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Chapter 8

Helminthic Infections and Asthma: Still a Challenge for Developing Countries

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1. Introduction

Asthma is one of the most common chronic diseases in the world. It is estimated that around 300 million people in the world currently have asthma [1]. Asthma has become more common in both children and adults around the world in recent decades. The increase in the prevalence of this disease has been associated with an increase in atopic sensitization, and is paralleled by similar increases in other allergic disorders such as eczema and rhinitis [1]. The rate of asthma increases as communities adopt western lifestyles and become urbanized. With the projected increase in the proportion of the world's population that is urban from 45% to 59% in 2025, there is likely to be a marked increase in the number of asthmatics worldwide over the next two decades [2]. Nevertheless the prevalence of asthma in rural developing countries has been under estimated for many years [3]. In many areas of the world persons with asthma do not have access to basic asthma medications or medical care and are not included in any statistical survey [4]. Increasing the economic wealth and improving the distribution of resources between and within countries represent important priorities to enable better health care to be provided. The burden of asthma in many countries is of sufficient magnitude to warrant its recognition as a priority disorder in government health strategies. Particular resources need to be provided to improve the care of disadvantaged groups with high morbidity. Resources also need to be provided to address preventable factors [1, 2]. It is estimated that asthma accounts for about 1 in every 250 deaths worldwide. Many of the deaths are preventable, being due to suboptimal long-term medical care and delay in obtaining help during the final attack. The economic cost of asthma is considerable both in terms of direct medical costs (such as hospital admissions and cost of pharmaceuticals) and indirect medical costs (such as time lost from work and premature death) [1]. Therefore there is a greater understanding of

the factors that cause asthma which may lead to novel public health and pharmacological measures to reduce the prevalence of asthma seems to be a worldwide priority.

Among the many factors influencing the prevalence of asthma in developing countries from the tropics are geo-helminthic infections [3], including those caused by *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm (*Ancylostoma duodenale* and *Necator americanus*). These infections have a worldwide distribution being present in almost all geographic and climatic regions. The prevalence of these infections tends to be highest in warm, moist climates; also they are closely correlated with poor environmental hygiene and lack of access to health services [5, 6]. The estimated global prevalence of *A. lumbricoides*, *T. trichiura* and hookworm are 1.5 billion, 1.3 billion and 900 million, respectively, and greater than 2 billion humans are infected with at least one of these parasites [5, 6]. Hookworm is transmitted through skin contact with free-living larvae in the soil, whereas *A. lumbricoides* and *T. trichiura* are transmitted through ingestion of embryonated eggs from the environment. *A. lumbricoides* and hookworm undergo a phase of larval migration through the lungs, whereas *T. trichiura* has a purely enteric life cycle. Infections with *A. lumbricoides* and *T. trichiura* peak in prevalence and intensity between 5 and 15 years of age in endemic areas and there is a decline in both epidemiological parameters in adulthood [5, 6]. Morbidity, including important effects on growth, nutrition and mental development in childhood tends to be greatest in heavily infected children and vulnerable adults (e.g. women of child-bearing age) with long exposure histories [6]. Epidemiological observations have provided evidence that geo-helminthic infections can influence the development of allergic diseases such as asthma. Different studies carried out mostly in rural areas from different countries have shown that infection by intestinal helminths stimulates the risk of asthma [7, 8, 9], whereas other studies in similar populations, have shown an inverse association between asthma and the infection of these parasites [10]. Whether helminthic infections increase or decrease the risk of asthma may depend on environmental factors determining time of exposure and the prevalence and intensity of the infection [3]. On the other hand the individual capacity of the immune system to recognize certain allergenic components of the many molecules involved in host parasite interactions as well as the possible role of parasite mediators to inhibit inflammatory processes may be important aspects in the modulation of the pathogenesis of asthma by these parasites.

2. Immunological aspects of asthma

It is well accepted that asthma is a chronic inflammatory disorder of the bronchial mucosa [11]. The symptoms include chest tightness, wheeze, and cough, and often variable obstruction of airflow through the bronchi. The clinical manifestation of asthma is the result of three events within the airways: reversible obstruction, airway hyper-reactivity and inflammation. Among these factors, airway inflammation is believed to play a major role in the development of the disease [11].

The bronchial inflammation process of asthma is stimulated by cells of the innate immune system (dendritic cells, mast cells, eosinophils, neutrophils, macrophages and NK-cells) and

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of the adaptive immune system (CD4 + T-lymphocytes, and antigen-specific IgE secreting B-lymphocytes). The innate and adaptive cells are of Th2 class, secreting the cytokines IL-13 and IL-4 prominently or responding to these cytokines through their transduction molecule STAT6 [12, 13]. Thus, the input of these cells into the bronchus and the release or secretion of many mediators (e.g. heparin, reactive lipids or eicosanoids, and enzymes including tryptase and chitinase) lead to increased permeability of blood vessels and consequent edema, increased mucus production, and exaggerated smooth muscle contraction [13] causing airflow obstruction and the symptoms described above. Also, continued inflammation results in remodeling of the airway in which it is thought that TGF-β cytokine may drive the metaplasia of the epithelium, increased vascularity, thickening of the basement membrane, and muscular hypertrophy, leading to lasting airflow obstruction and breathlessness [14, 15].

The induction of adaptive immunity requires antigen-presenting cells (APCs). It is well known that dendritic cells (DCs) are the main type of APC involved in the induction of Th2 responses to allergens in asthma [16]. In the lung, DCs can be found throughout the conducting airways, interstitium, vasculature and pleura and in bronchial lymph nodes. Lung DCs express many receptors, including Toll-like receptors, Nod-like receptors and C-type lectin receptors up regulate the expression of several co-stimulatory molecules (such as CD80 and CD86) and chemokines (such as CCL17 and CCL22) that attract T cells, eosinophils and basophils into the lungs[16-19]. In humans, monocyte-derived conventional DCs promote Th2 responses by secreting pro-inflammatory cytokines and up-regulating the expression of co-stimulatory molecules after antigen stimulation[20] suggesting that lung DCs are necessary for Th2 cell stimulation during airway inflammation.

As mentioned above, various inflammatory cells, such as basophils, eosinophils and mast cells are recruited to airways after allergen challenge. Although the main focus in asthma has been on their roles as inflammatory cells, increasing data suggest that these cells also function as APCs to initiate or enhance Th2 responses. Basophils, which are circulating granulocytes that express the high-affinity IgE receptor FcεRI, amplify immediate hypersensitivity responses by releasing histamine-containing granules and by producing large quantities of IL-4 [13]. Moreover, several studies have highlighted a crucial previously unknown role for basophils as APCs that drive Th2 responses through their expression of major histocompatibility complex (MHC) class II and co stimulatory molecules [21]. Also it has been proposed that MHC class II- dependent interactions between basophils, which are prominent at sites of allergic inflammation, and CD4+ T cells may have an important role in the induction of Th2-mediated inflammation [22, 23]. Another circulating granulocyte that is prominent at sites of allergic inflammation is the eosinophil. After being stimulated, eosinophils have an important pro-inflammatory role by producing leukotrienes, as well as Th1 cytokines (interferon-γ and IL-2) and Th2 cytokines (IL-4, IL-5, IL-10, IL-13 and TNF-α which contribute to airway inflammation [11]. In addition, eosinophils, like basophils, can also function as APCs [24]. Other relevant components of airway inflammation are the mast cells which express FcεRI and c-Kit and reside in tissues near mucosal surfaces and blood vessels. Mast cells can initiate immediate hypersensitivity reactions by de-granulating in response to both adaptive (IgE-mediated) and innate immune signals. For example, mast cells can be activated through cross-linking of antigen-specific IgE

bound to FcεRI [25] or in response to Toll-like receptor agonists, or to cytokines such as IL-33 [26]. In addition to producing histamine and leukotrienes, mast cells produce cytokines (IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-16, tumor necrosis factor and transforming growth factor-β) and chemokines (such as IL-8, lymphotactin, CCL1 (TCA-3), CCL5 (RANTES), CCL2 (MCP-1) and CCL3 (MIP1-α)[27].

An important mediator of airway inflammation is Nitric Oxide (NO) which it is a diffusible gas that can activate biochemical process either on the same cell that produced it or on neighboring cells [28]. NO is synthesized from L-arginine by enzyme nitric oxide synthase (NOS), of which there are three isoforms : NOS I or neuronal NOS (nNOS) was originally isolated from rat and porcine cerebellum; NOS II or inducible NOS (iNOS) from activated macrophages; NOS III or endothelial NOS (eNOS) from endothelial cells [28]. High NO levels could be harmful for asthmatic patients because at elevated concentrations, NO lead to the formation of reactive nitrogen species (RNS) and subsequent oxidation and nitration of proteins, which negatively affect protein functions that are biologically relevant to chronic inflammation in the asthmatic bronchial tissues [28,29]. In asthmatic patients, NO is mainly produced by iNOS expressed in bronchial epithelial cells and some inflammatory cells [30]. NO is also produced by neutrophils and macrophages in response to IFN-γ and a second signal provided by a PAMP ligand or TNF-α. iNOS expression is induced by these signals, this enzyme promotes the oxidation of the guadino nitrogen of L-arginine, resulting in the production of NO and citruline [31]. In addition, other mechanisms have been associated with NO production. It has been demonstrated that the ligation of CD23 (low affinity receptor for IgE FcεRII) on human macrophages is a strong inducer of NO [32]. Indeed, the cross-linking of CD23 by IgE, (IgE - immune complexes or by specific monoclonal antibodies) induces pro-inflammatory response, including NO production [33]. Therefore, allergic sensitization inside the lower airways may account for NO production. In this context, it has been reported that aeroallergen sensitization correlated with exhaled NO (eNO) in mild to moderated asthmatic subjects [34]. Also, the late-phase influx of eosinophils may contribute to NO production at the respiratory mucosa.

3. Stimulation of airway inflammation by helminths parasites

It is important to point out that there are close similarities between the allergic inflammatory responses stimulated in the host by environmental allergens (described above) with the immune responses elicited by parasite antigens. Gut inflammation stimulated by intestinal nematode also include innate (mastocytes, basophils and eosinophils) and adaptive cells of Th2 class which secret preferentially IL-13 and IL-4 cytokines. Pro- inflammatory cells like mastocytes and eosinophils stimulated by these cytokines may release many mediators (heparin, reactive lipids or eicosanoids, and enzymes including tryptase and chitinase) leading to increased permeability of blood vessels, increased mucus production and smooth muscle contraction [35]. Also, inflammation induced by most helminths in the host is associated with NO production through somatic and excretory-secretory antigens of adult worm and larvae [36-40]. These mechanisms may contribute to make a hostile microenvironment in the gut for the parasites promoting worm expulsion.

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The capacity of helminths, to stimulate inflammatory responses has been well documented and they are probably related to the complex lifecycle and the antigenic composition of this nematode. For example, there is evidence that after penetration of the intestinal mucosa *A. suum* larvae migrate to the liver, inducing the formation of granulomas, extensive inflammation and tissue injury [41]. Surviving larvae reach the lungs and generate an inflammatory infiltrate in the airways dominated by severe per-alveolar eosinophilia [41, 42]. Pulmonary eosinophilia due to the passage of helminth larvae through the lungs is referred to as Loeffler's syndrome [43]. Eosinophilic pulmonary infiltrates and respiratory symptoms due to *A. lumbricoides or A. suum* are generally part of a self-limited process due to the transient nature of larval passage through the lungs in the *Ascaris* life cycle [44]. The majority of patients remain asymptomatic, however 8 to 15% of infected individuals display morbidity, with respiratory symptoms occurring 9 to 12 days after the ingestion of eggs and lasting 5 to 10 days [45, 46]. Symptoms may include cough, dyspnea, wheeze, and hemoptysis and may progress to frank respiratory distress [43]. Peripheral eosinophilia is often present at the onset of symptoms, but the peak level of eosinophilia will have a delay of several days from presentation [47, 48]. Also, *Strongyloides stercoralis* may cause pulmonary symptoms and infiltrates as a manifestation of chronic infection or as a result of hyper-infection in immune-compromised hosts [49]. The unique life cycle of *S. stercoralis* allows a chronic infection of extended duration to occur due to the ability of new filariform larvae to continuously infect the human host through the perianal skin or bowel mucosa [50]. Patients with chronic infection may have repeated episodes of fever and pneumonitis that may be mistaken for recurrent bacterial pneumonias [51]. Eosinophilia, though often absent during the acute episodes, may occur during the intervening period between episodes [51]. Pulmonary involvement of strongyloidiasis has been reported as an asthma mimic.

The mechanisms by which these parasites induce airway inflammation are still not well elucidated. High levels of polyclonal and specific IgE against adult stages of the parasite are a characteristic of *A. lumbricoides* infection [52]. It has been shown that *Ascaris* can induce allergic sensitization in animal models [42] and in human beings, including immediate cutaneus hyperreactivity [52] and airway response after aerosol challenge with parasite extracts [53] suggesting the presence of an allergenic component on the stimulation of the respiratory symptoms by these parasites. Helminths harbor an arsenal of many pro- allergenic molecules which may be involved in airway inflammatory processes. One of the most studied is the *A. lumbricoides* body fluid antigen -1 (ABA-1) [54-57] which constitutes the most important of the group of antigens of the denominated family of nematode polyprotein allergens (NPA) for its capacity to stimulate strong IgE responses [58]. Recognition of ABA-1 may have a genetic basis [59, 60]. For example, evidences from studies carried out in Colombian endemic areas have shown that polymorphisms of LIG4 and TNFSF13B of the 13q33 region are associated with high levels of specific IgE to ABA-1 in *A. lumbricoides* infected children [60, 61]. However, the possible role of this allergen in airway inflammation remains unclear. Another important allergenic component of helminths is tropomyosin, which is a microfilament associated protein present in all eukaryotic cells, essential in the process of muscle work, proper action of the movement apparatus and the basic functionality of filaments within the cytoskeleton [62]. There is a high degree of homology among tropomyosins even of phylogenetically distant species of inver-

tebrates, but not with vertebrate tropomyosins [62]. Invertebrate tropomyosins induce IgE antibodies and are potent allergens for humans whereas vertebrate ones were reported to be non-allergenic [62, 63]. Tropomyosin from *A. lumbricoides* presents a high degree of sequence identity to those from other invertebrates, including cockroach, mites, and shrimp [64]. It is expressed in high levels in the third stage larvae (L3), which is the stage of pulmonary passage of the parasite and stimulates strongly the production of IgE [64], high positivity to skin prick tests and histamine release from basophils[64, 65]. *A.lumbricoides* tropomyosin cross-reacts with other invertebrate tropomyosins [64] thus enhancing the allergic response to other environmental allergens containing tropomyosin (cockroach, mites, and shrimp) [64, 65] which are known to induce airway inflammation and asthma [65]. Other important nematode allergens are chitins, an important component for egg shell integrity and for the structure of the rigid pharynx, including the buccal cavity and grinder, a specialized cuticle that is shed and resynthesized during molting [66]. There is evidence that chitins are involved in Th2 type inflammation. For example, experimental models of asthma using mice have shown that the intranasal administration of chitin induced an accumulation of eosinophils and basophils [67]. Exposure to chitin also stimulated the alternative activation of macrophages as indicated by the presence of arginase-expressing cells in the lungs as early as 6 h post intranasal administration of chitin [67]. The recruitment of innate immune cells has shown to be dependent both upon expression of the high affinity receptor for leucotriene B4, BLT1 and upon the presence of macrophages [68] suggesting a possible role of chitin in innate immune cell recruitment, leading to preferential Th2 type responses. In humans, The non-chitinolytic chitinase YKL-40 has been linked to allergic inflammation. YKL-40 levels are elevated in the serum and bronchoalveolar lavage (BAL) fluid of asthmatics [69]. Furthermore, increased YKL-40 levels correlated with asthma severity and are elevated in response to allergen challenge. Nematode proteases which constitute a group of highly evolutionary conserved molecules may exhibit allergenic properties such as other proteases like house dust mite-derived *Der p 1*, domestic cats- derived *Fel d1*, and fungal allergens [70, 71]. These allergens most often gain access to host tissues at mucosal sites and in some individuals elicit potent Th2 cytokine responses, reflecting the hallmarks of the immune response to helminthic infection including eosinophilia, goblet cell hyperplasia and elevated serum IgE levels as explained above. Basophils which are innate immune cells able to rapidly secrete IL-4 *in vitro* following stimulation with anti-IgE [72] as well as in response to allergens and helminth products [73], would be involved in the innate sensing of these products which may lead to the initiation of adaptive Th2 cytokine responses to parasite and/or environmental allergens. For example, immunization of mice with the cysteine protease allergen, papain, resulted in the transient recruitment of basophils to lymph nodes that peaked 1 day prior to the peak of IL-4 producing CD4+ T cells [74]. These papain-elicited basophils within the lymph node were shown to express thymic stromal lymphopoietin (TSLP), an IL-7-like cytokine produced predominantly by epithelial cells and implicated in CD4+ Th2 cell differentiation [74]. Given their multiple roles in regulating inflammation, cellular trafficking and epithelial barrier function members of the protease-activated receptor (PAR) family [75] would be potential molecular targets for helminth proteases.

Regardless of the intrinsic allergenic potential of these parasites, there are evidences that active infection can potentiate the allergic response to non-related antigens. For example, it has been

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shown that antigenic extracts of *A. suum* potentiate allergic responses to ovalbumin in pigs (76, 77). It has been also reported that co-administration of hen egg lysozyme with the excretory / secretory products of *N. brasiliensis* in mice results in the generation of egg-lysozyme-specific lymphocyte proliferation, IL-4 release and IgG1 antibody responses [78]. Furthermore, it has been shown that unidentified components in the body fluid of *A. suum* promotes a Th2 response and are adjuvant for specific IgE synthesis to some parasitic allergens like ABA-1 [79]. Because, in addition to this allergen, *A. lumbricoides* extract has at least 11 human-IgE-binding components, the adjuvant effect may be more generalized in humans beings, and because of co-exposure with other environmental allergens, this could happen for cross-reactive and non-cross-reactive mite allergens [61].These observations are consistent with early studies carried out in atopic Venezuelan children in which an elevated percentage of skin positivity as well as high levels of specific serum IgE toward aero-allergens, were found among children infected with *A. lumbricoides* compared to their non parasitized counterparts [80].

4. Epidemiological studies showing a positive association between helminthic infections and asthma

Human immune response to infections with helminths parasites may differ according to the profile of the infection. As mentioned above, acute or seasonal infections may include primary infections and repeated or intermittent infections without long period of continuous infections and may result from infrequent short exposures or intermittent exposure after treatment in endemic areas [3, 5]. It has been proposed that mild, seasonal helminthic infections stimulate preferentially inflammatory Th2 type immune responses among parasitized populations [3, 81] characterized by the production of high levels of serum specific IgE and allergic reactivity toward parasite soluble antigens [82] which may lead to the development of bronchial hyper reactivity and asthma [83, 84] particularly among atopic individuals [85]. This situation may be reflected on the increased prevalence of asthma and allergic diseases observed in many low and middle-income countries [86, 87] undergoing parasite eradication programs [5, 6]. For example, epidemiological studies carried out in different rural communities in China, have shown a strong association between Ascaris lumbricoides infection and the development of asthma [88]. These early results are consistent with a meta-analysis of many of studies investigating the association between the presence of geohelminth eggs in stool samples and asthma providing some evidence for parasite-specific effects [7]. In this work in which thirty-three studies were taken in account, *Ascaris lumbricoides* was associated with significantly increased odds of asthma (OR, 1.34; 95% CI, 1.05–1.71; 20 studies. Further studies carried out in urban Brazil have shown positive associations between Ascaris lumbricoides infection with recent wheeze [9] which in turn have been associated to allergic sensitization toward A. lumbricoides antigens [9]. Other studies carried out in Costa Rica have shown a relationship between sensitization (defined as a positive IgE) to A. lumbricoides and measures of asthma morbidity and severity in a population with low prevalence of parasitic infection but high prevalence of parasitic exposure [89]. In this work, a cross-sectional study of 439 children (ages 6 to 14 years) with asthma was carried out and linear regression and logistic regression were used for the

multivariate statistical analysis. Sensitization to A. lumbricoides was associated with having at least 1 positive skin test to allergens (odds ratio, 5.15; 95% CI, 2.36-11.21; P <.0001), increased total serum IgE and eosinophils in peripheral blood, reductions in FEV (1) and FEV (1)/forced vital capacity, increased airway responsiveness and bronchodilator responsiveness, and hospitalizations for asthma in the previous year (odds ratio, 3.08; 95% CI, 1.23-7.68; P = 0.02). Similarly, it has been also reported that sensitization to A. lumbricoides is associated with increased severity of asthma among Romanian children [90]. This association was mediated by a high degree of atopy among the asthmatic children sensitized to A. lumbricoides and belonging to a population with a low prevalence of helminthiasis. In according to these findings, studies carried out in Venezuela have shown strong associations between A. Lumbricoides infection and bronchial hyper-reactivity [84]. In this work, 470 school children from different rural and urban communities were evaluated. It was found that in rural children, bronchial hyper reactivity was associated with increased specific levels of anti- IgE ($p<0.0001$) and skin test positivity toward A lumbricoides antigens ($p<0.0001$). The percentage of FVE1 predictive values correlated inversely ($p<0.0001$) with anti-A lumbricoides IgE levels. Elevated numbers of circulating CD3+CD4+ and CD20+CD23+ cells were found in rural children with bronchial hyper reactivity compared to their asymptomatic counterparts. They correlated positively with anti-A lumbricoides IgE levels ($p<0.005$ and $p<0.0001$ respectively). In contrast, in urban children, bronchial hyper reactivity was associated with elevated anti-D pteronissinus IgE levels (p=0, 0089), skin hyper reactivity towards this aero allergen (p=0,003) and to an increase in the number of CD3+CD8+ ($p<0.0001$). These results were consistent with previous work showing that monthly treatments of parasitized asthmatic children with anti-helminthic drugs in Venezuela may reduce BHR, symptoms of wheeze and the need for asthma medications [2]. Taking together these findings suggest the importance of the atopic condition on the airway inflammatory response stimulated by these parasites [91]. On the other hand, studies performed in slum children from endemic areas have shown that parasitized non-asthmatic children can significant respond to bronchodilator inhalation, and that this response can be reversed by anti-helminthic treatment suggesting that these parasites cause bronchoconstriction [92]. Moreover, in a more recent study it was shown that infestation with *Ascaris lumbricoides* in Brazilian children increased the risk of non-atopic asthma [8] such that children with high load infestation (≥100 eggs/g) have been found to be five times more likely to have BHR than children with low load or no infestation [8]. Thus, regardless the atopic status of the individuals, the link between helminth infestation and non-atopic asthma could be mediated by the stimulation of transient inflammatory responses by parasite antigens in the pulmonary phase of the helminth life cycle such as those described according to the Loeffler's syndrome.

5. The other side of the coin: Chronic helminthic infection may suppress allergic manifestation and the development of asthma

Because parasites are in constant attack by a range of effective immune mechanisms, they have developed effective evasion mechanisms which may vary from simple avoidance to a more active modulation of the immune response in order to establish a non inflammatory environ-

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ment that allows the parasite to survive. Nematode parasites may enhance survival by directing the immune response to that of a less appropriate type. For example interference with the Th1/-Th2 response balance, the production of high levels of regulatory cytokines such as IL-10 and TGF- β which may lead to a general suppression of T and B cell responses and also mimicry of host proteins which direct the immune response to tolerance have been reported [93]. It has been proposed that because these suppressing mechanisms are not parasite- specific, they may affect the development of allergic reactions in chronically exposed populations [94, 95]. It has been proposed that the effect of geo-helminths on the suppression of atopy is more important early in life causing a deviated Th2 immune phenotype that is not changed later in life, after elimination of the infection [96]. Moreover, there is evidence that maternal helminthic infections could affect infant immunity [97, 98] raising the possibility that the immunologic effects of infection start in the fetus. Further, the inverse association between chronic helminthic infections and allergic disorders among school children from different rural populations from Venezuela, Gambia, Ethiopia, Taiwan, Ecuador and Ghana has been well documented [99].

The exact mechanisms by which these parasites dampen allergic responses are probably multiple. Chronic helminthic infections may protect against allergic disease because of their profound suppression of the host immune system, leading to a general T-cell hypo responsiveness that is facilitated by the activity of regulatory T (Treg) and B cells and the modulation effects of innate immune cells such as macrophages, dendritic cells (DCs) and local stromal cells, resulting in an anti-inflammatory environment characterized by increased levels of interleukin (IL)-10 and transforming growth factor (TGF)-β [100]. In humans, several studies have shown that Treg cell activity (both by natural CD4+CD25+FoxP3+ and adaptive CD4+IL10+ Tr1 cells) protects against allergic disease [100,101, 102]. Indeed, successful allergen specific immunotherapy in humans which leads to a reduction in allergic symptoms has been associated with the emergence of IL-10–producing Treg cells which may be involved in the increase in IgG4 and IgA responses and a simultaneous decrease in IgE [103]. Several studies carried out in distinct experimental models have revealed a number of active molecules in extracts of helminths that can modulate the immune system of the host. Early work conducted by Itami et al [104] have demonstrated that high molecular weight components purified by gel filtration chromatography from an *A. suum* adult worm extract were able to suppress the murine antibody production to a bystander antigen. This effect was attributed to a 200 KD a protein component called PAS-1. The protein was affinity purified using a monoclonal antibody (MAIP-1) produced against high molecular weight suppressive components. Pas-1 was shown to be capable of down regulating antibody production Th2 secretion; eosinophils recruitment and airway hyper-responsiveness induced by *A. suum* allergens [105]. This effect was mediated by the stimulating capacity of Pas-1 on the production of regulatory cytokines such as IL-10. Probably the best-characterized groups of helminth immunomodulators are the cystatins (cysteine protease inhibitors) [106] which can inhibit antigen processing and presentation [107], interfering with antigen-specific T cell responses and the proliferation of T and B cells. They can also modulate cytokine responses. Particularly they are involved in the up regulation of IL-10 that leads to the down regulation of co-stimulatory surface molecules of macrophages [108]. These properties contribute to induction of an anti-inflammatory environment, concomitant with a strong inhibition of cellular proliferation. Also, carbohydrates linked to pro-

teins and lipids of nematodes, particularly those of phosphorylcholine (PC)-modified carbohydrates [109] have attracted significant attention in the past years due to their immunogenic and immunomodulatory properties. Structural features of glycolipids including oligosaccharide backbone, substitution with PC, and ceramide composition are shared between all the parasitic nematode species with widespread anatomical location in the worm [109] suggesting the importance of these components in host parasite interactions. The secreted filarial nematode glycoprotein ES-62 constitutes a suitable example. Through PC modifications, ES-62 can inhibit the proliferation of CD4+ T cells and conventional B2 cells *in vivo*, and reduces CD4+ cell IL-4 and IFN-γ production [110]. Conversely, ES-62 promotes proliferation and IL-10 production by peritoneal B1 cells [111]. It has been proposed that inhibition of proinflammatory Th1 responses occurs as ES-62 interacts with toll-like receptor (TLR) 4 through its PC residues [112], also in mast cells the interaction of TLR 4 with ES-62 results in the inhibition of degranulation and release of inflammatory mediators [113]. On the other hand, like proteins, glycolipids can be target of antibody responses. In the case of helminths antibody reactivity to lipids has been described in schistosomiasis [114] and more recently in *A. lumbricoides* infection [115]. Epidemiological studies using *Ascaris* derived glicolipids have shown that children carrying heavy infections show highest IgG reactivity glycolipids compared to lightly or non-infected children [115]. In the same study IgG antibody reactivity to both glyco proteins and glycolipids were directed to the PC moiety as determined by either removal of this group or a competition assay suggesting that *A. lumbricoides* specific glycolipids have antigenic properties. The mechanism by which glycolipids can stimulate IgE and IgG responses is not clear. It is possible that antibodies could develop directly to glycolipids through activation of CD1d which is a non classical MHC lipid presenting molecule. Nevertheless, cross reactivity between glycolipids and PC present on proteins may also occur [115]. The immunomodulatory effects exhibited by PC- substituted molecules can be seen as a contribution to equilibrium in host -parasite interactions in which expanding of TH2 type responses enables the parasite to survive preventing harmful pro-inflammatory mechanisms in the host. Since PC substituted molecules from nematode differ clearly from those from the host, they would be a suitable target for the development of new anti inflammatory drugs.

6. Future challenges and research perspectives

As mentioned above, the prevalence of asthma in rural developing countries has been under estimated for many years and in many areas of the world in which persons with asthma do not have access to basic asthma medications or medical care and are not included in any statistical survey. Thus adequate control of asthma in developing countries would require improvements in health care and the development of technologies to obtain the information needed to identify high-risk groups (disease mapping) [3]. This goal would be difficult to achieve if countries do not allocate resources to enable better health care. On the other hand, since many years several global efforts have been made to address the health effects of human parasitism by helminths which results from poverty and exert a well known detrimental impact on the health status of children continuously exposed to these parasites. The World Health Assembly (WHA)

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has adopted several resolutions calling for the control or elimination of these diseases, and for the implementation of a number of large-scale control and elimination programs. However, despite such WHA/WHO resolutions, the control of morbidity and the elimination of these infections are still a big challenge for global health programs. Some of the identified obstacles include the current scarcity of tools for updated disease mapping, the development of new anthelmintic drugs and vaccines, the improvement of sensitive diagnostic tools and the monitoring of the progress of control interventions and quantification of changes in incidence of infection and disease [116]. However and according to the WHA/WHO resolution, mass chemotherapy have been widely implemented in rural areas of many developing countries in which sanitary limitations are far to be overcome [6]. Under these conditions, this approach would reduce worm burdens without elimination of the infection in endemic areas, which gradually will change the profile of the infection from a chronic pattern, with moderate to heavy worm burdens [5] to a more mild and seasonal pattern [5], thereby disrupting the regulatory, anti-inflammatory effect of chronic infections on the immune response, allowing allergic sensitization in atopic parasitized individuals [117, 118]. Thus, the development of diagnosis protocols facilitating rapid identification of atopic individuals among rural populations is an immediate challenge to achieve control of parasites without affecting the health status of a significant proportion of these populations. On the other hand, the presence of respiratory symptoms as a consequence of inflammation due to the parasite migratory phase in non atopic individuals [8] must also be considered. For these purposes, large birth cohort studies designed according to specific epidemiological objectives and based on results from cross-sectional studies, small longitudinal and pilot intervention studies would help to elucidate the role of the many parameters involved in host- parasite interactions contributing to the pathogenesis of asthma. Also, the identification of conserved features of helminth products that interact with innate immune cells to co-ordinate adaptive anti-parasite responses as well as of potent parasite derived allergens is a key challenge to improve the technology used in the diagnosis and monitoring of allergic diseases in the tropics. Noteworthy is the cross-reactivity of helminth antigens with environmental allergens which may explain the high prevalence of IgE sensitization to invertebrate allergens leading to the development of asthma and other allergic diseases [61]. Finally, the identification and characterization of individual helminth-derived immunomodulatory molecules that selectively induce regulatory immune responses will provide potential candidates for immunotherapy [119] and must be the subject for future research programs.

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