyporesponsiveness to orally administered proteins [19]; however, the co-administration of endotoxin improved the tolerizing effect [19,20]. This suggests again that the induction of tolerance to control inflammatory reactions is dependent on sufficient microbial exposure and that repeated exposure to an infection that enters via the gut or involves an intestinal phase could contribute to the establishment of a tolerogenic response.

Helminth infections

Relatively few studies have been described that link bacterial or viral infections to the prevalence of allergic diseases. In contrast, the number of studies on the association between allergic disorders and parasitic infections are growing. First examples were published by Lynch *et al.* [21,22], demonstrating that chronic infection with intestinal helminths (such as ascaris, trichuris, hookworms) protected from allergic reactivity. These observations have been confirmed by other studies in Ethiopia [23], in Gambia [24], and in Ecuador [25]. Also other helminths, such as schistosomes or filaria, appear to be associated with a lower prevalence of allergy, as shown in studies in Gabon [26•], Brazil [27], and Indonesia (Djuardi *et al.*, Unpublished data), respectively. Strikingly, anti-helminth treatment in Venezuelan or Gabonese children resulted in increased atopic reactivity to house dust mite [22,28••], supporting a direct link between helminth exposure and protection from allergy.

The Helminth Paradox

Helminths are long-living, multicellular parasites that are responsible for chronic infections. Helminths can be found in a great variety of niches, ranging from blood vessels to the gut, and from skin to various other internal tissues. Importantly, adult worms can be the source of millions of eggs that deposit over many years in the mucosa of the gastrointestinal tract and urinary bladder, causing, altogether, a very high morbidity, whereas direct mortality remains low. Helminths have strong polarizing effects on the immune responses of their hosts with diverse characteristics. There is a strong skewing of immune responses toward Th2, hallmarked by a secretion of interleukin (IL)-4, IL-5, and IL-13. Interestingly, allergic reactions are also mediated by allergen-specific Th2 responses. This presents a paradox, considering that the immunologic framework of the hygiene hypothesis was at first explained as a dysfunctional Th1/Th2 balance. It was suggested that, due to a lower exposure to Th1-inducing pathogens, the neonatal immune system would receive insufficient signals to correct Th2 responses during childhood. Neonatal Th2 responses are normally present at birth and are thought to be imposed by the maternal immune system during pregnancy to prevent Th1-mediated fetal rejection. However, recent characterization of helminth-induced immune responses have lead to a re-evaluation of this model, which is discussed later in the context of disordered immunoregulation.

Immune suppression

During the chronic phase of helminth infection, polarized Th2 responses, although present, are less pronounced than at the beginning [29]. This could result from T-cell hyporesponsiveness with elevated IL-10 levels, seen in helminth-infected individuals [26•,30]. It is argued that this immunosuppressed phenotype is instrumental in the parasite strategy for survival and may, at least in part, be accounted for by helminth-induced regulatory T (Treg) cells. Indeed, in patients suffering from onchocerciasis, such antigen-specific Treg cells could be isolated, characterized by the secretion of elevated levels of IL-10 and/or transforming growth factor (TGF)- β and the inhibition of the proliferation of other T cells [31–33]. Several observations indicate that this suppression is not strictly antigen-specific and is extended to third-party antigens [26•,30]. For example, several studies have described a protective effect from *Ascaris* infections on cerebral malaria attacks [34,35]. Alternatively, the additional burden of helminth infection increases the frequency of malaria attacks [36]. Furthermore, blunted responses have also been reported to tetanus toxoid (TT) immunization in *Schistosoma*- and *Onchocerca*-infected patients [37,38].

Profound immune modulation has been observed in experimental models of helminth infection. In addition to the systemic Th2 bias, immune responses to other antigens are often impaired. Functionally, *S. mansoni*-infected mice are impaired in vaccinia virus clearance, with weaker cytotoxic T lymphocyte (CTL) and type 1 cytokine responses

[39]. However, in the *Plasmodium berghei* mouse model, co-infection with *Brugia pahangi* larvae protected against the development of cerebral malaria, significantly prolonging their survival [40]. In addition, infection with *S. mansoni* modulates immune responses to non-parasite antigens, such as sperm whale myoglobin (SwMb), reducing SwMb-specific cytokine production and T-cell proliferation. Importantly, this inhibition was IL-10 dependent [41]. Additionally, in transplantation, *Nippostrongylus brasiliensis* delays the rejection (averaging 32 days in infected and 10 days in control animals) of allogeneic kidney grafts [42].

The question remains whether the suppressive effect on the immune system during the chronic phase of helminth infections can inhibit or prevent the onset of Th2-mediated allergic reactions or Th1-driven autoimmune responses. Animal models offer great opportunities to dissect the interplay between pathogens, such as helminths, and either allergic or autoimmune diseases. Several studies on both disease models have been reported recently.

Animal models of helminth-allergy interaction

Bashir *et al.* [43•] demonstrated that allergic responses, both allergen-specific IgE and IL-13 production to peanut, were downmodulated by infection with the nematode *Heligmosomoides polygyrus*, which is a natural infection in mice. Importantly, the effect was reversed when animals were treated with anti-IL-10. Additionally, Wilson and Maizels [44] used a chronic infection model of *H. polygyrus* and demonstrated a strong reduction in ovalbumin (OVA)-driven eosinophilic airway inflammation. Another study reported a similar inhibition of lung inflammation and airway hyperresponsiveness using *Ascaris suum* extract implants [45•] or infection with *N. brasiliensis* [46]. Importantly, infection with *N. brasiliensis* in IL-10-deficient mice strongly increased allergen-induced airway eosinophilia and other inflammatory parameters in comparison with control mice, supporting the view that immunosuppressive activities during helminth infections can inhibit allergic disorders [46].

However, there are also a number of studies showing no effect or a selective effect on a few immunologic markers, such as T-cell cytokine responses or allergen-specific IgE production, but no decrease in the ultimate eosinophilic airway inflammation [47,48]. Nevertheless, this could also reflect the difference between the acute phase compared with the chronic stage of infection. Parallel observations are also made in humans. In areas where helminth infections occur only occasionally and are more transient in nature, they appear to potentiate allergic reactions, and act as risk factors for atopic disorders [21,49].

Animal models of helminth-autoimmunity interaction

Disease models of various autoimmune disorders describe profound ameliorating effects of helminth infections. For example, in experimental encephalomyelitis (EAE), concomitant infection with *S. mansoni* reduces muscle paraly-

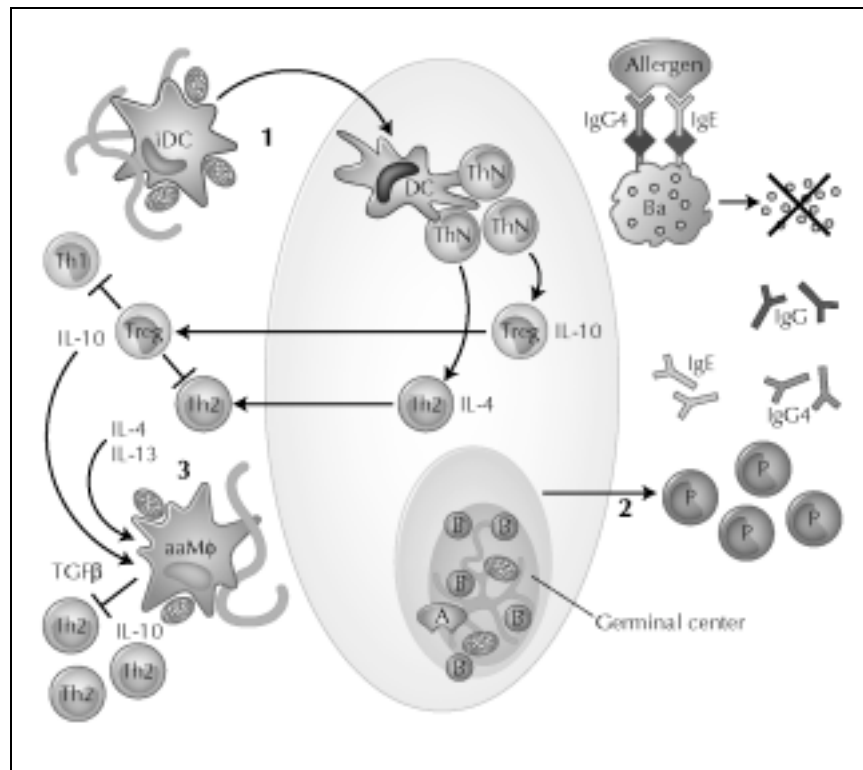


Figure 2. Overview of immune modulation by helminths (1). Immature dendritic cells (IDC) become activated by the exposure to either (compounds from) eggs (rod-shaped symbols) or worms and will migrate through the draining lymph nodes (LN), while acquiring a mature phenotype. In the LN, they will drive the development of polarized Th2 and regulatory T (Treg) cells, expressing IL-4 and IL-13 or IL-10, respectively. These Treg cells, once they have migrated to the local site of inflammation, can inhibit the proliferation and effector function of other T cells (2). Upon parasitic exposure together with harmless antigens, such as allergens, mature germinal centers (GC) are formed in the lymph nodes. In the GC, B cells (B) are selected that recognize specific antigens, such as allergenic antigens, and will receive signals to develop into antibody-producing plasma cells (P). Due to the fully mature GC formation, not only IgE-producing plasma cells are formed but also IgG4- and IgG-producing cells. Upon cross-linking of both allergen-specific IgG4 and IgE molecules on basophils, inhibitory signals by Fc γ RIIb will block IgE-driven signaling via the Fc ϵ RI, preventing the degranulation of the basophils (3). Both the cytokines of Th2 cells and Treg cells, such as IL-4, IL-13, and IL-10, as well as compounds from eggs or worms, can change the activation state of macrophages (M Φ), resulting in alternatively activated M Φ (aaM Φ). AaM Φ produce high levels of IL-10 and TGF- β , which is instrumental in inhibiting the proliferation of other T cells, such as Th2 cells. IL—interleukin; TGF—transforming growth factor.

sis and inflammatory cell infiltration in the central nervous system, while switching the cytokine profile from interferon (IFN)- γ to IL-4 [50]. Infection of nonobese diabetes (NOD) mice with *S. mansoni* reduces the incidence of diabetes by 50% [51]. Administration of *S. mansoni* eggs in an experimental model of Crohn's disease decreased the mortality from approximately 70% to 30%, while deviating the cytokine response from IFN- γ to IL-4 [52]. Additionally, intraperitoneal injection of the filarial-derived glycoprotein ES-62 during the development of collagen-induced arthritis (model for rheumatoid arthritis) strongly suppressed the severity of disease and was associated with a decreased production of proinflammatory/Th1 cytokines, such as tumor necrosis factor (TNF)- α , IL-6, and IFN- γ [53]. Although the studies discussed show clear reductions

in disease activity, it is unclear whether this is achieved by helminth-induced immunosuppression or by a shift from Th1 to Th2 cytokine profiles. Nevertheless, co-infection of *H. polygyrus* in the experimental model for gastric ulcers, an autoimmune-type pathology caused by *Helicobacter* infection, points toward immune-suppressive mechanisms, as the protective effect is associated with reduced inflammation and elevated levels of IL-10 and TGF- β [54].

It appears that helminth infections at chronic stages are associated with general immunosuppression, which can have protective effects in either allergy or autoimmune-disease models. The exact mechanism by which these parasites affect the immune system is still unclear, as well as which parasite antigens are responsible for dampening immune activation.

How Helminths Can Modulate Immune Responses

It is clear from a wealth of literature that both 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 proposed on how helminths suppress the host immune system and guarantee their own survival (Fig 2). Crucial elements are the development of Th2 and Treg cells in adaptive immune responses, excess inhibitory IgG4 production as a result of a “modified Th2 response,” and the induction of so-called suppressor, alternatively activated macrophages.

Polarized Th2 and Treg responses

Dendritic cells (DC), residing in the mucosal lining of various peripheral tissues, are central to the generation and polarization of adaptive immune responses. The main function of DC is 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 is completely determined by instructions from the DC. DC, but also other innate immune or resident tissue cells, are ultimately equipped to recognize a variety of different pathogen-associated molecular patterns (PAMP) by means of various families of pattern-recognition receptors (PRR), of which the families of the Toll-like receptors (TLR) and the C-type lectins, recognizing different carbohydrate moieties, are currently the best studied. As a consequence of ligation of different PRR, DC will receive signals that are subsequently translated into different sets of Th1-, Th2-, or Treg-polarizing molecules [55].

A few signature molecules of various helminths have been identified that can modulate DC to drive strong Th2 responses, a hallmark of helminth infections. An important molecule in this respect is ES-62, a secreted phosphorylcholine-containing glycoprotein of the filarial nematode *Acanthocheilonema viteae*. Also, soluble egg antigens (SEA) of *S. mansoni* contain several sugar structures that appear to play an important role in Th2 cell polarization, such as α 3-fucose- and β 2-xylose-containing N-glycans [56]. The molecule Lacto-N-fucopentaose III (LNFPIII) may be of particular importance in this respect, as it can confer Th2-inducing properties to non-schistosome proteins to which it is coupled [57]. Although LNFPIII specifically binds to the C-type lectin DC-specific intracellular adhesion molecule (ICAM)-3 grabbing non-integrin (DC-SIGN) via the Lewis X trisaccharide [58], its Th2-promoting activity appears to be dependent on the ligation of a different PRR—TLR4 [59]. Similarly, *N. brasiliensis* excretory-secretory (NES) glycoproteins have Th2-promoting activity on DC [60] and a Th2-inducing adjuvant function on bystander antigens [61]. The exact nature of molecules involved in NES are unknown; however, the activity is heat labile and protease sensitive [61]. The Th2-driving capacity of adult *Brugia* extracts also critically depends on the presence of intact glycans, as this

activity is abolished by periodate treatment [62]. It appears that helminth glycans provide a major contribution to the induction of Th2 development.

There is a strong case, both in human and animal studies, that chronic helminth infections are associated with a general hyporesponsiveness in which the activity of Treg cells may play a crucial role. Indeed, in animals infected with *S. mansoni*, the presence and function of Treg cells has clearly been established [31,63]. However, currently little is known about particular helminth molecules that can induce Treg cells. Nevertheless, it has recently been reported that schistosomal lyso-phosphatidylserine (lyso-PS), containing acyl chains that differ in length and possibly in the position of the double bond from mammalian lyso-PS, can modulate DC to drive polarized IL-10-producing Treg responses in vitro [64•]. Interestingly, this modulating activity was TLR2-dependent [64•]. Furthermore, unpublished data from our lab show that lipids with similar immunomodulatory activities can be isolated from *A. lumbricoides* (van Riet *et al.*, Unpublished data).

“Modified Th2 responses” and IgG4

In addition to the induction and prolonged activity of Treg cells, several other possibilities have also been put forward to explain the general immune suppression seen in helminth-infected patients and the subsequent protection from allergic manifestations. Recently, the concept of “modified Th2 responses” has been put forward by Platts-Mills *et al.* [65••], based on the observation that living indoors with cats forms a protective factor for the development of childhood allergy. Further examination revealed high allergen-specific IgG and IgG4 antibody levels instead of the IgE subtype for allergy-protected cat owners. IL-10 augments IL-4-dependent IgG4 antibody switching but reduces IgE antibody switching [66] and could contribute to the “modified Th2 response” launched by Platts-Mills *et al.* [65••]. The protective role of allergen-specific IgG4 antibodies in allergy has been supported by the findings that, upon allergen immunotherapy, in addition to IL-10-producing T cells, increasing levels of IgG4 antibodies are seen [67].

IgG4 antibodies do not activate complement and have little or no inflammatory activity. It has been proposed that IgG antibodies can function as blocking antibodies by competing with IgE for allergen binding to mast cells, basophils, and other IgE-expressing cells [68]. Another potential anti-inflammatory effect of IgG could be mediated through coaggregation of inhibitory Fc γ RIIb receptors with high-affinity Fc ϵ RI IgE receptors. Fc γ RIIb receptors contain a negative signaling immunoreceptor tyrosine-based inhibitory motif (ITIM) that can be phosphorylated by Fc ϵ RI-associated kinases, resulting in ITIM-dependent auto-inhibition of its own Fc ϵ RI signaling. Subsequent potentiation of this coaggregated receptor interaction by a chimeric Fc γ -Fc ϵ construct resulted in an inhibition of allergen-IgE-dependent histamine release by human basophils [68]. Interestingly, during chronic parasite infections, such as *Bancroftian* [69]

and *Brugian* [70] *filariasis*, extremely high levels of IgG4 have been demonstrated. Moreover, filarial antigen-specific IgG4 has been shown to block IgE reactivity in vitro [69]. Finally, recent studies in Ecuador showed that children with IgG4 to *Ascaris* have a lower frequency of atopy than those who were IgG4-negative [25].

Aalberse and Platts-Mills [71] have proposed a crucial potentiating role for danger signals in class-switching of B cells in germinal centers. It was suggested that the survival of IgE-switched B cells is compromised in an active germinal center. Thus, antigenic stimulation in the presence of an activating pathogenic (*ie*, helminth-derived) signal (*eg*, by triggering of several PRRs) will lead to the development of mature germinal centers in which IgE-switched B cells are eliminated. Depending on the cytokine microenvironment, several IgG- (and IgG4-) producing plasma cells will develop instead. In contrast, antigenic stimulation by allergens, in the absence of a pathogenic signal, fails to induce mature germinal centers, allowing the IgE-switched B cells to escape and mature into allergen-specific, IgE-producing plasma cells, a hallmark characteristic of allergic diseases.

The model suggests that once enough pathogenic signals are provided together with the cytokines IL-4 and IL-10, important switch factors for IgG4 antibody production, IgE production to allergens will be limited, resulting in reduced disease symptoms. Although this is an interesting model, the role of parasitic infections and stimulation of mature germinal centers by parasitic compounds still needs further explanation, because the total IgE level in helminth patients are very high. Nevertheless, in helminth-infected subjects, inhibition of IgE-mediated signals via co-aggregated FcγRIIb and FcεRI on basophils still remains a possibility.

Alternatively activated macrophages

Macrophages count among the most pleiotrophic cells of the immune system, exhibiting a range of biological functions, including phagocytosis, killing, and pro- and anti-inflammatory activities. It is well recognized that microbial products together with the cytokines produced by effector T cells influence the activation state of macrophages. Well known are the classically activated macrophages (caMΦ), induced in a Th1 cytokine environment, which release inflammatory products and nitric oxide (NO), and undergo oxidative burst, which is essential in protection against intracellular bacteria. Recently, it became clear that a different macrophage type arises in a Th2 environment. Because these cells exhibit a different activation program, they are called alternatively activated macrophages (aaMΦ) to distinguish them from the deactivated macrophages formed in an exclusive IL-10 environment [72•]. Alternatively, activated MΦ express high levels of PRR, but fail to generate NO and produce high amounts of IL-10 and TGF-β instead. Accordingly, aaMΦ exert selective immunosuppressive functions and inhibit T-cell proliferation. They are found in healthy individuals in the placenta, lungs, and immune privilege sites, as well as during chronic inflammatory diseases.

The presence of aaMΦ was demonstrated during several parasitic infections, both in human filariasis [73] and schistosomiasis [74] and in animal infection models for *Brugia malayi* [75] or chronic *Taenia crassiceps* infection [76]. These cells were shown to be involved in a cell contact-dependent suppression of T-cell–proliferative responses. Although in *B. malayi* infection this phenomenon appeared to be IL-4 dependent, studies on *S. mansoni* egg-derived glycoconjugates, such as LNFPIII and Lacto-N-neotetraose (LNnT), showed that parasite-derived molecules can directly induce aaMΦ-like cells. Intraperitoneal injection of LNFPIII or LNnT coupled to dextran induced the expression of a GR1⁺CD11b⁺F4/80⁺CD11c macrophage population, which did not secrete NO or PGE₂, but instead produced high levels of IL-10 and TGF-β. The LNFPIII- and LNnT-primed macrophages also suppressed the proliferation of anti-CD3/CD28-stimulated T cells in vitro [77•]. These data suggest that in the presence of a Th2 environment, aaMΦ cells, which normally may have an important tolerizing function at immune-privileged sites, are also generated by parasites during chronic infection, which contributes to the general immune hyporesponsiveness observed in helminth-infected individuals.

Therapeutic Application

There is increasing support for the view that the epidemic rise in immunologic disorders in westernized countries, in particular for allergic diseases, can be explained by a dysfunctional immune regulation, owing to a decrease of microbes/pathogens that enter via the gut or have an intestinal phase, such as helminth infections. Nevertheless, caution should be taken in this respect because some parasitic infections do not harbor an intestinal phase, such as filarial worms, which mainly reside in the lymphatics but also seem to protect from allergic symptoms. The question remains of how this newly gained insight can help to stop the allergic march or to treat patients once they have become allergic. Of course, infecting children with helminths or other orofecal microorganisms is not a realistic option. Nevertheless, Summers *et al.* [78•] treated four patients with active Crohn's disease with eggs from a harmless porcine whipworm, *Trichuris suis*, and demonstrated that multiple doses do not cause any side effects but lead to clinical improvement in all patients treated, which was sustained with a three times weekly maintenance therapy. The medical world awaits the results of a double-blind, crossover trial before the beneficial effect of treatment with helminths is established unequivocally. An alternative option to using whole parasites is the thorough analysis of parasite molecules that are responsible for suppressed host immune responses observed in helminth-infected patients. These immunomodulatory, parasite-derived compounds, such as *Schistosoma* egg-derived lyso-PS, or glycoconjugates such as LNFPIII or LNnT, would form an ideal basis for therapeutic application in the treatment of hyperinflammatory disorders. However, one caveat in this immunoregulatory scenario is the possible interfer-

ence with essential responses to other antigens, to vaccinations, or to life-threatening pathogens. Therefore, serious efforts should be made to generate antigen-specific immunoregulation, to circumvent dangerous side effects.

Conclusions

Numerous studies have pointed to a role for helminth infections in suppressing allergic disorders. Dissection of helminth-induced immune responses reveals both Th2 polarized responses and general T-cell hyporesponsiveness, which seems to be in part mediated by helminth-induced regulatory T cells. The suppression of host immune responses by regulatory T cells will help to prevent excessive inflammation and, thereby, protect the host, and may at the same time account in part for the protective effect of helminth infections on allergic disorders. Future intervention studies, both in animal models and in humans, should examine whether Treg cells play a crucial role in helminth-mediated suppression or whether other mechanisms are equally or more important. In the meantime, it is also important to identify the increasing number of immunomodulatory helminth-derived molecules with the view to future therapeutic application.

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