

Parasites and asthma

Lin Wuhao^{1,2} · Chen Ran^{1,2} · He Xujin³ · Wu Zhongdao^{1,2,4} · Paron Dekumyoy⁵ ·
Lv Zhiyue^{1,2,4}

Received: 26 March 2017 / Accepted: 26 June 2017
© Springer-Verlag GmbH Germany 2017

Abstract Nowadays, many studies have found low morbidity of asthma in epidemic areas of parasitic diseases, as shown by the hygiene hypothesis. It is obvious that some parasite infections can prevent asthma and studies have been carried out to clarify the mechanism of the preventive effect and search for the future asthmatic therapies. Previous findings have indicated that this mechanism may be related to the immune response switching from Th1 to Th2 and important cells induced by parasites, including the regulatory T cells, regulatory B cells, dendrite cells, and alternatively activated macrophages. Cytokine IL-10 also plays a nonredundant role in protection against allergic airway inflammation in asthma. This review focuses on the relationship between parasites and asthma, and the potential protection mechanism involved.

Keywords Parasite · Asthma · Prevention · Therapy

Lin Wuhao, Chen Ran, He Xujin are the joint first authors

✉ Paron Dekumyoy
paron.dek@mahidol.ac.th

✉ Lv Zhiyue
lvzhiyue@mail.sysu.edu.cn

¹ Zhongshan School of Medicine, Sun Yat-sen University, 74 2nd Zhongshan Road, Guangzhou 510080, China

² Key Laboratory of Tropical Disease Control (Sun Yat-sen University), Ministry of Education, Guangzhou 510080, China

³ The Affiliated High School of South China Normal University, Guangzhou 510630, China

⁴ Provincial Engineering Technology Research Center for Biological Vector Control, Guangzhou 510080, China

⁵ Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand

Introduction

Asthma is a chronic inflammatory disease of the airways of the lungs, especially the bronchi and bronchioles. Inflammation can cause the hypertrophy, hyperplasia and increased contractibility of the smooth muscle of the airway, the hyperplasia of the glands, and infiltration of the inflammatory cell, especially the eosinophils (Maddox and Schwartz 2002). The characteristic symptoms of asthma are chest distress, breath shortness, wheezing, and coughing, occasionally with sputum. These symptoms often exacerbate at night, in the early morning, during exercising, and in cold air (British Thoracic Society Scottish Intercollegiate Guidelines N 2008). A variety of factors are associated with asthma, such as environmental factors and genes. For example, some allergens like dust mites and pollen can cause asthma, and air pollution like NO₂, O₃, and airborne traffic-related pollutants can result in exacerbation of asthma (Kelly and Fussell 2011). Infections of the respiratory syncytial virus (RSV) can also give rise to asthma (Gern and Busse 2002). In addition, many genes are closely related to asthma, like ADAM33, ADRB2, CD14, FCER1B, HLA-DQB1, HLA-DRB1, IL13, IL4, IL4RA, and TNF which are mainly located on chromosomes 5q31–33, 6p21, and 12q13–q24 (Ober and Hoffjan 2006). Now, there are many drugs available for treatment. β_2 -agonists, such as salbutamol, are helpful to rapid symptoms, and inhaled corticosteroids are effective in long-term control (National Asthma and Prevention 2007). However, these treatments show no effect on some asthmatics. As more and more molecular studies on asthma are being performed, specific targeting therapy may be developed in the future (Gauthier et al. 2015).

Nowadays, along with the development of the hygiene hypothesis, many diseases have been linked to exposure to bacteria and parasites. What interests us is that parasites have

been found to protect against many autoimmune diseases like inflammatory bowel disease (IBD) and multiple sclerosis (MS), in previous studies (Lin et al. 2014). It has been postulated that immune system modulation can be induced by infectious agents like parasites, which coevolve with their hosts (Rook 2010). A rapid increase of asthma incidence is found in developed countries, but does not appear in developing countries, especially in some parasite-prevalent countries. According to the hygiene hypothesis, this may relate to the diminishment of parasite infection, which can modulate the immune response and establish a special microenvironment that fits both the worm and the host. This provides a new area in which to search for more effective approaches for treatment and prevention of asthma.

Helminth and prevention of asthma

Epidemiological studies

According to meta-analysis, parasites are linked to asthma. The analysis of epidemiological studies showed that helminth infection such as hookworm can attenuate the risk of the asthma, but not all helminths protect against asthma (Leonardi-Bee et al. 2006; Ponte et al. 2014). A large cohort study reported that the early heavy infection of *Trichuris trichiura* or *Schistosoma* infection provided a protective effect, reducing reactivity to allergen shown in the house-dust mite skin prick test, which is a measurement of atopy similar to asthma (Rodrigues et al. 2008; van den Biggelaar et al. 2000). Moreover, it was demonstrated that *Schistosoma* infection can relieve wheezing in asthmatic children in Brazil (Medeiros et al. 2003). Yet, another study found that asthma is less common in *Enterobius*-infected primary school children in Taiwan (Huang et al. 2002). Therefore, there is an association between parasite-infection and asthma, of which the mechanism is gradually being revealed.

Immune deviation of Th2 response and important cytokines

Among all kinds of asthma, Th2 asthma is the most common. Its characters include the proliferation of CD4⁺ Th cells; elevated levels of Th2 cytokines such as IL-4, IL-5, and IL-13; increased production of IgE; and eosinophil infiltration (Robinson 2000). This kind of asthma also leads to inflammation of the bronchi. Th2 asthma can be inhibited by increased Th1 response or suppression of the Th2 response (Huang et al. 2001). IL-5 induces progenitor cells from bone marrow to differentiate into eosinophils and produce IL-4 in the lung, which amplifies the Th2 response (Chen et al. 2004; Rzepecka et al. 2013). And IL-4 or IL-13 plays an important role in antibody class-switching of IgE, which is the key

antibody involved in Th2 asthma, and regulates the growth and differentiation of mast cell and eosinophil (Hsieh et al. 1992; Rincon et al. 1997). In addition, IL-13 promotes the hyperplasia of goblet cells that contributes to asthma (Palframan et al. 1998). Thus, the production of IL-4, IL-5, and IL-13 may be critical in the pathogenesis of asthma. Infection of *Heligmosomoides polygyrus*, *Schistosoma mansoni*, and *Litomosoides sigmodontis* can induce suppression of IL-5 production in murine asthma model (Dittrich et al. 2008; Kitagaki et al. 2006; Pacifico et al. 2009). Not only helminth infection but also products of helminth can achieve the same effect. Cystatin, a secreted protease inhibitor of nematodes, can modulate cytokine responses and result in an anti-inflammatory environment (Hartmann and Lucius 2003). Cystatins from filaria and from *Angiostrongylus cantonensis* can suppress the production of IL-4, IL-5, and IgE, thus providing an effect of reduced allergic airway hyperreactivity in ovalbumin (OVA)-induced asthma model (Ji et al. 2015; Schnoeller et al. 2008). However, OVA models are difficult to be extended to clinical allergic asthma. While grass pollen-induced allergic model may be more convincing. Filarial cystatin was found to be preventative of airway hyperreactivity and inflammation in the grass pollen-induced allergic model, when administrated to mice in the sensitization phase (Danilowicz-Luebert et al. 2013). And data has shown that the Th2 responses, like secretion of IL-4, IL-5, and IL-13, were suppressed (Danilowicz-Luebert et al. 2013). In addition, treating human peripheral blood mononuclear cells (PBMCs) from patients who are sensitive to timothy grass pollen with filarial cystatin caused a Th1 polarization, pointing to a potential therapy for asthmatics (Danilowicz-Luebert et al. 2013). In addition to cystatins, ES-62, a phosphorylcholine-containing glycoprotein secreted by *Acanthocheilonema viteae*, was shown to inhibit OVA-induced allergic airway hyperresponsiveness (AHR) in mice by balancing the Th1/Th2 response through increased IFN- γ production and downregulation of Th2 cytokines like IL-4, IL-5, and IL-13 and the level of IgE. And Treg cells were not involved (Rzepecka et al. 2013). Extracts of *Ascaris lumbricoides* and *Angiostrongylus costaricensis* also led to a significant reduction of IL-5 in bronchoalveolar lavage (BAL) of OVA model (Pitrez et al. 2015). IL-17, which may promote Th2 polarization and eosinophil and neutrophil recruitment and contribute to severe asthma, is critical in the pathogenesis of asthma. Cystatins for *A. cantonensis* and ES-62 of *A. viteae* can ameliorate the asthmatic response accompanied by reduction of IL-17 (Dias and Banerjee 2013; Iwakura et al. 2011; Ji et al. 2015; Murdock et al. 2012; Rzepecka et al. 2013). However, whole infectious agents or intact proteins may raise side effects to patients, so peptides can be a safer choice for prevention or treatment purposes (Ren et al. 2016). Overlapping peptides of *Schistosoma japonicum* protein SjP40 can reduce Th2 cytokine responses, like IL4 and IL5,

and increase Th1 cytokine responses, like IFN- γ , thus resulting in decreased airway inflammation and mucus production in OVA-induced allergic asthma mice (Ren et al. 2016). In addition to IL-4, IL-5, and IL-17, other cytokines may also participate in the preventive effect against asthma. *A. costaricensis*-infected mice showed a decreased OVA-challenged pulmonary inflammatory response, which may arise through a downregulation of IL-1 β and neutrophils, because IL-1 β and neutrophils were found to be increased in some asthma subjects. However, eosinophil counts were not decreased in these experiments (Pinto et al. 2004). Previous studies further point to the different immune responses triggered via extracts or whole worm infection.

It is well known that parasite infection can induce a shift to Th2 response. However, this kind of infection can actually ameliorate AHR rather than enhance it (Moncayo and Cooper 2006). The mechanisms may rely on immune response deviation, which refers to the suppression of Th2 response to protect them from the host immunity and facilitate their survival in the human body. And the Th2 response biasing may be induced by the increased production of IFN- γ , because anti-IFN antibodies blocked protection against airway inflammation (Rzepecka et al. 2013). And immune regulation, like the elevated production of IL-10 and increased population of Treg cells, may contribute to the alleviation of asthma.

Immune regulation of IL-10

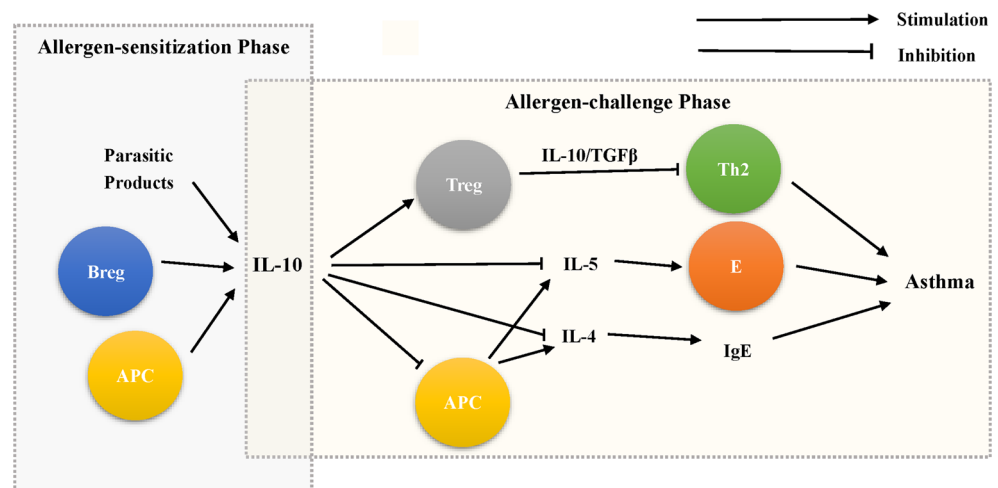
IL-10 plays an important role in the suppression of the symptoms of asthma (Fig. 1). It downregulates the production of IL-5, antigen-presenting cell (APC) functions, and IgE production (Jeannin et al. 1998; Moore et al. 2001; Schandene et al. 1994). The suppressive role of IL-10 induced by *Schistosoma haematobium* infection was found in atopy, which may present as allergic asthma (van den Biggelaar et al. 2000). IL-10-producing B cells have been shown to alleviate AHR, and this

may relate to the downregulation of Th2 cytokines and other anti-inflammatory response (Barnes 2001; Mangan et al. 2006). Therefore, further study of IL-10 will be important in the search for asthma therapy. Infection of *S. mansoni* and *H. polygyrus* can suppress asthma and exhibit an increased level of IL-10 (Amu et al. 2010; Kitagaki et al. 2006). *Trichuris muris*-infected mice experienced an increase of IFN- γ and IL-10, resulting in inhibition of allergic airway inflammation (AAI) development induced by papain. Moreover, IFN- γ and IL-10 play nonredundant roles in protection against AAI, given that the upregulation of IL-10 in Rag1^{-/-} mice without IFN- γ responses does not reduce the airway inflammation (Chenery et al. 2016). In addition to the parasite infection, extracts or products of parasite can also induce the elevated level of IL-10. Schistosomula tegument (Smtg) can increase IL-10 production from CD11b⁺F4/80⁺IL-10⁺ and CD11c⁺CD11b⁺IL-10⁺ cells, and it may be the main substance that cause the similar result in *S. mansoni* infection experiments (Marinho et al. 2016). Extracts from *A. lumbricoides* and cystatins of *A. cantonensis* can reduce eosinophilic inflammation in mice with OVA-induced asthma with an increased IL-10 production, while inhibition of airway inflammation by *A. costaricensis* extract exposure was still observed in IL-10-deficient mice (Ji et al. 2015; Pitrez et al. 2015). Furthermore, products can also function on human cells. ES products of *Marshallagia marshalli* and human macrophage migration inhibitory factor (MIF)-like protein (As-MIF) isolated from helminths induce an increase on IL-10 production when culturing with PBMCs from asthmatics, which can potentially be used as an prevention or therapy for asthma (Jabbari Azad et al. 2017).

Immune regulation of Tregs

IL-10 can be produced by various kinds of immune cells such as CD4⁺CD25⁺FoxP3⁺ cells, and can also induce CD4⁺CD25⁺FoxP3⁺ cells (Amu et al. 2010), so the preventive

Fig. 1 Schematic illustration about IL-10's function in the relationship between parasitic infection and asthma. Asthmatic response can be ameliorated in an IL-10-dependent manner induced by parasites. APC antigen-presenting cell, *E* eosinophil, *Th2* T helper cell-producing type 2 cytokines, *Treg* regulatory T cell, *Breg* regulatory B cell



effect of IL-10 against asthma may be closely related with CD4⁺CD25⁺FoxP3⁺ cells. Suppression of AAI in OVA-sensitized mice occurs as IL-10-dependent induction of Treg (CD4⁺CD25⁺FoxP3⁺) cells by IL-10-producing CD1d^{high} B cells in *S. mansoni*-infected mice (Amu et al. 2010). The preventive effect against allergen-induced atopy asthma of *H. polygyrus* is IL-10-dependent and may occur through IL-10-induced CD4⁺CD25⁺FoxP3⁺ T cells (Kitagaki et al. 2006). But the preventive effect of Treg against asthma may be IL-10-independent in other studies, too. The *S. mansoni* infection can ameliorate OVA-induced asthma via CD4⁺CD25⁺FoxP3⁺ T cells in an IL-10-independent manner (Pacífico et al. 2009). And the infection of *H. polygyrus* alleviates the allergen-induced airway inflammation and hyperreactivity in OVA or house-dust mite allergen Der p 1 model in an IL-10-independent manner via Treg, and TGF- β may be an important candidate for this AAI suppression (Hansen et al. 2000; Wilson et al. 2005). The discrepancy between the studies can be explained by the difference of insufficient blocking of IL-10 response and complete abrogation of the cytokine in the IL-10^{-/-} mouse (Kitagaki et al. 2006). TGF- β is reported to be capable of inducing T cells to Tregs (Fantini et al. 2004). Therefore, TGF- β or TGF- β -like substance may play an important role in the prevention of asthma. Foxp3-expressing Treg cells induced by *H. polygyrus* excretory-secretory (HES) antigen in vitro were found to protect against OVA-challenged allergic airway inflammation in mice. Moreover, the induction of Treg may occur through TGF- β -like signaling, which is distinct from TGF- β (Grainger et al. 2010). Further study found that inhibition of IL-33 release, which can promote release of IL-5 and IL-13 for initiation of asthma, contribute to this suppressive effect in *Alternaria*/OVA model (Cayrol and Girard 2014; McSorley et al. 2014). *Trichinella spiralis* infection can also induce the CD4⁺CD25⁺FoxP3⁺ T cell and ameliorate the inflammation of the bronchial tree and AHR in the airways of OVA-challenged mice both in chronic infection form (Aranzamendi et al. 2013; Park et al. 2011). In addition, the splenic CD4⁺ T cells isolated from the chronic infected group can provide a partial protection, as well (Aranzamendi et al. 2013). Administration of CD4⁺CD25⁺Foxp3⁺ T cells induced by the *T. spiralis* infection before sensitization can produce a more preventive effect in reducing the allergic airway inflammation compared to the group which received CD4⁺CD25⁺Foxp3⁺ T cells from uninfected mice, which demonstrate the function of Treg more precisely than Aranzamendi's study. Th2 cytokine expression, like IL-4, IL-5, and IL-13, decreased in the infected Foxp3⁺ group; this is consistent with the above study indicating that suppression of Th2 response is critical in the prevention of this type of asthma (Kang et al. 2014).

Above all, the infection of different helminths may have preventive effects on asthma through regulation of different immune responses. Thus, what will happen if infection is

relieved by anti-parasite treatment? Studies have reported that anthelmintic treatment increased mite skin test reactivity in chronically infected children, which is the measurement for atopy (van den Biggelaar et al. 2004). However, no significance positive relationship with clinical asthma was found when treating helminth-infected children with albendazole (Cooper 2009; Flohr et al. 2010). Lack of causality, incomplete helminth eradication, or repeated infection in the epidemic area may be attributed to this phenomenon (Flohr et al. 2010).

Helminth and therapy of asthma

Tregs or Bregs

As mentioned above, one effective therapy is transferring the regulatory lymphocytes in parasite-infected subjects to uninfected sensitized ones, either through an IL-10-independent or IL-10-dependent mechanism. Transfer of CD4⁺CD25⁺ T cells of mesenteric lymph node cells from *H. polygyrus*-infected mice to uninfected sensitized mice before challenge resulted in a reduction in airway inflammation among the recipient mice. And to further demonstrate the mechanism, CD4⁺ T cells were transferred from the mesenteric lymph node of the IL-10 deficit group with chronic infection to the sensitized wild-type group without infection. This also led to a significant reduction in eosinophilia and airway infiltration, which suggested that IL-10 did not play an essential role in this suppressive pathway (Wilson et al. 2005). Further studies found that transfer of the CD19⁺ CD23hi B cell from wild-type and IL-10 defective mice with *H. polygyrus* chronic infection to the Der p 1 sensitized mice could both lead to the suppression of the allergen-induced airway eosinophilia and a decreased production of IL-5 (Wilson et al. 2010). Reduced levels of IL-5 and IgE and a higher ratio of Treg cells were also detected when HES was added to OVA for sensitization, in which the recipient mice experienced a suppressive allergic airway response and reduced cell infiltration. Interestingly, the heat-treated HES lost the ability of suppression after sensitization but still retained the ability after challenge, indicating that the different components of HES regulate the immune response in different ways (McSorley et al. 2012). These studies showed that both the regulatory lymphocytes and IL-5 play key roles in the protective effect provided by *H. polygyrus*. While transferring *S. mansoni*-induced, IL-10-producing Bregs to OVA-sensitized recipient murine models can inhibit allergic airway inflammation via CD4⁺CD25⁺FoxP3⁺ T cells (Amu et al. 2010). Later, it was further demonstrated that the suppressive effect on ovalbumin-induced allergic airway inflammation is IL-10-dependent and only partly dependent on FoxP3(+) regulatory T cells (van der Vlugt et al. 2012).

Antigen-presenting cells

Besides Tregs and Bregs, other immune cells like dendritic cells (DCs) and macrophages, as antigen-presenting cells, are also involved in parasites' curative effect on asthma. Transferred *S. japonicum* infection-induced DC can suppress inflammatory reactions such as mucus production in the OVA-sensitized and challenged mice, with increased level of IL-10 and reduction in IL-4/5 production, but INF- γ not significantly affected (Liu et al. 2010). Besides, parasitic products can alter DC's function. Total protein derived from *Clonorchis sinensis* can ameliorate OVA-induced AAI and methacholine-induced AHR by interfering with the activating function of DCs in naive T cells and Treg induction, mediated indirectly by IL-10 (Jeong et al. 2011), which was consistent with what we mentioned before that IL-10 may be an important cytokine in inhibiting airway inflammation. While *Ascaris suum* pseudocoelomic fluid (PCF), a substitute for *A. suum* infection, provides suppression of bronchial inflammation in an IL-10-independent manner through interference with the DC function (McConchie et al. 2006). Furthermore, activation of *Nippostrongylus brasiliensis*-induced alveolar macrophages can alleviate airway responsiveness and lung inflammation (Reece et al. 2008). Filarial cystatin, secretory products from filarial nematodes, can alleviate allergic airway hyperreactivity and result in decreased production of IL-4 and IgE when administrated to sensitizing or sensitized mice before OVA challenge, in which macrophages and IL-10 play a key role in this suppressive pathway because their depletion leads to loss of curative effects (Schnoeller et al. 2008).

TLRs

Studies show that TLRs play a key role in asthma, because the involved immune cells are all armed with TLRs. It has been reported that TLR ligands provide therapeutic potential for asthma (Kawai and Akira 2010). Since parasites may modulate the immune response and facilitate survival in the human body via TLR which recognize conserved structure of pathogen, TLRs may be a potential mechanism that can explain the therapeutic effect of parasite infection in asthmatics and should be a target of further studies (Zakeri et al. 2016). In 2015, a study showed that the recombinant type II macrophage migration inhibitory factor homolog (rAs-MIF) secreted from *Anisakis simplex* ameliorated AAI induced by OVA in normal mice, but the suppressive effect diminished in mice subjected to TLR2 blocking, indicating the key role of TLR2 (Cho et al. 2015). ES-62, a molecule secreted by filarial nematodes, also has a TLR-4-dependent inhibiting effect on the mast cell response, which can promote bronchus remodeling, leading to hyperreactivity, and thus shows therapeutic potential (Melendez et al. 2007).

Additionally, parasites can enhance the suppressive function of Tregs by reacting with TLRs. Secretory products from *Schistosoma* can promote Treg expansion via TLR-2 signaling (Layland et al. 2007). Tregs suppress inflammation via TLR2-dependent ERK signaling in the SEA-treated model (Correale and Farez 2013). And SJMHE1, from *S. japonicum*, both enhances Treg proliferation and promotes their suppressive activity via TLR2 stimulation (Wang et al. 2009). *Schistosoma*-specific phosphatidylserine (PS) activates TLR2 and promotes the ability of mature DCs to induce IL-10-producing Tregs (van der Kleij et al. 2002). Though their direct effects on asthma have not yet been found, they do provide a new insight for studying the mechanism and potential for more effective asthmatic therapies.

Studies on the challenge phase

Nowadays, studies of therapies mostly focus on the sensitization phase, which can be used to prevent airway inflammation and achieve a curative effect in the sensitized patients, but fewer attention are paid to the challenge phase. This may result from the long time to achieve a steady immune status that the parasites or extracts of parasites take. However, there are still some studies concerning about this aspect. The administration of CD4⁺CD25⁺Foxp3⁺ T cells induced by the *T. spiralis* infection during challenge can produce a therapeutic effect in reducing the allergic airway inflammation when compared to a group receiving CD4⁺CD25⁺Foxp3⁺ T cells from uninfected mice, but with no Treg recruitment in spleen comparing with before-challenge group (Kang et al. 2014). Macrophage migration inhibitory factor (MIF)-like protein from *A. simplex* third-stage larvae have been shown to ameliorate AHR and suppress eosinophilia and goblet cell hyperplasia via recruitment of CD4⁺CD25⁺Foxp3⁺ T cells to the OVA-induced asthma model during the challenge phase. Meanwhile, an obvious reduction of Th2 cytokines (IL-4, IL-5) and elevated levels of IL-10 and IFN- γ have also been found (Park et al. 2009).

Arthropod and asthma

In addition to helminths, the arthropod may also have preventive or therapeutic effect toward asthma. Studies show that IL-9 derived by Th9 cells plays a significant role in inducing the symptoms of asthma. IL-9 production can be inhibited by the salivary product of hard tick *Ixodes scapularis*, sialostatin L, an inhibitor of immunosuppressive cysteine protease, and thus prevent experimental asthma (Horka et al. 2012). wAnother salivary protein of *I. scapularis*, Salp15, can also reduce AHR and eosinophilia, through inhibiting the activation of T cells and IL-2 secretion in the OVA-challenged allergic asthma mice models (Paveglia et al. 2007). Ha24, a kind of lipocalin

protein of the tick *Hyalomma asiaticum*, was found to be effective in relieving the symptoms of asthma model mice by binding to histamine, showing a reduction of the inflammation and protein secretion, and destruction of tissue (Wang et al. 2016). These protective effects show different mechanisms, compared to those mentioned above, thus providing us more new ideas to fight against asthma.

Not all parasite protects against asthma

However, not all parasites are helpful in prevention of asthma in children. In 2010, Feary, J et al. found that mice infected with *Necator americanus* larvae experienced a nonsignificant increased dose of inhaled adenosine monophosphate and no significant improvement in bronchial responsiveness. This result may be attributed to an inadequate dose of worm infection to establish a fit immune environment or the inhalation of corticosteroid, which suppressed the proliferation of Tregs (Feary et al. 2010). Unlike *N. americanus*, *Toxocara* not only provides no protection against asthma but even enhances asthma. Allergic manifestations or morbidity of asthma were positively associated with *Toxocara* seropositive in children in cross-sectional studies in the Netherlands and Acre State, northwestern Brazil (Buijs et al. 1997; Ferreira et al. 2007).

Furthermore, the elevation of IL-4 in *Toxocara canis*-infected mice may account for the exacerbation of experimental allergic airway inflammation and the phenomenon talked above (Pinelli et al. 2008). However, in 2016, a study showed that the seropositivity to *Toxocara* sp. is not significantly associated with the risk of asthma in children (Cadore et al. 2016). The conflicting results may be explained by the participants' family history of asthma, different environments, or diagnostic standards and techniques (Cadore et al. 2016; Ferreira et al. 2007).

In rural China, *A. lumbricoides* infection in children increased the risk of asthma and allergic sensitization (Palmer et al. 2002). In the Netherlands, a positive association of antibodies against *A. suum* and allergic symptoms and sensitization were reported among 4-year-old children (Pinelli et al. 2009). This may result from the IgE cross-reactivity of tropomyosin in *Ascaris* with that in house-dust mites, which cause allergic asthma. Interestingly, the tropomyosin sequence identity of *Ascaris* and *Schistosoma* is relatively low, and this may explain the different effects of these two parasites in the development of asthma (Arruda and Santos 2005). And it may provide a new prospect for further studies on the mechanism of this item. However, studies also found that in rural tropics, *A. lumbricoides* infection can reduce the reactivity of allergen skin tests in children of school age. The opposite effect may be

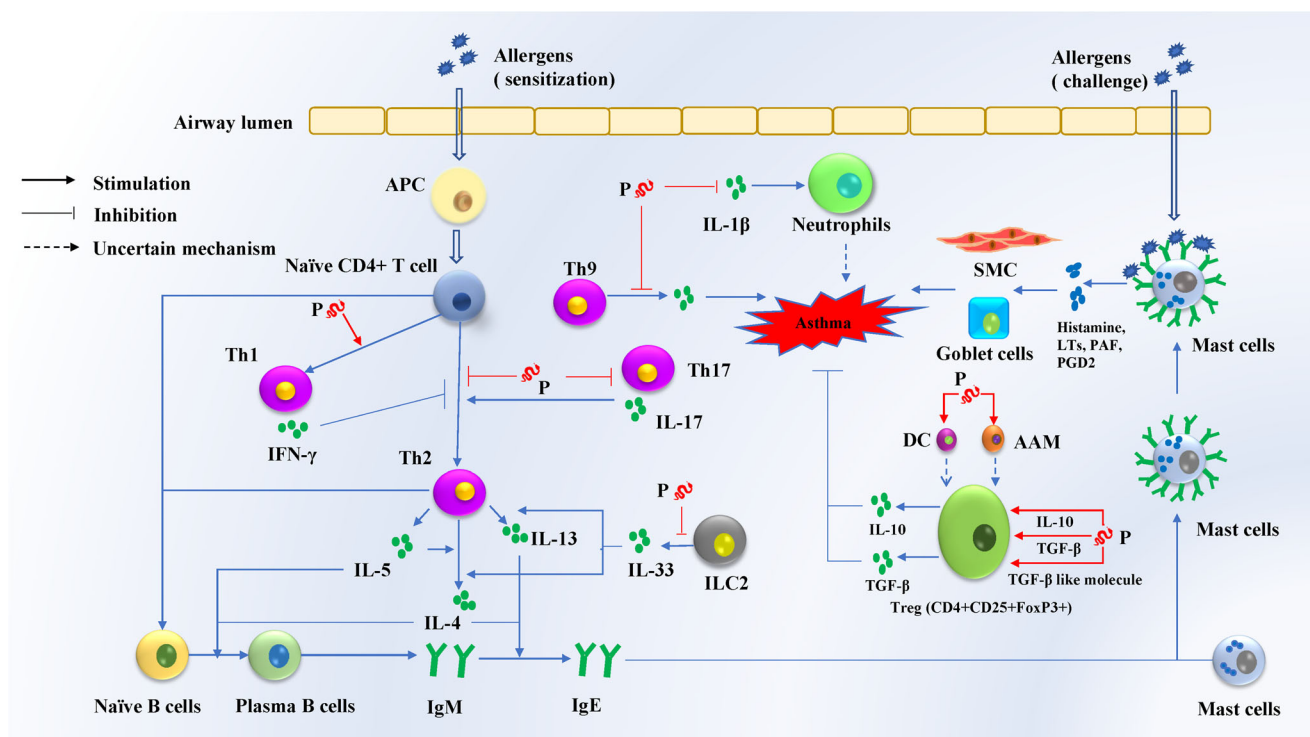


Fig. 2 Potential mechanisms of parasite-associated immune regulation of asthma. Parasites or products of parasites can promote Th1 cytokine production and suppress Th2 cytokine production and other cytokine like IL-1β, IL-9, or IL-33. Besides, they can stimulate Treg (CD4⁺CD25⁺FoxP3⁺) production through different pathways. And they

protect individuals against asthma through these potential mechanisms. AAMs alternatively activated macrophages, APCs antigen-presenting cells, DCs dendritic cells, ILC2 type 2 innate lymphoid cells, P parasites or products of parasites, SMCs smooth muscle cells

Table 1 General information of parasites and their functional components related to asthma and the potential mechanisms

Parasites	Functional components	Main mechanisms		Effects on asthma	References
		Cytokines	Immune cells		
Helminth					
Trematodes					
<i>Clonorchis sinensis</i>	Extracts of adult worms	Increased IL-10	Dendritic cells (DCs) and Treg (CD4 ⁺ CD25 ⁺ FoxP3 ⁺)	Protection	Jeong et al. (2011)
<i>Schistosoma japonicum</i>	^a	Decreased IL-5; increased IL-10	Treg (CD4 ⁺ CD25 ⁺ FoxP3 ⁺) IL-10-producing CD1d ^{high} B cells	Protection	Amu et al. (2010)
	^a	Increased IL-10; decreased IL-4 and IL-5	DCs	Protection	Liu et al. (2010)
	SjP40	Increased IFN-γ; decreased IL-4 and IL-5		Protection	Ren et al. (2016)
<i>Schistosoma mansoni</i>	Schistosomula tegument (Smtg)	Increased IL-10		Protection	Marmho et al. (2016)
	^a	Decreased IL-5	Treg (CD4 ⁺ CD25 ⁺ FoxP3 ⁺)	Protection	Pacifico et al. (2009)
Nematodes					
<i>Acanthocheilonema viteae</i>	Excretory-secretory antigen (ES)-62	Increased IFN-γ; decreased IL-4, IL-5, IL-13, and IL-17		Protection	Rzepecka et al. (2013)
<i>Angiostrongylus cantonensis</i>	Cystatin	Decreased IL-4, IL-5, and IL-17; increased IL-10		Protection	Ji et al. (2015) and Schnoeller et al. (2008)
<i>Angiostrongylus costaricensis</i>	^a	Decreased IL-1β	Neutrophils	Protection	Pinto et al. (2004)
<i>Anisakis simplex</i>	Recombinant type II macrophage migration inhibitory factor homolog (rAs-MIF)			Protection	Cho et al. (2015)
	Macrophage migration inhibitory factor (MIF)-like protein	Increased IFN-γ and IL-10; decreased IL-4 and IL-5		Protection	Park et al. (2009)
<i>Ascaris lumbricoides</i>	Extracts of adult worms	Decreased IL-5; increased IL-10		Protection	Pitrez et al. (2015)
<i>A. lumbricoides</i>	Tropomyosin			Increasing the risk	Palmer et al. (2002)
<i>Ascaris suum</i>	^a		DCs	Protection	McConchie et al. (2006)
<i>Heligmosomoides polygyrus</i>	<i>H. polygyrus</i> excretory-secretory antigen (HES)	TGF-β-like signaling	Treg (CD4 ⁺ CD25 ⁺ FoxP3 ⁺)	Protection	Grainger et al. (2010)
	^a	Decreased IL-5; increased TGF-β	Treg (CD4 ⁺ CD25 ⁺ FoxP3 ⁺)	Protection	Hansen et al. (2000) and Wilson et al. (2005)
	^a	Decreased IL-5; increased IL-10 and TGF-β	Treg (CD4 ⁺ CD25 ⁺ FoxP3 ⁺)	Protection	Kitagaki et al. (2006)
	HES	Decreased IL-5	Treg (CD4 ⁺ CD25 ⁺ FoxP3 ⁺)	Protection	McSorley et al. (2012)
	HES	Decreased IL-33, IL-5, IL-4, and IL-13		Protection	McSorley et al. (2014)
<i>Litomosoides sigmodontis</i>	^a	Decreased IL-5		Protection	Dittrich et al. (2008)
<i>Marshallagia marshalli</i>	ES products	Increased IL-10		Protection	Jabbari Azad et al. (2017)

Table 1 (continued)

Parasites	Functional components	Main mechanisms		Effects on asthma	References
		Cytokines	Immune cells		
<i>Necator americanus</i> ^a				No significant improvement	Feary et al. (2010)
<i>Nippostrongylus brasiliensis</i> ^a			Macrophages	Protection	Reece et al. (2008)
<i>Toxocara canis</i> ^a		Increased IL-4		Exacerbation	Pinelli et al. (2008)
<i>Toxocara</i> sp. ^a				No significant association	Cadore et al. (2016)
<i>Trichinella spiralis</i> ^a			Treg (CD4 ⁺ CD25 ⁺ FoxP3 ⁺)	Protection	Aranzamendi et al. (2013) and Park et al. (2011)
<i>T. spiralis</i> ^a		Decreased IL-4, IL-5, and IL-13	Treg (CD4 ⁺ CD25 ⁺ FoxP3 ⁺)	Protection	Kang et al. (2014)
<i>Trichuris muris</i> ^a		Increased IFN- γ and IL-10		Protection	Chenery et al. (2016)
Arthropod					
<i>Hyalomma asiaticum</i>	Ha24			Protection	Wang et al. (2016)
<i>Ixodes scapularis</i>	Sialostatin L	Decreased IL-9		Protection	Horka et al. (2012)

^a Infection with the parasite

explained by the intensity of infection and the acute or chronic type of the infection (Cooper et al. 2003).

Conclusion

Current epidemiological studies have been carried out to describe the association of parasites and asthma. Most of the results point to a negative association between parasite infection and the incidence of asthma, as the hygiene hypothesis has demonstrated. Further studies have been performed to describe the mechanism of this phenomenon. As the results show (Fig. 2 and Table 1), the key point of the protective effect may be the immune regulation of parasites, which causes the Th response switch and induction of some immune-related molecule and cells. Some parasites or products from parasites can shift the Th2 response to the Th1 response, thus ameliorating airway inflammation. Some may interact with the immune system to induce Tregs and Bregs to achieve a protective effect. Moreover, some of these models act in an IL-10- or IFN- γ -dependent manner, while some are IL-10 or IFN- γ independent. In addition, DCs, alternatively activated macrophages, and mast cells also play significant roles in this pathway. Interestingly, *A. lumbricoides* provides both preventive and worsening effects on asthma models in different studies. All of these results suggest us that different parasites modulate the immune system in various ways, and the intensity and types of the infection can also affect the result. As we can see, most of the models are established in an OVA-induced way, but allergens like dust mites and pollen are more prevalent in real life, so more attention should be paid to these models. What is more, many studies infect the mice before sensitization or apply the products or cells during the sensitization phase, whereas few studies focus on the challenge phase of asthma treatment. Therefore, therapies should also focus more on ongoing asthma. Another question is whether parasite infection or therapeutic molecules and cells are capable of attenuating the repeated challenge of allergens, as patients may encounter allergic substances many times in their life. Nowadays, few human studies have been carried out due to the following considerations. First, widespread parasite infection can lead to corresponding syndromes, so the specific molecules that work in the therapy or prevention should be identified. Even if the molecule is identified, we should avoid immune suppression to human, in case of other complications. Therefore, anti-inflammation responses will be better if they are restricted to the local site and are allergen specific. All in all, parasites and their related molecules have potential in the prevention and therapy of asthma, but there is a long way to go to clarify the mechanism and find more effective strategies for fighting against asthma.

Acknowledgements This work was supported by grants from the National Key Research and Development Program of China (grant nos. 2016YFC1202003, 2016YFC1202005, and 2016YFC1200500); the National Natural Science Foundation of China (grant nos. 81371836, 81572023, 81271855, and 81261160324); Project of Basic Platform of National Science and Technology Resources of the Ministry of Sciences and Technology of China (grant no. TDRC-2017-22); Guangdong Natural Science Foundation (grant no. 2014A030313134); Science and Technology Planning Project of Guangdong Province (grant no. 2016A050502008); Science and Technology Planning Project of Guangzhou (grant no. 201607010029); the Fundamental Research Funds for the Central Universities of China (17ykpy11); the Undergraduates Innovation Training Program of Guangdong Province (201410558274, 201601084); the Laboratory of Parasite and Vector Biology, MOPH (grant no. WSBKTKT201401); and Teaching Reform Project of Sun Yat-sen University (grant no. 2016012).

References

- Amu S, Saunders SP, Kronenberg M, Mangan NE, Atzberger A, Fallon PG (2010) Regulatory B cells prevent and reverse allergic airway inflammation via FoxP3-positive T regulatory cells in a murine model. *J Allergy Clin Immunol* 125(5):1114–1124
- Aranzamendi C, de Bruin A, Kuiper R, Boog CJP, van Eden W, Rutten V, Pinelli E (2013) Protection against allergic airway inflammation during the chronic and acute phases of *Trichinella spiralis* infection. *Clin Exp Allergy* 43(1):103–115
- Arruda LK, Santos ABR (2005) Immunologic responses to common antigens in helminthic infections and allergic disease. *Curr Opin Allergy Clin Immunol* 5(5):399–402
- Barnes PJ (2001) Cytokine-directed therapies for asthma. *J Allergy Clin Immunol* 108(2 Suppl):S72–S76
- British Thoracic Society Scottish Intercollegiate Guidelines N (2008) British guideline on the management of asthma. *Thorax* 63 Suppl 4:iv1–121
- Buijs J, Borsboom G, Renting M, Hilgersom WJ, van Wieringen JC, Jansen G, Neijens J (1997) Relationship between allergic manifestations and *Toxocara* seropositivity: a cross-sectional study among elementary school children. *Eur Respir J* 10(7):1467–1475
- Cadore PS, Zhang LJ, Lemos LD, Lorenzi C, Telmo PD, dos Santos PC, Mattos GT, Vignol FS, Prietsch SOM, Berne MEA, Scaini CJ (2016) Toxocariasis and childhood asthma: a case-control study. *J Asthma* 53(6):601–606
- Cayrol C, Girard JP (2014) IL-33: an alarmin cytokine with crucial roles in innate immunity, inflammation and allergy. *Curr Opin Immunol* 31:31–37
- Chen L, Grabowski KA, Xin JP, Coleman J, Huang Z, Espiritu B, Alkan S, Xie HB, Zhu Y, White FA, Clancy J Jr, Huang H (2004) IL-4 induces differentiation and expansion of Th2 cytokine-producing eosinophils. *J Immunol* 172(4):2059–2066
- Chenery AL, Antignano F, Burrows K, Scheer S, Perona-Wright G, Zaph C (2016) Low-dose intestinal *Trichuris muris* infection alters the lung immune microenvironment and can suppress allergic airway inflammation. *Infect Immun* 84(2):491–501
- Cho MK, Park MK, Kang SA, Park SK, Lyu JH, Kim DH, Park HK, Yu HS (2015) TLR2-dependent amelioration of allergic airway inflammation by parasitic nematode type II MIF in mice. *Parasite Immunol* 37(4):180–191
- Cooper PJ (2009) Mucosal immunology of geohelminth infections in humans. *Mucosal Immunol* 2(4):288–299
- Cooper PJ, Chico ME, Rodrigues LC, Ordonez M, Strachan D, Griffin GE, Nutman TB (2003) Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. *J Allergy Clin Immunol* 111(5):995–1000
- Correale J, Farez MF (2013) Parasite infections in multiple sclerosis modulate immune responses through a retinoic acid-dependent pathway. *J Immunol* 191(7):3827–3837
- Danilowicz-Luebert E, Steinfelder S, Kuhl AA, Drozdenko G, Lucius R, Worm M, Hamelmann E, Hartmann S (2013) A nematode immunomodulator suppresses grass pollen-specific allergic responses by controlling excessive Th2 inflammation. *Int J Parasitol* 43(3–4):201–210
- Dias PM, Banerjee G (2013) The role of Th17/IL-17 on eosinophilic inflammation. *J Autoimmun* 40:9–20
- Dittrich AM, Erbacher A, Specht S, Diesner F, Krokowski M, Avagyan A, Stock P, Ahrens B, Hoffmann WH, Hoerauf A, Hamelmann E (2008) Helminth infection with *Litomosoides sigmodontis* induces regulatory T cells and inhibits allergic sensitization, airway inflammation, and hyperreactivity in a murine asthma model. *J Immunol* 180(3):1792–1799
- Fantini MC, Becker C, Monteleone G, Pallone F, Galle PR, Neurath MF (2004) Cutting edge: TGF- β induces a regulatory phenotype in CD4⁺CD25⁺ T cells through Foxp3 induction and down-regulation of Smad7. *J Immunol* 172(9):5149–5153
- Feary JR, Venn AJ, Mortimer K, Brown AP, Hooi D, Falcone FH, Pritchard DI, Britton JR (2010) Experimental hookworm infection: a randomized placebo-controlled trial in asthma. *Clin Exp Allergy* 40(2):299–306
- Ferreira MU, Rubinsky-Elefant G, de Castro TG, Hoffmann EHE, da Silva-Nunes MN, Cardoso MA, Muniz PT (2007) Bottle feeding and exposure to *Toxocara* as risk factors for wheezing illness among under-five Amazonian children: a population-based cross-sectional study. *J Trop Pediatr* 53(2):119–124
- Flohr C, Tuyen LN, Quinnell RJ, Lewis S, Minh TT, Campbell J, Simmons C, Telford G, Brown A, Hien TT, Farrar J, Williams H, Pritchard DI, Britton J (2010) Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam. *Clin Exp Allergy* 40(1):131–142
- Gauthier M, Ray A, Wenzel SE (2015) Evolving concepts of asthma. *Am J Respir Crit Care Med* 192(6):660–668
- Gern JE, Busse WW (2002) Relationship of viral infections to wheezing illnesses and asthma. *Nat Rev Immunol* 2(2):132–138
- Grainger JR, Smith KA, Hewitson JP, McSorley HJ, Harcus Y, Filbey KJ, Finney CAM, Greenwood EJD, Knox DP, Wilson MS, Belkaid Y, Rudensky AY, Maizels RM (2010) Helminth secretions induce de novo T cell Foxp3 expression and regulatory function through the TGF- β pathway. *J Exp Med* 207(11):2331–2341
- Hansen G, McIntire JJ, Yeung VP, Berry G, Thorbecke GJ, Chen L, DeKruyff RH, Umetsu DT (2000) CD4(+) T helper cells engineered to produce latent TGF- β 1 reverse allergen-induced airway hyper-reactivity and inflammation. *J Clin Invest* 105(1):61–70
- Hartmann S, Lucius R (2003) Modulation of host immune responses by nematode cystatins. *Int J Parasitol* 33(11):1291–1302
- Horka H, Staudt V, Klein M, Taube C, Reuter S, Dehzad N, Andersen JF, Kopecky J, Schild H, Kotsyakis M, Hoffmann M, Gerlitzki B, Stassen M, Bopp T, Schmitt E (2012) The tick salivary protein sialostatin L inhibits the Th9-derived production of the asthma-promoting cytokine IL-9 and is effective in the prevention of experimental asthma. *J Immunol* 188(6):2669–2676
- Hsieh CS, Heimberger AB, Gold JS, O'Garra A, Murphy KM (1992) Differential regulation of T helper phenotype development by interleukins 4 and 10 in an alpha beta T-cell-receptor transgenic system. *Proc Natl Acad Sci U S A* 89(13):6065–6069
- Huang SL, Tsai PF, Yeh YF (2002) Negative association of *Enterobius* infestation with asthma and rhinitis in primary school children in Taipei. *Clin Exp Allergy* 32(7):1029–1032

- Huang TJ, MacAry PA, Eynott P, Moussavi A, Daniel KC, Askenase PW, Kemeny DM, Chung KF (2001) Allergen-specific Th1 cells counteract effector Th2 cell-dependent bronchial hyperresponsiveness and eosinophilic inflammation partly via IFN-gamma. *Eur J Immunol* 166(1):207–217
- Iwakura Y, Ishigame H, Saijo S, Nakae S (2011) Functional specialization of interleukin-17 family members. *Immunity* 34(2):149–162
- Jabbari Azad F, Kiaee F, Rezaei A, Farid Hosseini R, Soleimani N, Borji H (2017) Downregulation of immune responses in asthmatic humans by ES products of *Marshallagia marshalli*. *Clin Respir J* 11(1):83–89
- Jeannin P, Lecoanet S, Delneste Y, Gauchat JF, Bonnefoy JY (1998) IgE versus IgG4 production can be differentially regulated by IL-10. *J Immunol* 160(7):3555–3561
- Jeong YI, Kim SH, Ju JW, Cho SH, Lee WJ, Park JW, Park YM, Lee SE (2011) *Clonorchis sinensis*-derived total protein attenuates airway inflammation in murine asthma model by inducing regulatory T cells and modulating dendritic cell functions. *Biochem Biophys Res Commun* 407(4):793–800
- Ji P, Hu H, Yang X, Wei X, Zhu C, Liu J, Feng Y, Yang F, Okanurak K, Li N, Zeng X, Zheng H, Wu Z, Lv Z (2015) AcCystatin, an immunoregulatory molecule from *Angiostrongylus cantonensis*, ameliorates the asthmatic response in an aluminium hydroxide/ovalbumin-induced rat model of asthma. *Parasitol Res* 114(2):613–624
- Kang SA, Park MK, Cho MK, Park SK, Jang MS, Yang BG, Jang MH, Kim DH, Yu HS (2014) Parasitic nematode-induced CD4(+)Foxp3(+) T cells can ameliorate allergic airway inflammation. *PLoS Negl Trop Dis* 8(12)
- Kawai T, Akira S (2010) The role of pattern-recognition receptors in innate immunity: update on toll-like receptors. *Nat Immunol* 11(5):373–384
- Kelly FJ, Fussell JC (2011) Air pollution and airway disease. *Clin Exp Allergy* 41(8):1059–1071
- Kitagaki K, Businga TR, Racila D, Elliott DE, Weinstock JV, Kline JN (2006) Intestinal helminths protect in a murine model of asthma. *J Immunol* 177(3):1628–1635
- Layland LE, Rad R, Wagner H, Da Costa CUP (2007) Immunopathology in schistosomiasis is controlled by antigen-specific regulatory T cells primed in the presence of TLR2. *Eur J Immunol* 37(8):2174–2184
- Leonardi-Bee J, Pritchard D, Britton J (2006) Asthma and current intestinal parasite infection—systematic review and meta-analysis. *Am J Respir Crit Care Med* 174(5):514–523
- Lin CH, Kadakia S, Frieri M (2014) New insights into an autoimmune mechanism, pharmacological treatment and relationship between multiple sclerosis and inflammatory bowel disease. *Autoimmun Rev* 13(2):114–116
- Liu P, Li J, Yang X, Shen Y, Zhu Y, Wang S, Wu Z, Liu X, An G, Ji W, Gao W, Yang X (2010) Helminth infection inhibits airway allergic reaction and dendritic cells are involved in the modulation process. *Parasite Immunol* 32(1):57–66
- Maddox L, Schwartz DA (2002) The pathophysiology of asthma. *Annu Rev Med* 53:477–498
- Mangan NE, van Rooijen N, McKenzie ANJ, Fallon PG (2006) Helminth-modified pulmonary immune response protects mice from allergen-induced airway hyperresponsiveness. *J Immunol* 176(1):138–147
- Marinho FV, Alves CC, de Souza SC, da Silva CM, Cassali GD, Oliveira SC, Pacifico LG, Fonseca CT (2016) *Schistosoma mansoni* Tegument (Snteg) induces IL-10 and modulates experimental airway inflammation. *PLoS One* 11(7):e0160118
- McConchie BW, Norris HH, Bundoc VG, Trivedi S, Boesen A, Urban JF, Keane-Myers AM (2006) *Ascaris suum*-derived products suppress mucosal allergic inflammation in an interleukin-10-independent manner via interference with dendritic cell function. *Infect Immun* 74(12):6632–6641
- McSorley HJ, Blair NF, Smith KA, McKenzie ANJ, Maizels RM (2014) Blockade of IL-33 release and suppression of type 2 innate lymphoid cell responses by helminth secreted products in airway allergy. *Mucosal Immunol* 7(5):1068–1078
- McSorley HJ, O’Gorman MT, Blair N, Sutherland TE, Filbey KJ, Maizels RM (2012) Suppression of type 2 immunity and allergic airway inflammation by secreted products of the helminth *Heligmosomoides polygyrus*. *Eur J Immunol* 42(10):2667–2682
- Medeiros M, Figueiredo JP, Almeida MC, Matos MA, Araujo MI, Cruz AA, Atta AM, Rego MAV, de Jesus AR, Taketomi EA, Carvalho EM (2003) *Schistosoma mansoni* infection is associated with a reduced course of asthma. *J Allergy Clin Immunol* 111(5):947–951
- Melendez AJ, Hamett MM, Pushparaj PN, Wong WF, Tay HK, McSharry CP, Harnett W (2007) Inhibition of Fc epsilon RI-mediated mast cell responses by ES-62, a product of parasitic filarial nematodes. *Nat Med* 13(11):1375–1381
- Moncayo AL, Cooper PJ (2006) Geohelminth infections: impact on allergic diseases. *Int J Biochem Cell Biol* 38(7):1031–1035
- Moore KW, de Waal MR, Coffman RL, O’Garra A (2001) Interleukin-10 and the interleukin-10 receptor. *Annu Rev Immunol* 19:683–765
- Murdock BJ, Falkowski NR, Shreiner AB, Sadighi Akha AA, McDonald RA, White ES, Toews GB, Huffnagle GB (2012) Interleukin-17 drives pulmonary eosinophilia following repeated exposure to *Aspergillus fumigatus* conidia. *Infect Immun* 80(4):1424–1436
- National Asthma E, Prevention P (2007) Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol* 120(5 Suppl):S94–138
- Ober C, Hoffjan S (2006) Asthma genetics 2006: the long and winding road to gene discovery. *Genes Immun* 7(2):95–100
- Pacifico LG, Marinho FA, Fonseca CT, Barsante MM, Pinho V, Sales-Junior PA, Cardoso LS, Araujo MI, Carvalho EM, Cassali GD, Teixeira MM, Oliveira SC (2009) *Schistosoma mansoni* antigens modulate experimental allergic asthma in a murine model: a major role for CD4+ CD25+ Foxp3+ T cells independent of interleukin-10. *Infect Immun* 77(1):98–107
- Palframan RT, Collins PD, Williams TJ, Rankin SM (1998) Eotaxin induces a rapid release of eosinophils and their progenitors from the bone marrow. *Blood* 91(7):2240–2248
- Palmer LJ, Celedon JC, Weiss ST, Wang BY, Fang ZA, Xu XP (2002) *Ascaris lumbricoides* infection is associated with increased risk of childhood asthma and atopy in rural China. *Am J Respir Crit Care Med* 165(11):1489–1493
- Park HK, Cho MK, Choi SH, Kim YS, Yu HS (2011) *Trichinella spiralis*: infection reduces airway allergic inflammation in mice. *Exp Parasitol* 127(2):539–544
- Park SK, Cho MK, Park HK, Lee KH, Lee SJ, Choi SH, Ock MS, Jeong HJ, Lee MH, Yu HS (2009) Macrophage migration inhibitory factor homologs of *Anisakis simplex* suppress Th2 response in allergic airway inflammation model via CD4(+)CD25(+)Foxp3(+) T cell recruitment. *J Immunol* 182(11):6907–6914
- Paveglia SA, Allard J, Mayette J, Whittaker LA, Juncadella I, Anguita J, Poynter ME (2007) The tick salivary protein, Salp15, inhibits the development of experimental asthma. *J Immunol* 178(11):7064–7071
- Pinelli E, Brandes S, Dormans J, Gremmer E, van Loveren H (2008) Infection with the roundworm *Toxocara canis* leads to exacerbation of experimental allergic airway inflammation. *Clin Exp Allergy* 38(4):649–658
- Pinelli E, Willers SM, Hoek D, Smit HA, Kortbeek LM, Hoekstra M, de Jongste J, van Knapen F, Postma D, Kerkhof M, Aalberse R, van der Giessen JWB, Brunekreef B (2009) Prevalence of antibodies against *Ascaris suum* and its association with allergic manifestations in 4-year-old children in the Netherlands: the PIAMA birth cohort study. *Eur J Clin Microbiol Infect Dis* 28(11):1327–1334
- Pinto LA, Pitrez PMC, Fontoura GR, Machado DC, Jones MH, Graeff-Teixeira C, Stein RT (2004) Infection of BALB/c mice with

- Angiostrongylus costaricensis* decreases pulmonary inflammatory response to ovalbumin. *Parasite Immunol* 26(3):151–155
- Pitrez PM, Gualdi LP, Barbosa GL, Sudbrack S, Ponzi D, Cao RG, Silva ACA, Machado DC, Jones MH, Stein RT, Graeff-Teixeira C (2015) Effect of different helminth extracts on the development of asthma in mice: the influence of early-life exposure and the role of IL-10 response. *Exp Parasitol* 156:95–103
- Ponte EV, Rasella D, Souza-Machado C, Stelmach R, Barreto ML, Cruz AA (2014) Reduced asthma morbidity in endemic areas for helminth infections: a longitudinal ecological study in Brazil. *J Asthma* 51(10):1022–1027
- Reece JJ, Siracusa MC, Southard TL, Brayton CF, Urban JF, Scott AL (2008) Hookworm-induced persistent changes to the immunological environment of the lung. *Infect Immun* 76(8):3511–3524
- Ren JL, Hu LZ, Yang J, Yang L, Gao F, Lu P, Fan MY, Zhu YJ, Liu JY, Chen LL, Gupta S, Yang X, Liu PM (2016) Novel T-cell epitopes on *Schistosoma japonicum* SjP40 protein and their preventive effect on allergic asthma in mice. *Eur J Immunol* 46(5):1203–1213
- Rincon M, Anguita J, Nakamura T, Fikrig E, Flavell RA (1997) Interleukin (IL)-6 directs the differentiation of IL-4-producing CD4⁺ T cells. *J Exp Med* 185(3):461–469
- Robinson DS (2000) Th-2 cytokines in allergic disease. *Br Med Bull* 56(4):956–968
- Rodrigues LC, Newcombe PJ, Cunha SS, Alcantara-Neves NM, Genser B, Cruz AA, Simoes SM, Fiaccone R, Amorim L, Cooper PJ, Barreto ML, Scaala (2008) Early infection with *Trichuris trichiura* and allergen skin test reactivity in later childhood. *Clin Exp Allergy* 38(11):1769–1777
- Rook GAW (2010) 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: Darwinian medicine and the ‘hygiene’ or ‘old friends’ hypothesis. *Clin Exp Immunol* 160(1):70–79
- Rzepecka J, Siebeke I, Coltherd JC, Kean DE, Steiger CN, Al-Riyami L, McSharry C, Harnett MM, Harnett W (2013) The helminth product, ES-62, protects against airway inflammation by resetting the Th cell phenotype. *Int J Parasitol* 43(3–4):211–223
- Schandene L, Alonso-Vega C, Willems F, Gerard C, Delvaux A, Velu T, Devos R, de Boer M, Goldman M (1994) B7/CD28-dependent IL-5 production by human resting T cells is inhibited by IL-10. *J Immunol* 152(9):4368–4374
- Schnoeller C, Rausch S, Pillai S, Avagyan A, Wittig BM, Loddenkemper C, Hamann A, Hamelmann E, Lucius R, Hartmann S (2008) Helminth immunomodulator reduces allergic and inflammatory responses by induction of IL-10-producing macrophages. *J Immunol* 180(6):4265–4272
- van den Biggelaar AH, Rodrigues LC, van Ree R, van der Zee JS, Hoeksma-Kruize YC, Souverijn JH, Missinou MA, Borrmann S, Kremsner PG, Yazdanbakhsh M (2004) Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese schoolchildren. *J Infect Dis* 189(5):892–900
- van den Biggelaar AHJ, van Ree R, Rodrigues LC, Lell B, Deelder AM, Kremsner PG, Yazdanbakhsh M (2000) Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* 356(9243):1723–1727
- van der Kleij D, Latz E, Brouwers JFHM, Kruize YCM, Schmitz M, Kurt-Jones EA, Espevik T, de Jong EC, Kapsenberg ML, Golenbock DT, Tielens AGM, Yazdanbakhsh M (2002) A novel host-parasite lipid cross-talk—schistosomal lyso-phosphatidylserine activates toll-like receptor 2 and affects immune polarization. *J Biol Chem* 277(50):48122–48129
- van der Vlugt LEPM, Labuda LA, Ozir-Fazalikhhan A, Lievers E, Gloudemans AK, Liu KY, Barr TA, Sparwasser T, Boon L, Ngoa UA, Feugap EN, Adegnika AA, Kremsner PG, Gray D, Yazdanbakhsh M, Smits HH (2012) *Schistosomes* induce regulatory features in human and mouse CD1d(hi) B cells: inhibition of allergic inflammation by IL-10 and regulatory T cells. *PLoS One* 7(2)
- Wang XF, Zhou S, Chi Y, Wen XY, Hoellwarth J, He L, Liu F, Wu C, Dhesi S, Zhao JQ, Hu W, Su C (2009) CD4(+)CD25(+) Treg induction by an HSP60-derived peptide SJMHE1 from *Schistosoma japonicum* is TLR2 dependent. *Eur J Immunol* 39(11):3052–3065
- Wang YA, Li Z, Zhou YZ, Cao J, Zhang HS, Gong HY, Zhou JL (2016) Specific histamine binding activity of a new lipocalin from *Hyalomma asiaticum* (Ixodidae) and therapeutic effects on allergic asthma in mice. *Parasit Vectors* 9(1):506
- Wilson MS, Taylor MD, Balic A, Finney CAM, Lamb JR, Maizels RM (2005) Suppression of allergic airway inflammation by helminth-induced regulatory T cells. *J Exp Med* 202(9):1199–1212
- Wilson MS, Taylor MD, O’Gorman MT, Balic A, Barr TA, Filbey K, Anderton SM, Maizels RM (2010) Helminth-induced CD19(+)CD23(hi) B cells modulate experimental allergic and autoimmune inflammation. *Eur J Immunol* 40(6):1682–1696
- Zakeri A, Borji H, Haghparsat A (2016) Interaction between helminths and toll-like receptors: possibilities and potentials for asthma therapy. *Int Rev Immunol* 35(3):219–248