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Abstract: Allergic diseases are on the rise globally, in parallel with a decline in parasitic infection. The inverse association between parasitic infections and allergy at an ecological level suggests a causal association. Studies in humans have generated a large knowledge base on the complexity of the inter-relationship between parasitic infection and allergy. There is evidence for causal links, but the data from animal models are the most compelling: despite the strong Type 2 immune responses they induce, helminth infections can suppress allergy through regulatory pathways. Conversely, many helminths may cause allergic-type inflammation including symptoms of "classical" allergic disease. From an evolutionary perspective, individuals with an effective immune response against helminths may be more susceptible to allergy. This narrative review aims to inform readers on the most relevant up to date evidences on the relationship between parasites and allergy. Experiments in animal models have demonstrated the potential benefits of helminth infection or administration of helminth-derived molecules on chronic inflammatory diseases, but clinical trials in humans have not so far demonstrated unequivocal clinical benefits. Nevertheless, there is sufficiently strong evidence to support the continued investigation of the potential benefits of helminth-derived therapies for the prevention or treatment of allergic and other inflammatory diseases.

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Global Issues in Allergy and Immunology

Parasite infections and Allergy

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Abstract

Allergic diseases are on the rise globally, in parallel with a decline in parasitic infection. The inverse association between parasitic infections and allergy at an ecological level suggests a causal association. Studies in humans have generated a large knowledge base on the complexity of the inter-relationship between parasitic infection and allergy. There is evidence for causal links, but the data from animal models are the most compelling: despite the strong Type 2 immune responses they induce, helminth infections can suppress allergy through regulatory pathways. Conversely, many helminths may cause allergic-type inflammation including symptoms of "classical" allergic disease. From an evolutionary perspective, individuals with an effective immune response against helminths may be more susceptible to allergy. This narrative review aims to inform readers on the most relevant up to date evidences on the relationship between parasites and allergy. Experiments in animal models have demonstrated the potential benefits of helminth infection or administration of helminth-derived molecules on chronic inflammatory diseases, but clinical trials in humans have not so far demonstrated unequivocal clinical benefits. Nevertheless, there is sufficiently strong evidence to support the continued investigation of the potential benefits of helminth-derived therapies for the prevention or treatment of allergic and other inflammatory diseases.

Keywords: Allergy, asthma, parasite infection, helminths, epidemiology, mechanisms.

Abbreviations:

AcK1 - a large family of ShK-related peptides
AAMΦs - alternatively activated macrophages
BmK1 - a large family of ShK-related peptides
CAMΦs - classically activated macrophages
$CD11c_{high}$ DC – conventional dendritic cells
CD4+ T cells – T Helper Lymphocytes
CD4+ CD25+ FOXP3+ - regulatory T cells
CTLA-4 - inhibitory molecule cytotoxic T lymphocyte- associated antigen 4
DC – dendritic cells
ES - excretory-secretory molecules of helminths
FEV_1 - Forced expiratory volume in 1 second
HIC – high income countries
iNOS – inducible nitric oxide synthase
LMIC – low- and middle-income countries
IL – interleukin
ILC – Innate lymphoid cells
IL2R – interleukin 2 receptor
IFNγ – interferon gama
LD - linkage disequilibrium
PBMC – peripheral blood mononuclear cells
PG – prostaglandin
SPT – skin prick test
STH – soil transmitted helminths
SWAP – *Schistosoma* soluble adult worm antigen
ST2 – IL33 receptor
sST2 – a soluble form of ST2
sIgE – specific IgE
tIgE – total IgE
Th – T helper cells
TLR –toll like receptors
TGFB - Transforming growth factor beta
TSLP - Thymic stromal lymphopoietin

Type 2 immune response – pattern of immune response including the Th2 cells (CD4+ cells), ILC2s and other to the cytokine milieu formerly related exclusively to Th2 activation

WHO – World Health Organization

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Introduction

The frequency of allergic disease has been rising in urban and urbanizing populations,[1] while an overall decline in rates of infections has been observed. Studies of the inverse association between parasitic infections and allergy suggest the existence of a causal link.

While humans can be infected with some 300 species of worms and over 70 species of protozoa[2] we will focus on soil-transmitted helminths (STH). Worldwide, it is estimated 1.5 billion humans are infected with one of these species.[3] We will also refer to *Schistosoma spp*. that infect humans through contact of skin with water infested with larvae and it is estimated to infect 230 million people.[4]

For example, Figure 1 shows typical features of a rural household in a village of Conde, Northeast Brazil, from 2005, in which the prevalence of helminth infections was 83.5%.[5] In the City of Salvador, 185 km away, the frequency of helminth infection among children was below 20%.[6] An ecological study including all Brazilian municipalities reported hospitalization rates due to asthma were lower in those endemic for *S. mansoni* or for STH parasites.[7] A typical urban underserved neighborhood of Salvador, is presented in Figure 2.

Insert Figure 1.

Typical features of a rural household in a village in the municipality of Conde, Northeast Brazil

Insert Figure 2.

Typical urban underserved neighborhood of Salvador, Northeast Brazil

The purpose of this narrative review is to inform clinicians and researchers on the most current evidence on this topic, from epidemiological studies to mechanisms and molecules identified in helminths that are candidates for novel therapeutics.

Global trends in parasite infections and allergy

Global trends

Allergic diseases are among the most common chronic diseases[1] particularly in populations undergoing urbanization.[8] Individual risk of allergy is considered to reflect a complex interaction between genetic predisposition and environmental exposures over the life course.[9] Geographic differences in the prevalence of allergy between and within populations is more likely to reflect exposures to common environmental factors that may either increase or decrease risk. The most consistent environmental exposures considered to reduce risk of allergy are those associated with rural residence and include farming, animal exposures[10] and infections with parasites.[11]

Protective immunity against STHs is mediated through type 2 immune mechanisms[11] and parasites can survive to cause chronic infections by modulating these allergic inflammatory responses. The prevalence of STH infections is declining worldwide. This reflects a combination of factors leading to reductions in transmission of these infections, including reductions in extreme poverty and improvements in the living environment (potable water and disposal of feces) and the wide availability of anthelmintic drugs. Reductions in

157 STH prevalence, while beneficial, might raise concerns in case of being causally associated
158 with allergy.

159

160 *Epidemiological evidence for associations between parasites and allergy*

161 There is evidence in support of protection against allergy by STH infections, but many
162 studies in human populations present discordant effects.

163 Meta-analyses of observational studies have shown differences in effects on asthma
164 symptoms for different parasites: while *A. lumbricoides* was associated with an increased risk
165 of asthma, hookworm infection was associated with a reduced risk.[12] In contrast, studies that
166 have measured the presence of *Ascaris*-specific IgE - recommended by some as a marker of
167 infection in areas of low prevalence[13] but perhaps more appropriately used as a marker of
168 allergic sensitization to *Ascaris* - have shown consistently positive associations with asthma
169 symptoms and even disease severity.[14,15]

170 In the case of atopy, generally measured by allergen SPT reactivity, most cross-
171 sectional studies have shown inverse associations with STH infections.[16] A meta-analysis of
172 cross-sectional studies showed that current STH infections were protective against atopy, an
173 effect that was consistent for all 3 of the most common STH infections and also
174 schistosomiasis.[16] STH infections are not alone in their SPT attenuating effects. A cross-
175 sectional study showed that, in addition to *A. lumbricoides*, several different childhood
176 infections were independently and inversely associated with SPT, including visceral worm
177 *Toxoplasma gondii*, *Herpes simplex* and Epstein-Barr virus infections.[6] This observation
178 raises the possibility that rather than mediating protection directly, STH infections might be
179 markers of poor environmental conditions that mediate protection through alternative

mechanisms. Interestingly, in the study mentioned above, *T. gondii* was the only organism associated with a reduction in allergen-specific IgE in this population.[6]

Few prospective studies have explored the effects of geohelminths on the development of allergy. It has been suggested that the key effects of protective environmental exposures, occur during early life during which there may be a limited window of opportunity for such exposures to mediate their effects.[9] If this is the case, prospective studies of the effects of STH infections on allergy should start in early childhood, ideally before birth to measure any potential *in utero* effects of maternal STH infections. Four such prospective studies have been published to date; i) a birth cohort in Ethiopia where the prevalence of helminthiasis was considered to be too low to explore effects on wheeze and eczema to 5 years;[17] ii) an observational analysis within a randomized-controlled trial of anthelmintic treatment during pregnancy showed that maternal and childhood hookworm and childhood *T. trichiura* were associated with a reduced risk of eczema to 5 years;[18] iii) a prospective study showed that *T. trichiura* infections during the first 5 years of life were associated with a reduced risk of SPT in later childhood;[19] and iv) a birth cohort in a rural area did not show an effect of maternal STH infections on SPT, wheeze, or eczema during the first 3 years of life,[20] but follow-up of the cohort is in progress to determine if childhood infections may affect risk of allergy at school age.[21]

Another way used to test the causal link has been the interventional studies in which the protective exposure (i.e. STH) is removed through anthelmintic treatment thus intended to reverse any existing effects. If helminths are truly protective, one might expect to observe an increase in the prevalence of allergy in the group receiving treatment. Several intervention studies have inconsistent findings.[22,23,24] None of the studies were able to show an effect on the prevalence of asthma symptoms, one showed that a single dose of anthelmintic drugs given during the latter part of pregnancy was associated with an increased risk of eczema in

infancy,[22] and two showed an increase in either the incidence[23] or frequency[24] of positive SPT after at least 1 year of treatments.

Overall, the evidence suggests that *A. lumbricoides* infection and particularly *Ascaris*-specific IgE is associated with an increased risk of asthma symptoms in endemic areas but that STH infections may reduce the prevalence of positive SPT, but not specific IgE (sIgE) to aeroallergens. There is still very limited evidence that STH infections protect against allergic symptoms in human populations, and the effects of early life exposures to STH infections on the development of allergy in childhood, either through maternal or childhood infections, is still insufficiently studied.

In case of schistosomiasis, all published studies have been cross-sectional showing an inverse association between *Schistosoma mansoni* infection and SPT reactivity to common aeroallergens in most cases[16]. A recent study in Uganda was unable to demonstrate an association between *S. mansoni* infection and wheeze but an earlier study in Brazil showed that *S. mansoni* infection was associated with a milder form of asthma.[25]

Host immune response against parasites

Helminths are the largest organisms to infect vertebrate hosts, leading to the release of large quantities of parasite molecules that interact with the immune system. It might be expected that helminth infections should induce an overwhelming immune response, resulting in the elimination of the parasites, while causing potentially damaging inflammation. However, co-evolution of hosts and parasites over millennia has allowed both host and parasite to survive through the development of mechanisms that dampen the host inflammatory response to the parasite or even allow the parasite to evade the host immune response, resulting in infections

that are often asymptomatic.[11] For example, *Schistosoma spp* adults, that live within the human vascular system, can survive for many years without inducing strong host inflammatory responses.[26]

Although the most widely studied host immune response against helminths is the acquired Th2-type response, we shall discuss both innate and adaptive host immune responses to helminth parasites. The Th2 type response is characterized by the production of high levels of the cytokines IL4, IL5, IL9, IL10, IL13, IL21, IL33. These cytokines orchestrate immediate hypersensitivity that involves B cell class switching to IgG4 and IgE, eosinophilia, goblet cell hyperplasia and mastocytosis, alternative activation of macrophages, and the influx of inflammatory cells such as eosinophils that contribute to parasite killing. Such a response may control parasite numbers by killing them in tissues or expelling them from the intestinal lumen.≈ The host response to helminth infections is associated with allergic phenomena that are a consequence of killing or an attempt to kill or expel these parasites.[27] Examples are shown in Table 1.

Although helminth parasites are universal in inducing all or most of these Th2 effector pathways in the host, the specific effector pathway mediating protection varies between different parasites, life cycle stages, and site of infestation. For example, the intestinal helminths, *Heligmosomoides polygyrus* and *Trichinella spiralis*, are expelled from the intestinal lumen by several Th2 effector pathways such as IgE-mediated activation of mucosal mast cells. Th1 responses may also have a role in protective immunity against some helminth parasites such as *S. mansoni* infection,[28] while the control of parasite burden in strongyloidiasis is highly dependent on type 2 responses.[29]

The parasite's first contact with the host's immune system is through $CD11c_{high}$ DC which undergo alternative activation for example, in response to excretory-secretory (ES)

molecules from the murine intestinal helminth parasites *Heligmosomoides polygyrus* and *Nippostrongylus brasiliensis*.[30] Helminth molecules bind to TLR2, 3, 4 receptors on the dendritic cell membrane driving the acquired immune response from naive Th0 to a Th2 profile.[31]

An important group of innate immunity cells, the innate lymphocyte (ILCs), which lack B or T cells antigen specific receptors, and do not express myeloid or dendritic cell markers, has been shown to comprise three sub-sets: ILC1 (related to T1 profile), ILC2 (related to T2) and ILC3 (related to ThI7).[32] ILC2 produce a large set of T2 cytokines (IL4, IL5, IL9, IL13 and IL21) in response to stimulation with IL25, IL33 and TSLP[32] and play an important role in protection against helminths. However, unlike Th2 cells, ILC2 are stimulated by alternatively activated macrophages (AAMΦs), express MHC-II, and are able to endocytose and process antigen.[33] AAMΦs are phenotypically distinct from classically activated macrophages (CAMΦs) that are typical of Th1 type responses. AAMΦs do not produce IFNγ and instead of inducible nitric oxide synthase (iNOS), have upregulated expression of Arginase-1 that has higher affinity for arginine, competing with iNOS present in CAMΦs. AAMΦs are induced during infections with several helminth parasites.[34] Interestingly, an interaction between ILC2 and Th2 cells for maintaining AAMΦs in lungs of hookworm-infected mice has been reported.[35]

Other immune cells reported to play a role in immunity against helminth infection are the Th17, derived from CD4(+) T cells after antigen maturation. Th17 cells are important for the clearance of several extracellular pathogens, such as bacteria and helminths.[36] In *S. japonicum*-infected mice, there was an increase in Th17 cells following granuloma development, attributed to the presence of induced factors (e.g. TGFB, IL23 and IL21) in greater amounts than inhibitory factors (e.g. T_{reg} and T2 cells, and IL-4).[37]

Helminths have developed several mechanisms to suppress or avoid host anti-parasite responses. For example, *S. mansoni* has developed parasite stage-specific evasion strategies. Entry of cercariae through the skin is followed by the release of larval ES products (e.g. PGD2) that cause host cells to release PGE2.[38] Both host and parasite-derived prostaglandins induce the production of *IL10* in the skin that inhibits the migration of epidermal Langerhans cells to the invasion site.[39]

The most remarkable evasion strategy used by helminths, particularly those dwelling within host tissues and in blood and lymphatic systems, is the down-modulation of the host immune system leading to a form of immunologic tolerance that, itself, may have effects on host responses to other infections and allergy. The cells mediating this effect are the T_{reg} sub-set of the CD4+ T lymphocytes that produce the immune modulatory cytokines IL10 and TGFB. The presence of regulatory cells is associated with a reduction in Th2 cells and the development of a modified type 2 immune response. Other cells involved are alternatively activated macrophages and B-regulatory cells.[11]

Insert Figure 3.

Schematic representation summarizing the findings from epidemiological studies of the relationships between helminth parasites and atopy and asthma

Commonalities between the immune response to parasites and allergy

The host immune response to helminth parasites has many features in common with allergy. Bronchial inflammation of atopic asthma is coordinated by cells of the adaptive immune system, but also by ILC2 of the innate response, which together induce a type 2 response.[40]

299 During helminth infections type 2 immunity is initiated at the site of parasite invasion by
300 epithelial cells, which release the alarmins IL25 and IL33 to prompt ILCs to produce IL13
301 and other cytokines that are also involved in the pathoetiology of asthma. In the absence of
302 either IL25 or IL33, resistance to helminth infections is severely impaired.[41] T_{regs} cells have a
303 dual role in helminth infections: they protect the host from excessive inflammatory responses
304 during infection, but they also may decrease protective immunity and, thereby, permit
305 parasite persistence.[42] In the case of asthma, several studies have shown allergic patients to
306 have lower numbers of T_{regs} in both the bronchoalveolar lavage and peripheral blood
307 monocytes cells (PBMC).[43] Thus, there are notable parallels between the immune responses
308 associated with allergy and those observed in response to helminth infection.

309 Host type 2 immune responses to parasites and allergens are induced by a limited
310 number of protein families that contain allergens such as tropomyosins. There is extensive
311 structural homology between allergens from helminths and other environmental sources.[44]
312 Further, allergen homologues derived from parasites and aeroallergens do not just exhibit IgE
313 cross-reactivity but can also induce cross-sensitization in murine models.[45] Cross-reactivity
314 between helminths and aerollergens has a number of important consequences including false-
315 positive reactions for specific IgE when used in the diagnosis of allergy and also a potential
316 increase in morbidity caused by inflammatory reactions directed against cross-reactive
317 allergens. In the case of the latter, cross-reactivity could help drive the exaggerated responses
318 associated with inflammatory syndromes that have been reported in human helminth
319 infections such as tropical pulmonary eosinophilia in the case of lymphatic filariasis[46] and
320 Loeffler's syndrome in ascariasis.[47] Likewise, it has been suggested that immune modulation
321 during chronic helminth infections, which subvert Th2-mediated inflammation permitting
322 parasite survival, could affect atopic responses to common aeroallergens through either
323 bystander effects or immunological cross-reactivity.[45]

Insert Figure 4.

Helminths suppress autoimmunity and allergy via type 2 or regulatory immune response.[48]

Genetic determinants of protection against helminths and risk of allergy

Characterization of parasite genomes and subsequent comparison of parasites to more complex species such as mammalian hosts have contributed to our understanding of the mechanisms of parasite evolution and have provided evidence for the role of host–parasite interaction in genetic adaptation. An understanding of that genetic adaptation has elucidated candidate genes, which may drive susceptibility to other diseases of the immune system, including atopy and asthma.[49] Thus, genetic variants affecting any of the classical key-roles inflammation inducing factors as well as proteins related to controlling inflammation through immune regulatory mechanisms such as T_{reg} may play a role on both helminth resistance and allergic conditions. Genetic studies have highlighted common variants (MAF >10-30%) that affect allergy in many different ways. In Figure 5, an analysis using PANTHER version 11[50] is presented showing different pathways related to the main genes described in GWAS to date, in which one may observe 3 out of the top 4 pathways linked to asthma are related to interleukin signaling and inflammation.

The genetic variants that affect protection against helminths and risk of allergy, can be organized in two main groups: those affecting Th2 immune response and those affecting regulatory mechanisms.

Insert Figure 5:

Pathway analysis using Panther 11 version for the top SNPs associated in GWAS for asthma to date.

Variants that affect Th2 immune response

Common genetic variants of type 2 immune signaling relating to allergy and asthma provide credence to the hypothesis that the origin of these allergy-promoting variants derives from evolutionary mechanisms and their selection occurred in the presence of widespread, endemic helminth infection.[51] A region on chromosome 5, 5q31-q33, for example, has been associated with resistance to *S. mansoni* through the presence of genes such as those of granulocyte-macrophage factor (*CSF2*), *IL3*, *IL4*, *IL5* and *IL13*, that are important in protective immunity against *S. mansoni*.[52] The same locus (5q31-q33) has been linked to asthma and atopy. Other relevant loci that are also linked to asthma are 7q and 21q.[53]

In terms of asthma susceptibility, several immune molecules have been associated with asthma/allergy. In both GWAS and candidate genes studies some 200 genes have been associated with asthma or related phenotypes. Among these genes, there are those related to a possible modulation of plasma tIgE levels.[54] Association studies of genes encoding the epithelial cell-derived cytokines, *IL33* and *TSLP*, and the *IL1RL1* gene encoding the IL33 receptor, ST2, highlight the central roles for innate immune response pathways that promote

368 the activation and differentiation of Th2 cells. These genes are the most consistent variants
369 associated with asthma, allergy and helminth infections across ethnically diverse
370 populations.[55]

371 In this context, GWAS studies for allergic diseases have pinpointed *IL33* and *IL1RL1*
372 as key susceptibility genes for allergic asthma, underscoring the pivotal role of this pathway
373 in the pathophysiology of this diseases.[56] Studies involving the genes codifying the *IL33/ST2*
374 route have been widely replicated in different populations,[57] confirming their association with
375 asthma[58] and blood eosinophilia.[59] The mechanism whereby the *IL33/ST2* axis induces Th2-
376 inflammation was demonstrated recently.[60] Local airway soluble ST2 (sST2) levels, as well
377 as circulating plasma sST2 levels, contribute to neutralization of IL33 in the tissues.

378 The role of human genetic determinants of *IL33/ST2* in helminth infection is poorly
379 understood. Using a generalized estimating equation model, three SNPs associated with
380 higher SWAP specific IgE/IgG4 (a measure of resistance to *S. mansoni*) were found.[61] The
381 most significant SNP mapped to intron 1, and the allele, which has been shown to confer
382 asthma risk in an African-American population, also conferred protection against
383 schistosomiasis.

384 Major polymorphisms within the 5q31-q33 genomic region, previously associated
385 with resistance to *S. mansoni* infection have been studied.[52,53] The region includes several
386 genes related to immune function including IL-4, IL-5, and IL-13 genes in the Th2 cluster.
387 Resistance to *S. haematobium* was associated with the *IL13*-1055T/T genotype[62] which has
388 also been implicated in asthma exacerbations.[63] Further, a functional *IL13* polymorphism,
389 rs1800925T, was shown to contribute to the risk of late-stage schistosomiasis caused by *S.*
390 *japonicum*.[64] In another study, two quantitative traits, tIgE levels (representing Th2 pathway
391 activation) and *S. mansoni* egg counts, that reflect host immunity to helminths were

investigated, providing a unique opportunity for the genetic dissection of the Th2 pathway in the context of schistosomiasis.[7] Significant associations were seen between two functional variants on the IL13 gene and *S. mansoni* egg counts, indicating IL13 to be protective, but no associations of IL13 gene variants with tIgE levels. Since the functional effect of both variants on the gene product, IL13, is to increase its amount or activity, this finding suggests IL13 functions to increase anti-helminth immunity, and functional variants may be an evolutionary vestige of selective forces that may now favor atopic phenotypes.[5]

Variants that affect immune regulatory mechanisms

Alterations in regulatory cytokine levels are believed to play an important role in mediating immune suppression in helminth immune response. Genetic variants affecting *IL10* and *TGFB1* may be associated with both asthma/allergy and heminthiasis. We described a variant (rs3024496, G allele) in the IL-10 gene associated with the suppression of IL-10 production in *A. lumbricoides* antigen-stimulated cultures of peripheral blood leukocytes, and also, other variants within the same gene, were both positively associated with atopy and asthma and negatively associated with helminth co-infections.[65]

Several *IL10* promoter polymorphisms have been extensively studied. Some variants were significantly associated with high PBMC proliferative responses to *Onchocerca volvulus* antigen.[66] One of these promoter variants, the G-1082A was also associated with immune-related diseases including type 2 diabetes, multiple sclerosis, and asthma.[67] Moreover, the same variant was associated with pediatric asthma.[68] In an endemic area for *S. mansoni* alleles at the three promoter SNPs were associated with high tIgE levels in the same direction as in atopic individuals, but not with egg counts. IL10 promoter polymorphisms appear to influence non-specific tIgE levels, but not schistosomiasis-specific immunity.[7]

Genetic polymorphisms in *TGFB1* are associated with airway responsiveness and exacerbations in children with asthma.[69] Common variants in *TGFB1* gene affect both asthma/allergy and helminth infections. We demonstrated a negative association between rs1800470 (C allele), atopic wheezing and markers of allergy. In contrast, a positive association was observed between the haplotype ACCA and *T. trichiura* and *A. lumbricoides* infection. This later haplotype was also associated with increased IL10 production.[70]

The main cellular source of both IL10 and TGFB1 are T_{regs}, critical for the maintenance of immune homeostasis. The activation of FOXP3 transcriptional factor is pivotal for T_{regs} function. The human FOXP3 gene is located on the X-chromosome (Xp11.23) and because of sex differences among X-variants, insufficient efforts have been made to include X variants in GWAS. Ppolymorphisms in the FOXP3 gene have been evaluated in association studies for allergy[71] but only a few studies on asthma have been reported. A study reported a significant interaction between SNPs in FOXP3-IL2R genes and sIgE for worm eggs and asthma.[72] The SNPs rs2294019 and rs5906761 were associated with the risk of egg sensitization only in females.[71] The heterozygote genotype for rs3761547 was a risk factor for allergic rhinitis, and this association was reproduced in gene-gene interaction analysis with rs3761548.[72]

The immune regulation of allergic disease results not only from protective environmental factors including helminths, but also from genetic factors relating to *IL10* production or hyperactivation of type 2 immune responses. From an evolutionary perspective, the selective advantage acquired by humans able to mount an efficient protective immune response to helminth infections may make them more vulnerable to atopy and asthma.

Immunoregulation by helminths and clinical practice

Insert Table 1.

Examples of helminth infections and the allergic-type inflammatory responses with which they are associated.

Treatment of allergic diseases with systemic corticosteroids at immunosuppressive doses increase the risk of opportunistic infections. The helminth reported to affect immune suppressed hosts most frequently is *Strongyloides stercoralis*, occasionally resulting in uncontrolled dissemination of the parasite in the potentially fatal hyper-infection syndrome. *Strongyloides* hyperinfection has been associated also with other immunosuppressive drugs, lymphomas, and infection with HTLV-1 virus.[73] Because of the presumed central role of IgE in protective immunity against helminth parasites, treatment of severe asthma with anti-IgE antibody raised concerns about risk of severe or disseminated helminth infections. A multicentre randomized controlled trial of omalizumab for the treatment of asthma and rhinitis was safe in a population at risk of STH infections, although there was a modest increase in geohelminth infection.[74] The same safety concerns will be present in populations at risk of helminthiasis for other immunomodulatory compounds for treatment of allergic diseases, particularly those targeting specific type 2 effector pathways such as anti-IL5 and anti-*IL13/IL4*.

Helminth infections induce cellular immune hyporesponsiveness.[11] Such hyporesponsiveness has been associated with suboptimal vaccine responses.[75,76] Among pregnant women, soluble parasite antigens cross the placenta and modify fetal immune responses in such a way as to possibly affect vaccine responses in childhood.[77] Modification of the host immune response to helminths affects how humans respond immunologically to other pathogens such as those causing malaria[78] and tuberculosis,[79] however, effects on clinically measurable outcomes are less clear.

Insert Clinical Notes I.

Notes of relevance for clinical allergy practice on immunopathology of helminth infections.

Reports have indicated possible benefits of helminth infections on autoimmune diseases, inflammatory bowel disease, and even in the metabolic syndrome.[80] For example, an inverse association between lymphatic filariasis and type II Diabetes was reported,[81] and past infection with *S. japonicum* was associated with a lower prevalence of metabolic syndrome.[82] Intestinal helminth infections were inversely associated with risk factors for cardiovascular diseases, such as body mass index and lipid levels.[83]

Insert Clinical Notes II.

Notes of relevance on protection against allergy and other chronic diseases.

Exploring the immunomodulatory potential of helminths and helminth molecules

Helminth infection and immunomodulation of diseases

An observational study of patients with multiple sclerosis, who had acquired gastrointestinal helminth infections, reported remission of multiple sclerosis for over 4 years. Patients infected with parasites had reduced inflammatory cytokine responses and enhanced production of *IL10* as well as *TGFB*. Six of these subjects were followed up and remission continued into the sixth year, when four patients were offered anthelmintic treatment due to gastrointestinal problems. Subsequently their multiple sclerosis activity resumed while *IL10* and *TGFB* levels declined.[84]

Experimental infections of humans with live parasites employing either the pig whipworm, *T suis*, or the human hookworm, *N. americanus* have been reported.[85] The premise is that the immune system can be modulated with amelioration or remission of the inflammatory disease. In the case of treatment with *T. suis*, parasite eggs are administered orally. Initial studies reported a beneficial effect on Crohn's disease and ulcerative colitis.[86] *T. suis* eggs have been used to treat other immune disorders. A randomized controlled trial tested the efficacy of *T. suis* for the treatment allergic rhinitis in Denmark but showed no efficacy. Although *T. suis* infection generated a measurable anti-parasite response, infection did not affect allergen-specific responses.[87] Patients with Crohn's patients were infected with *N. americanus*, with the majority showing improvements in symptom scores.[88] A trial of *N. americanus* in patients with coeliac disease was unable to demonstrate clinical benefit.[89] A small randomized control trial in patients with asthma showed no significant benefit of hookworm infection on clinical symptoms, bronchial responsiveness or SPT reactivity.[90]

What may be the reasons for the disappointing findings of clinical trials to date? Experimental animal models have demonstrated helminth parasites reduce allergic reactivity, but most studies have been designed to prevent the development of allergic reactivity rather than treat established disease. Only a handful of studies have reported the effects of these infections on already established allergic reactivity.[91] Most of the experimental data available suggest that once the allergic reaction is established, helminth infections can do little to revert the disease process, raising the question whether there is any reasonable possibility of obtaining benefit through infections of individuals with active disease. Nonetheless, there are sufficient doubts with respect to optimal timing of treatment, the dose and systemic versus non-systemic infections, to justify future well-designed and justified randomized-controlled trials of helminth therapy for inflammatory conditions.

Tests with helminth molecules as immunomodulatory candidates

Recombinant proteins can reproduce the biological effects observed in infections with live worms. In experimental models of inflammatory disease, recombinant proteins derived from helminth molecules induce anti-inflammatory and inhibit pro-inflammatory cytokine production, promote regulatory cell recruitment and immune deviation.[92]

In mouse models, helminth ES molecules, and helminth-derived synthetic molecules have shown usefulness in treating or preventing the development of inflammatory diseases such as inflammatory bowel diseases, type 1 Diabetes, multiple sclerosis, rheumatoid arthritis and asthma. The synthetic production of ES-derived immune modulators avoids concerns raised by the use of live organisms.[93] Further, the molecule-based helminth treatment offers the advantage of delivery directly to the site of pathology.

We present in Table 2 a summary of pre-clinical and clinical studies of helminth molecules for the treatment of chronic inflammatory conditions affecting humans.

Insert Table 2.

Helminth molecule candidates for the treatment of inflammatory diseases.

Discussion

There is conflicting evidence of an inverse association between exposure to helminth infections and human chronic inflammatory diseases including allergic conditions. A possible causal relationship is supported largely by the findings from experimental animal models, while evidence from human studies has been equivocal. Evidence from clinical trials of live helminth parasites has been disappointing.

One explanation for the associations between allergy and helminths in epidemiological studies is the genetic evolutionary advantage of mounting strong type 2 responses protective against helminth infection although increasing the risk of allergy.[65] Alternatively, the sort of environmental and unhygienic living conditions where parasite infections are likely to occur also expose populations to multiple other microorganisms which may contribute to the modulation of inflammatory responses.[94,95] Moreover, there is evidence that several other contextual factors not always controlled for in observational studies might contribute to the inverse association between helminthes and allergy. Such factors include diet, nutrition, obesity, gut microbiome, physical activity, exposure to air pollution, stress and use of vaccines and antibiotics, all of which are related to an urbanized lifestyle, which has clearly been an important risk factor for allergy.[96,97]

How do we interpret the negative results of clinical trials of live helminth infections when helminth infections or helminth-derived molecules have proved so effective in controlling animal models of inflammatory diseases? The effects of helminth infections in humans are related to parasite burden and duration of infection. Clearly, there are safety and ethical concerns with treating humans with large infectious doses and maintaining infections for period of years that may be required to induce clinically relevant immune modulatory effects. Further, trials in humans have attempted to modify preexisting disease while most animal models have studied the ability of helminths to prevent disease.

Conclusions

There is consolidated evidence from studies in humans for a negative association of helminth infection with allergy, although the effect seems to vary by helminth species, parasite burden, and age of infection. Helminth infections may also provoke symptoms of allergy, although

such allergic inflammation tends to be modulated during chronic infections. Experiments in animal models of chronic inflammatory diseases have demonstrated the potential benefits of helminth infection or the use of helminth-derived molecules against allergic disease, but clinical trials in humans have been disappointing. We still have an inadequate understanding of the complex interplay between helminths and allergy and there is a need for more studies in humans and experimental studies in animal models to understand these interactions more fully. Certainly, the exploitation of helminth-derived molecules for the treatment of inflammatory conditions offers promising new avenues for research and development.

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Clinical Notes Box I.

Notes of relevance for clinical allergy practice on immunopathology of helminth infections.

- *Accuracy of allergy testing*
  when dealing with patients from endemic areas for helminth infections, an allergy workup including specific IgE may be more sensitive than SPT, but in subjects with a very high total IgE, *in vitro* tests may be false positive

- *Interpretation of total IgE and blood eosinophilia*
  elevated total IgE and peripheral blood eosinophilia may indicate helminth infection

- *Potential reduction in efficacy of vaccines for prevention of infectious diseases*
  it is important children and adults are free of worms for optimal efficacy of vaccines

- *Risks of prolonged use of systemic corticosteroids and immunobiological supressors of T2 inflammation mediators (Anti-IgE, Anti-IL5, Anti-IL4/13)*

treatment of severe asthma with continuous oral corticosteroids, *Anti-IgE, Anti-IL5 or Anti-IL4/13* poses risk of helminth superinfection. It is advisable to observe the patient closely, investigate and treat if necessary, when living or coming from a region that is endemic for worms.

Clinical Notes Box II.

Note of relevance on protection against allergy and other chronic diseases

- *Inverse association between helminth infection and allergy and other chronic diseases* there is compelling evidence of a strong inverse association between infection by various helminths and biomarkers of chronic inflammatory diseases and allergy
- *A causal association is plausible*
  a direct causality is plausible, taking into consideration experimental studies in animal models and humans

- *No robust association between helminth infection and protection against diseases*
  we found no robust evidence for causal associations between helminth infection and clinically relevant protection against disease, however

- *Exposure to helminths occur in a diverse environment that may be itself protective*
  in the real world, exposure to helminths often occur in a markedly different environmental, ethnical and lifestyle context, including contrasts in ancestrality, physical activity, diet, nutrition, stress, exposure to air pollution and to microorganisms

- *A protective environment may overshadow the effects of helminth infection*
  the potential influence of multiple factors in the health and diseases balance may overshadow the impact of exposure to parasites

- *The inverse associations may not be directly causal*
  the inverse associations between helminth infections and biomarkers of chronic inflammatory diseases and allergy may not be directly causal, but linked to conditions related to parasite infections

FIGURE LEGEND

Figure 1. Typical features of a rural household in a village in the municipality of Conde, Brazil, in which the prevalence of helminth infections was 83.5% (Grant et al, 2008) (picture taken in 2005).

Figure 2. Typical urban underserved neighborhood of Salvador, Brazil, in which the prevalence of helminth infection among children was below 20% (Alcantara-Neves et al, 2011).

Figure 3. Schematic representation summarizing the findings from epidemiological studies on the relationships between helminth parasites, atopy and asthma.

Figure 4. Helminths suppress autoimmunity and allergy via type 2 or regulatory immune response. Immunomodulatory molecules (IMs) of parasites activate innate immune cells that promote either Th2 or T_{reg} responses. IMs that induce TGFβ, IL10 by dendritic cells (DCs) or macrophages (Mθ) prime IL10 or TGFβ-producing T_{reg} cells suppress Th2 responses,Th1 or Th17 responses. A separate set of helminth-derived IMs activate type 2 innate cells, including basophils, M2 macrophages, and type 2 innate lymphoid cells (ILC2) and induce innate IL-4 production, which drives differentiation of Th2 cells. Th2 cells and type 2 innate immune cells can suppress Th1 and Th17 responses (modified from Finlay et al, 2014[48]).

Figure 5. Pathway analysis using Panther 11[87] version for the top SNPs associated in GWAS for asthma to date.

Tables

Helminth infection	Allergic-type reactions and syndromes
Intestinal helminths	
Ascaris lumbricoides	'Asthma-like' syndrome
Trichiura trichiura	Tropical dysentery syndrome
Hookworm	Ground itch/allergic enteritis
Strongyloides stercoralis	Larva currens/urticaria/'asthma-like' syndrome
Enterobius vermicularis	Itchy anus
Schistosomiasis	
S. mansoni	Cercarial dermatitis/acute schistosomiasis/urticaria/ 'asthma-like' syndrome
S. haematobium	
S. japonicum	
Filariasis	
Wuchereria bancrofti	Tropical pulmonary eosinophilia/acute lymphangitis
Onchocerca volvulus	Sowda/acute popular onchodernatitis/punctate keratitis
Loa loa	Calabar swellings
Others	
Toxocara spp.	Visceral larva migrans/'asthma-like' syndrome
Anisakis spp.	'gastroallergic'/asthma-like syndrome/urticara/anaphylaxis
Paragonimus spp.	Asthma-like syndrome
Trchinella spiralis	Acute trichinosis
Echinococcus granulosus	Acute anaphylaxis associated with rupture of cyst
Ancylostoma braziliense	Cutaneous larva migrans

Table 1. Examples of helminth infections and the allergic-type inflammatory responses with which they are associated.

Tables

Table 2. Helminth molecule candidates for the treatment of inflammatory diseases.

Molecule	Study phase	Treatment	Results	References
Excretory/secretory-62	animal models	rheumatoid arthritis and systemic lupus erytematosus	reduce disease severity and progression	Rodgers at al, 2015[159]
Neutrophil inhibitory Factor (NiF)	animal models and humans (Phase I/II)	acute stroke, allergen induced lung inflammation and diabetic retinopathy	no benefit in human stroke, favourable results in mouse models of lung inflammation and retinopathy	Krams et al, 2003;[160] Schnyder-Candrian et al, 2012;[161] Veenstra et al, 2013[162]
Migration inhibitory Factor (MiF)	animal models	colitis and allergic airway inflammation	favorable	Cho et all, 2011;[163] Park et al, 2009[164]
Cystatins	animal models	colitis and allergic airway inflammation	favorable	Whelan et al, 2014[165]
Helminth defense molecules	animal models	LPS-induced inflammation	favorable	Alvarado et al, 2017[166]
Anti-inflammatory protein-2 (AIP-2)	animal models	model of asthma	favorable	Navarro et al, 2016[167]
TGFB Pathway Manipulation	studies *in vitro*	molecular biology stage	promising	Freitas et al, 2009[168]
Prostaglandin E2 (PGE2)	studies *in vitro*	molecular biology stage	promising	Liu et al, 2013[169]
ShkT domains	animal models and humans (Phase I and II)	human psoriasis	unknown results	Beeton et al, 2006[170] and NCT02435342
AcK1 and BmK1	studies *in vitro*	immunology stage	promising	Steinfelder et al, 2016[171]

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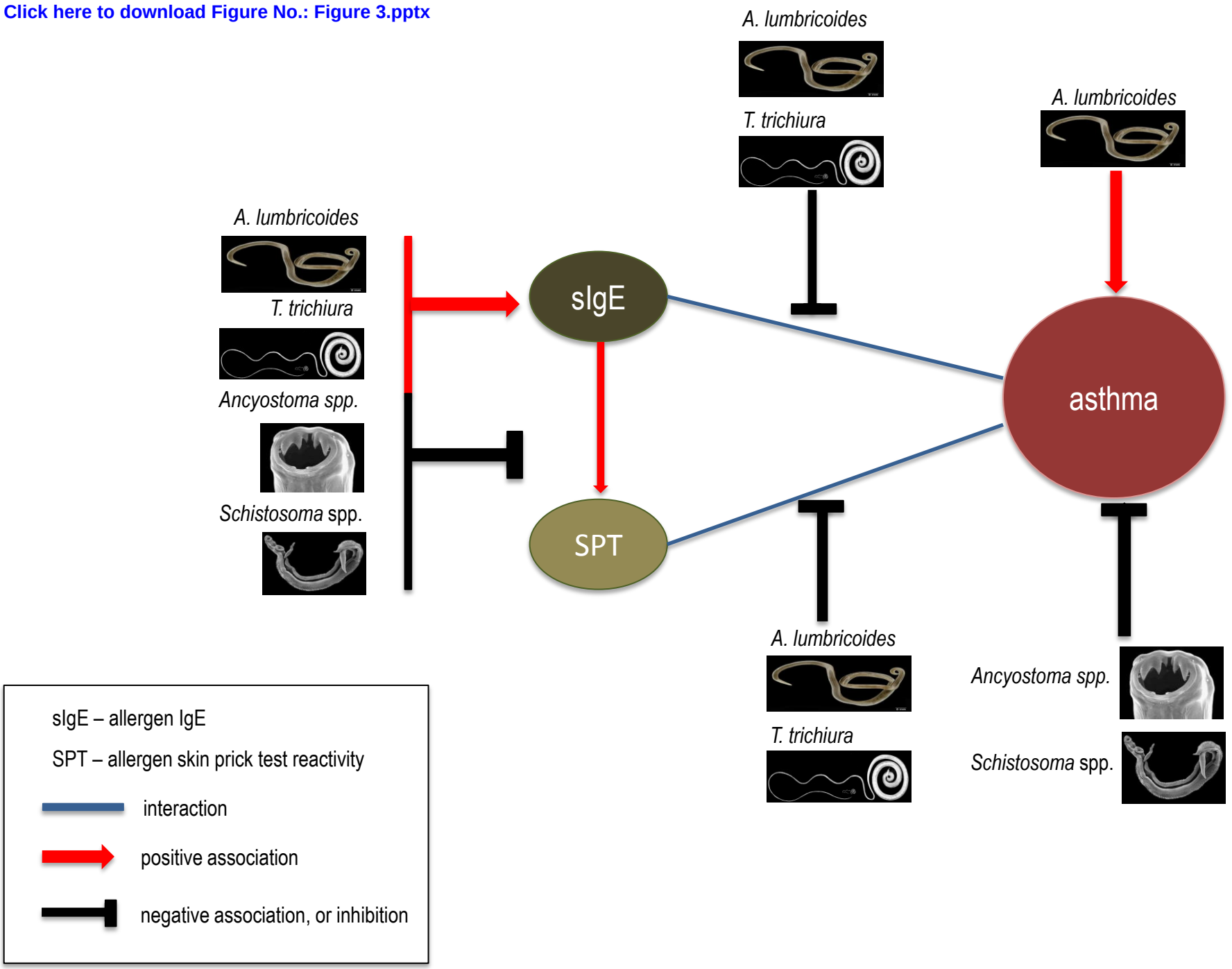

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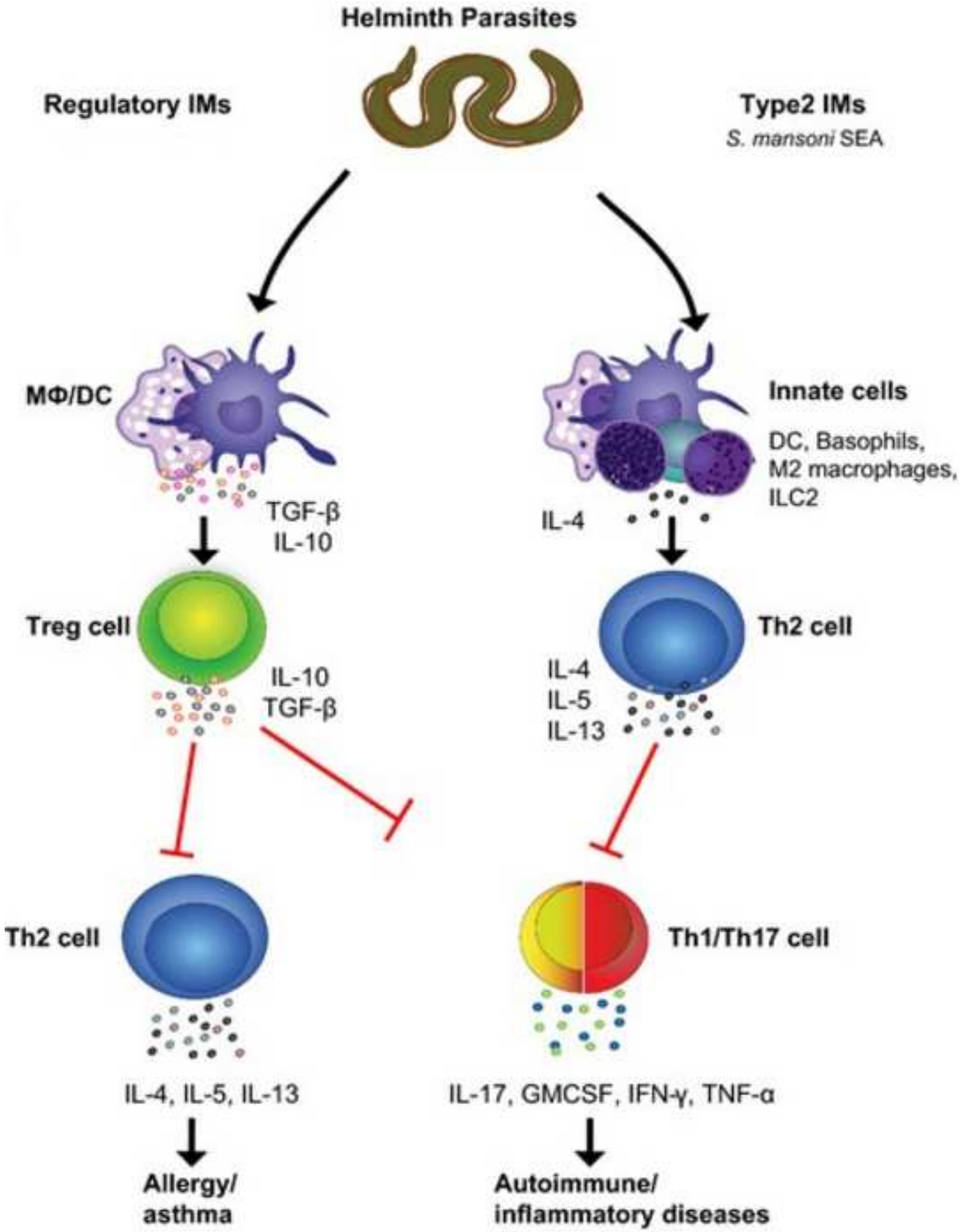

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