

Review article

Helminths can protect themselves against rejection inhibiting hostile respiratory allergy symptoms

The ability of common environmental allergens to stimulate IgE responses and thus to produce allergic diseases has tended to overshadow the fact that helminthic parasites are possibly the most potent inducers of this immunoglobulin that exists in nature. Although it has been well established that during these infections there is a stimulation of IgE against their own antigens as well as a strong induction of nonspecific TH₂/IL-4 polyclonal IgE, similarly to the allergic processes, many authors debate if the presence of these infections correlates inversely or not with the rate prevalence of atopy or respiratory allergy. Interpreting this relationship, we suggest that sometimes the intensive infections of hosts, especially with soil helminths which migrate in the respiratory ways or use there as entrance, can induce the production of some mediators ('helminth(k)ines'), to reduce the possibility of their reactive expulsion from the host. The ability to suppress hostile allergic symptoms despite the simultaneous induction of IgE response and local inflammation maybe is established due to the selective evolution, to assure for the parasites better chances for an effective life and reproduction within their mammalian hosts.

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Tous est faux, tous est possible, tous est douteux!
Gui de Maupassant

Relationship hostile organism – Parasitic organism

The relationship between hosts and parasites seems to be complex and often poorly understood (1). In many studies performed from different allergy research groups describe the impact of parasitic infection in the hostile immunity and they discuss the controversially of their results. A topic of the debates is if the presence of helminthic infections induces a suppression of atopy and respiratory allergic symptoms as well as a decrease of prevalence rates in respect of these diseases (2–4). They support their opinions regarding the impact of these infections with induction of immunologic mechanisms like the switch TH1/TH2 and the induction of eosinophilic allergic inflammation (2, 3, 5). These mechanisms explain the presence of IgE response and the similarity between allergic response and hostile anti-parasitic response, but they do not explain sufficiently why these infections suppress respiratory atopic symptoms or what the importance of this behaviour for the parasitic organisms is. Also, irrespective of the abundant literature of the inverse association between exposure to helminths and the occurrence of atopic diseases, no definite conclusions of the causality of this association are yet warranted (6). In this respect, we will try to explain in this review the evolutionary why of parasitic behaviours in human or

mammalian organisms regarding the suppression of allergic respiratory symptoms like sneezing, cough or the bronchial hyper-responsiveness. All these clinical symptoms are defences of hostile organism because through them it tries to expulse the foreign ones.

On the contrary the parasites or other infectious organisms aim to reproduce and develop themselves successfully into the hosts. In this respect, it is well known, that from the selective evolution are favoured the species of parasitic and infectious organisms which dispose adaptive mechanisms. These mechanisms allow them a more successful development and maturation at the 'environment' host. Also, many parasites induce characteristic changes in behaviour of their hosts during the infection (7). For example, some parasites like *Toxoplasma gondii* dispose the ability to manipulate the personality profile of the intermediate host (8). The toxoplasmosis-infected people are more predisposed to take a risk, or are less watchful for example in the motorways, whereas toxoplasmosis-infected rats can even lose the cat predation risk (9). This behavioural manipulation already is considered from Havlicek and his colleagues to be an evolutionary adaptation aimed to increase the probability of transmission of the parasite into its definitive host, in this case into the cat, by predation. Berdoy and collaborators share the opinion that these facts mean that a parasite may alter host behaviour for its own benefit, often by enhancing its transmission rate through the food chain (10). Also the

loss of predation risk by rats or the loss of watchfulness by humans at least at the prehistoric time before the invention of entombment, after a toxoplasmic infection, led usually to the rip of their bodies from some carnivore and also to the transmission of the parasite into its definitive host like felines. In evolutionary history this kind of parasite-induced changes is adaptive for Havlicek and his colleagues only from the point of view of parasitic transmission (8).

Regarding the helminths, it is worldwide known that migration by their larvae as well through the tissues of their mammalian hosts can cause considerable pathology through the IgE response or eosinophilic inflammation, but yet the evolutionary factors responsible for this migratory behaviour are poorly understood. Of course, navigation and survival in an array of different habitats must require costly biochemical and morphological adaptations (1). According to Read and Skorpington the undergoing of an extensive migration by nematodes only in one habitat spare them the host skin penetration and the necessary of intermediate host, which are very dangerous and need much energy consumption from these parasites. They mean that because migrating larvae risk becoming lost or killed by the host, natural selection should therefore remove such behaviour unless there are compensating benefits (1).

That is why we want to propose that migration as a selectively advantageous life-history strategy has obtained its means for its own survival like the suppression of respiratory allergic symptoms (1). Also, we suggest that these results are consistent with the hypothesis presented by Berdoy and his colleagues that such parasites only affect the behaviour traits with selectively benefit the parasite, rather than causing a general alteration of host behaviour (11).

Immune responses by helminthic infections and respiratory allergies

The immuno-inflammatory response to parasitic helminthic infections and allergic diseases have some similarities, the most profound being the increases in eosinophils and serum total IgE concentration (5, 12). For Lynch et al. (2) this immunoglobulin is an important component of host-protective immune responses against the helminthic parasites which are endemic in the majority of world population. They share the opinion that the atopic subpopulations experience less intensive helminthic infections than the nonatopic ones. Indeed, the same authors argue that helminthic parasites are possibly the most potent inducers of this immunoglobulin that exists in nature (2). Both entities – helminthic infections and atopic response are TH₂/IL-4 inducers, but helminthic infections not only stimulate specific IgE responses against their own antigens, but also they induce a strong nonspecific polyclonal synthesis of this immunoglobulin

(2). According to Martin (3), the experimental injection of atopic serum and the serum of patients infected with *Ascaris* into the peritoneal cavity of the rats produce after 24 h an increase in mast cells of the mesentery together with vascular congestion.

On the contrary, Buijs et al. (13) reported that experiments by guinea pigs and mice infected with the parasitic worms *Toxocara canis* developed eosinophil airway inflammation. Also guinea pigs developed few large eosinophilic inflammatory foci, whereas mice demonstrated progressive multifocal inflammation in which their airways were infiltrated with eosinophils and lymphocytes, forming perivascular as well as a partial peribronchial infiltrate in an oedematous submucosa (13). In this respect, several studies on experimental animals like there performed by Kannan, Johnson and their colleagues had demonstrated that immune and functional responses against allergic antigens as well as against parasitic antigens involve predominantly arachidonate lipoxygenase products, which lead to respective clinical diseases (14, 15). Taken together these data, we can share the opinion with Peisong et al. (16), that TH₂ immune signalling predicts an increased resistance to parasitic worm infections, whereas this genetic variation by humans may represent one origin for asthma and atopy. That is why these mechanisms cannot explain the presence of low respiratory allergic or atopic prevalence rates in the intensive helminth-infected subpopulations of tropical areas.

Relationship between prevalence rates of parasitic infections and respiratory allergies

As we mentioned above, there is considerable evidence that IgE antibody is an important component of immune protection against helminthic infections (2). Also Lynch and colleagues reported that children with a strong atopic background demonstrated IgE responses concordant with an enhanced protective response against helminthic parasites, and they had significantly lower intensities of infection than their nonatopic counterparts (2, 17). Also as a consequence, after experimental sensitization of dog or rats with atopic serum, in *Ascaris*-infected human serum as well as after the passive immunization with *Ascaris* antigen Asc SI there was an induction of the increase of mast cell histamine release (3, 4). Moreover, according Lynch et al. (2), the helminths are the most potent IgE-response inducers in the nature.

On the contrary, several studies had demonstrated that helminthes – which are potent TH₂ inducers – are surprisingly protective against the presence of allergy (6, 18). In this respect, Lynch et al. (2) reported that the prevalence of allergic diseases, particularly asthma and rhinitis, in Venezuelan children from urban slum area, is substantially lower than in children of higher socioeconomic levels. The evidence has been obtained to suggest

this is due to at least in part to suppressive effects of the helminthic parasites that are endemic in such underprivileged groups (2). Also in populations with similar living conditions and infections prevalence with helminths, the subgroup with more intensive infections from *Ascaris lumbricoides* had a lower prevalence of atopic immune response (2, 6). Similar data in respect of this relationship are obtained by Woolcock and colleagues in Papua, New Guinea in studies regarding the intensity of Hookworm infections, which together with *Trichuris trichiura* and *A. lumbricoides* are the most prevalent endemic soil-transmitted helminths by humans (2, 19–21). A negative association of *Enterobius* infestation with asthma and rhinitis in children is reported by Huang and collaborators too (6, 22). According to a study performed in schoolchildren of a rural area in Ecuador, allergic symptoms (like recent wheeze) were of low prevalence, whereas prevalence of skin test reactivity was relatively high. Moreover, Cooper et al. (20) reported that presence of geohelminth infections was protective against allergen skin test reactivity. In comparison with industrialized countries where sensitization to common environmental aeroallergens is a strong risk factor for allergic diseases, studies conducted in the less-developed regions of the world have shown that atopy is either a weak risk factor for the allergic disease or not a risk factor at all (6, 20). According Cooper et al. (20), analysis of the data from this population of school-age children indicates that allergen skin test reactivity and geohelminthic infection are quite strongly inversely associated, and the effect of one on symptom prevalence may be the result of the other.

Similar studies performed in Europe by Dold, de Almeida and their colleagues, did not reported decreased atopy prevalence rate in helminths-infected subpopulations (6, 23, 24). Also children in former East Germany who were *Ascaris*-IgE seropositive had higher levels of total IgE and higher prevalence rates of allergen-specific IgE seropositivity. They also had a higher prevalence of allergic rhinitis and asthma (23). According to the same study, the subgroup which became *Ascaris*-seropositive had a threefold increase of sensitization against *Dermatophagoides pteronissinus*. In contrast reported Dold et al. (23), in children who became *Ascaris*-seronegative was found decreased total and specific IgE. Similarly, according to a study performed by de Almeida et al. (24) in Caucasian children with same socioeconomic conditions, intestinal parasitosis prevalence in atopy asthmatic group was not statistically different from the intestinal parasitosis in control group. This data indicate that contact with low doses of helminthic antigen is associated with an increase of total and specific IgE production and vice versa, whereas high contacts with these antigens suppress the induction of respiratory allergies (23).

These facts have led to the question, what additional mechanisms drive the inhibition of allergic inflammation or allergic career. In this respect, interesting results are

reported by Buijs and colleagues from studies in guinea pigs and mice, which are infected with the parasitic worm *T. canis*. These animals represented tracheal hypo-responsiveness despite the presence of eosinophilic airway inflammation (5, 13). In a murine model of asthma, in which was conducted a simultaneous immunization of mice with ovalbumine and extract of the adult worm *Ascaris suum*, were reported an inhibition of eosinophilic inflammation as well as an inhibition of airway hyper-reactivity to metacholine. Wang and collaborators reported that a pre-existing infection with *Strongyloides stercoralis* prior to ovalbumin immunization and intra-tracheal challenge can decrease subsequent allergic responses in the lungs of BALB/cByJ mice like the airway eosinophil accumulation (12). According Lima, Wang and their colleagues, these effects correlated with a marked reduction of IL-5 and IL-4 levels as well as the level of eotaxine in bronchoalveolar lavage and lung tissue (12, 25). The suppression of IgE antibody responses and thus of allergic reactivity is explained by Lynch and colleagues as a consequence of saturation of Fcε mast cell receptors by high level of IgE, whereas Soares and his colleagues propose the suppression of IgE antibody production by *Ascaris* extract as cause of IgE response reduction (25, 26). Mangan and collaborators demonstrated that *S. mansoni* infection protects mice from an experimental model of systemic fatal anaphylaxis whereas Bashir and collaborators reported that presence of gut helminths protect from food anaphylaxis (18, 27). Furthermore, worm infection of mice increases the frequency of IL-10-producing B cells compared with that in uninfected mice. Also Mangan et al. (27) demonstrated that mechanisms which can protect against allergic hypersensitivity are dependent on an IL-10-producing B cell population. Recently, it has been demonstrated that helminths induce suppressed host immune responses by the priming for regulatory T cells. Detailed analysis of helminth-induced immune responses showed that helminths not only prime for polarized Th2 responses but also potentially induce T-cell hypo-responsiveness (28). It is proposed that this regulatory T cell-inducing activity accounts for the protection observed in the development of allergic disorders. Ferreira and colleagues reported the impairment of T cells in *Ascaris* extract-immunized mice and the reduction of IgM, IgG1, IgG2a and IgE responses (25, 29). The same work group as well as the one guided by Yazdanbakhsh reported that during such intensive parasitic infections the TH2 response without clinical atopy is possible due to the immuno-regulatory role of IL-10 and TGF-β (25, 30). These opinions have shared many authors in their reviews like von Hertzen, Black, or Platts-Mills (6, 17, 31). It is likely that T regulatory cells are important for T-cell hypo-responsiveness seen in chronic helminth infections and IL-10 act in both T and B lymphocytes (30).

Given that helminths are such potent inducers of immune hypo-responsiveness, it is conceivable that these

organisms form a rich source of immuno-modulatory molecules that may be of potential use to combat inflammatory diseases such as allergies. Recent studies in schistosomes show that particularly lipids are able to induce down-modulation of immune response via the induction of T regulatory cells (18). In this respect, van der Kleij and colleagues had found that only schistosome-specific phosphatidylserine can activate Toll-like receptor TLR2 and affect hostile dendritic cells such that mature dendritic cells gained the ability to induce the development of IL-10-producing regulatory CD4/CD25 T cells (18, 32). Moreover TLR2 can downstream NF- κ B activation, which is an inflammatory response inducer (32). TLR2 is shown to be stimulated from other helminths like *A. lumbricoides* lipids (16). Similar effects regarding immuno-modulatory properties are found in other helminth lipid compounds like glycolipids, cyclopentenone prostaglandins or lysophospholipids which enhance IL-10 in dendritic cells (18). This interaction may be crucial to long-term survival of the parasite and limited host pathology. According van der Biggelaar and colleagues the anti-inflammatory cytokine IL-10, induced in chronic schistosomiasis, appears central to suppressing atopy in African children (18, 33). Cooper et al. (20) reported that presence of geohelminth infections in schoolchildren or a rural area of Ecuador was protective against exercise-induced wheeze, but not against atopic eczema or other allergic symptoms. A prevalence reduction of recent wheeze was described in Hookworm or *A. lumbricoides* infected children in a case-control study performed by Scrivener and collaborators in a tropical country (20). Several studies, examining the relationship between allergies and parasitic infections in areas where transmission is intense, have revealed that children with chronic helminth infections have a lower risk of wheeze or of skin-prick-test positivity for house-dust mite (18). Taken together the mentioned data, we can suggest that parasites dispose lipid immuno-modulatory compounds which induce these effects (Figs 1 and 2).

Relying for fatty acids supply and retaining the capability to modify fatty acids by chain elongation, which are not present in noninfected hosts, helminths may specifically target the immune system via specific receptors actively, leading to the development of T regulatory cells involved in immuno-suppression (18). On the contrary, the immuno-modulatory lipids, which are released in different conditions from hostile membrane phospholipids and converted through action of lipoxygenases and cyclooxygenases in leukotrienes and some prostaglandins, are well known for their proinflammatory and allergic actions, whereas other prostaglandins and lipoxins exert anti-inflammatory signals (18). Also anti-inflammatory prostaglandin D2 and prostaglandin E2 are induced or produced from self parasites. These molecules together with lipoxins (like lipoxin A4) are shown to limit inflammatory cytokine-induced tissue pathology during these infections as well as maybe anti-

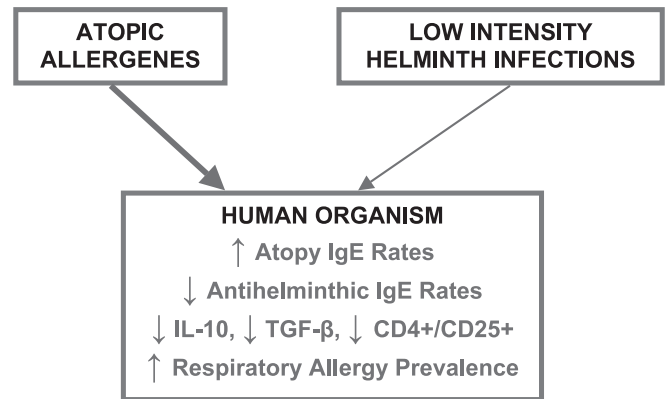


Figure 1. The impact of low intensity respiratory migrating helminthic infections in the expression of hostile respiratory allergy symptoms. Especially in affluent countries the low intensity helminth infections allow the human organism to develop commonly respiratory allergies towards atopic allergens. In this case, the low level of helminthic immuno-modulatory compounds in non infected/low intensity infected mammals cannot induce in the regulatory cells the attainment of a sufficient concentration of respective cytokines like IL-10 and TGF- β , and therefore respiratory allergic symptoms can be present in these subjects. The thicker the arrow, the higher the intensity of respective factor influences.

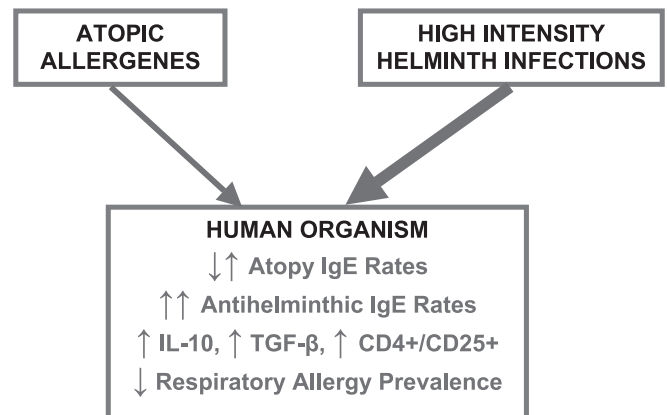


Figure 2. The impact of high intensity respiratory migrating helminthic infections in the expression of hostile respiratory allergy symptoms. Contrarily, especially in poor rural and subequatorial regions the high intensity helminth infections inhibit the human organism to develop commonly respiratory allergies towards atopic allergens, despite the induction of very high IgE rates. The suppression of allergic symptoms avoids their rejection from hostile organism and therefore, assures for themselves better chances for an effective life and reproduction within their mammalian hosts. These immuno-modulatory effects are possible due to influence of some compounds like helminth-specific glycolipids or lipoxins, which induce by mammalian regulatory cells CD4+/CD25+ the increasing of regulatory cytokines IL-10 and TGF- β . The thicker the arrow, the higher the intensity of respective factor influences.

parasitic responses (18). Also lipoxin A4 can act on the G-protein-coupled receptor designated ALXR, to inhibit NF- κ B activation and inflammatory responses (18, 34). Furthermore, lipoxin levels are shown to be higher in subjects with mild asthma compared with individuals who suffer the severe one (18, 35). These data support the opinion that IgE antibody is not only an important component of immune protection against these parasites, but also the allergic diseases, which represent undesirable reactions against towards normally inoffensive environmental materials, are experienced particularly in situations in which parasitic infections occur rarely (2, 36–38). The intensification of the helminth infections leads to the IL-10-dependent immuno-modulatory effects of T regulatory cells, which are induced from some specific parasitic lipid compounds.

Alternatively, it is not excluded that the presence and intensity of infections with geohelminth parasites are likely to reflect exposure to a microbially contaminated environment and could therefore be only surrogate markers for levels of environmental endotoxins, which are potent TH2/Th1 switch inducer (6, 17, 20). Also this similar relationship regarding the infections intensity and occurrence of respiratory atopic diseases is shown between human organism and some bacterial micro-organisms like *Mycobacterium* or gram-negative gastroenteric infections (6, 17, 31). It is explained till nowadays by ‘hygiene hypothesis’ and TH2/TH1 switch, even though its viability is not complete (6, 17, 31).

However, the risk of allergic disease associated allergen skin test reactivity do appear to be smaller in a rural area of the tropics compared to those in an industrialized country, despite the likelihood of significant exposure to aeroallergens in both populations. Even if in a few studies are described relatively high (‘West European’) levels of allergen skin test reactivity in tropical rural areas, it has been reported always an essential dissociation between atopy and respiratory allergic symptoms (20).

The meaning of relationship between prevalence rates of parasitic infections and respiratory allergies

Parasitic helminths have probably afflicted humans for millennia, just as they do today, in greater than one billion humans (20, 39). They can secrete various substances during their life in hostile organisms. Substances secreted by different helminths trigger local inflammation and production of TH₂ type cytokines and IgE antibodies (2–4). This reaction assures humans and other mammals a better resistance to helminthic infections (39). Such defensive reactions are developed against different chemicals, in this respect the respective defences for the respiratory system are the respiratory allergy-like symptoms such as sneezing, cough, airway obstruction and airway hyper-responsiveness. Through such mechanisms the body liberates from them. On the

contrary, several studies have shown an inverse association between exposures to (*T. gondii*) or harbouring of parasites (*Schistosoma* or Intestinal helminths) and allergy or mentioned allergic symptoms (18). The mechanisms behind such protective effects have provided new insights and theories on the ability of parasite derived molecules to down-regulate immune responses and thereby to control inflammatory diseases such as allergies (40). These pathogens have evolved to live and to reproduce effectively within their mammalian hosts, and in order to do so appear to express a diverse array of molecules that have immune suppressive effects (18). Therefore, parasites try to alter the host behaviour for its own benefit in the different ways, altering its genetic, biochemic, immunologic or physiologic functions as well as altering its personality, activity etc as we mentioned above (1, 10, 11).

Analysing all presented data in this review, our opinion is that even the prevalence reduction of respiratory allergic symptoms (like wheeze or airway hyper-reactivity) as well as atopy in intensive helminth-infected populations of tropical rural regions, where these species are endemic, is practically an evolutionary adaptation from the point of view of parasites. The reduction of these allergic symptoms assures a better chance for their reproduction and development in the environment ‘host’, because the liberation mammalian efforts against these parasites are suppressed. The mentioned helminths (*Toxocara*, *Ascaris*, *Trichuris* and Hookworm) have a phase of larval migration into the respiratory system or at least, their entrance way (as eggs) in the human body is the nose or the mouth (20). Also to assure their penetration into the host and latter their reproduction or development, these parasites need to affront or avoid the reactive (including allergic) response of the host (like the cough, airway obstruction and airway hyper-responsiveness).

That is why intensive chronic exposure to geohelminth parasites, particularly those that have a respiratory phase of larval migration, may have anti-inflammatory effects and suppress allergic inflammation in the airways, or they suppress more often at least respiratory allergic symptoms which is very essential, despite the simultaneous presence of eosinophilic allergic inflammation or atopic response (5, 20, 25). Their specific extracts in experimental animal or *in vitro* studies suppress IgM, IgG1, IgG2a and IgE responses, inhibit eotaxins as well as they decrease the level of cytokines IL-4 and IL-5, maybe through the induction of immuno-regulatory role of IL-10 and TGF- β by T regulatory cells due to influence of their specific lipid immuno-modulatory compounds (18, 25).

The mentioned helminthic possessed immunosuppressive substances (we propose to call there ‘Worm(k)ines’ or ‘Helminth(k)ines’ – a conjunction of the words ‘worm’ or ‘helminth’ with word ‘cytokines’), can neutralize at least locally the allergic reactivity. Therefore, the expression of allergic reactivity in heavily helminth-infected populations might be modulated by these compounds (25).

Maybe their purification, their characterization and finally the use of possible allergy suppressing helminth-derived molecules in animal experiments and clinical trials could indicate us in the future the importance of our hypothesis. If it were true, some helminthic compounds could have respiratory anti-allergic effects and they could become useful even as medicaments.

In this review, we have tried to interpret the relationships between human organism, helminths and the respiratory

allergy prevalence rates, which are represented under 'hygiene hypothesis' concept, from the viewpoint of parasite evolutionary interests (6, 31, 40). We conclude that these parasites, like many infective pathogenic organisms which suppress the allergic carrier of their hosts, are not at all our natural allies but user of the environment 'mammalian or human body' only for their self benefit. However, maybe we can assure in the future more benefits from these parasites than we do contemporary.

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