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Allergy and worms: let's bring back old friends?

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Summary
Purpose of review In order to survive in their host, parasitic worms (helminths) have evolved cunning strategies to manipulate the host immune system, some of which may lead to protection from immune dysregulatory diseases such as allergy. Thus, loss of exposure to helminths due to a highly hygienic life style might have contributed to the fact that living in an industrialized country is being associated with an increased prevalence of allergic diseases. However, it must be pointed out that certain helminth infections can in fact induce an allergic phenotype. Factors such as different parasite species, timing of infection in relation to allergic sensitization, or duration and intensity of infection may influence the association between helminth infections and the development or clinical course of allergic disease. In the present article, we review studies that have explored the interaction between helminth infections and allergy in epidemiological and experimental studies. Furthermore, the possibility of using helminths or helminth-derived molecules for the treatment of allergic diseases is discussed with a focus on evidence from clinical trials.

Recent findings During the past 10 years, many exciting and important studies have found that certain helminth infections protect against the development of allergic diseases. Not surprisingly, several clinical trials investigated the effects of deliberate exposure to parasites like porcine whipworm (*Trichuris suis*) or hookworm (*Necator americanus*) to develop "helminth therapies". Although they proved to be a safe option to control aberrant inflammation, the final goal is to identify the parasite-derived immunnomodulatory molecules responsible for protective effects.

Keywords Helminths · Allergy · Immunomodulation

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Allergie und Würmer: Sollen wir uns gute alte Freunde zurückholen?

Zusammenfassung
Ziel des Reviews Helminthen haben hoch differenzierte Strategien entwickelt um das Immunsystem des Wirts zu manipulieren und damit ihr Überleben im Wirt zu sichern. Es ist bekannt, dass diese Manipulationen/Evasionsmechanismen nicht nur das Überleben der Parasiten selbst fördern, sondern auch eine schützende Wirkung auf den Wirt haben können, z.B. im Falle von Allergien. Der deutliche Rückgang von Wurminfektionen in westlichen Industrieländern mit hohen hygienischen Standards, wird vielfach mit der steigenden Prävalenz an allergischen Erkrankungen in Verbindung gebracht. Jedoch können bestimmte Wurminfektionen selbst auch Allergien auslösen. Verschiedene Faktoren, wie die Parasitenspezies, der Zeitpunkt der Infektion in Bezug auf allergische Sensibilisierung, sowie die Dauer und Schwere der Infektion können einen Einfluss auf die Entstehung und den klinischen Verlauf allergischer Erkrankungen haben. Ziel dieses Reviews ist es, die Ergebnisse epidemiologischer und experimenteller Studien, die die Wechselwirkungen zwischen Wurminfektionen und Allergien beschreiben, näher zu beleuchten. Außerdem soll die mögliche therapeutische Anwendung von Parasiten, aber auch von Parasitenmolekülen in klinischen Studien kritisch diskutiert werden.

Neueste Ergebnisse In den letzten zehn Jahren konnten zahlreiche Studien zeigen, dass bestimmte Parasiteninfektionen das Auftreten von allergischen Erkrankungen verhindern können. Im Zuge klinischer Studien wurden

die immunologischen Auswirkungen bestimmter Wurminfektionen, wie z.B. dem Schweinepeitschenwurm (*Trichuris suis*) oder dem Hakenwurm (*Necator americanus*), untersucht, um sogenannte „Helminthen-basierende Therapien (oder: Helminthen-/Wurmtherapien)“ zu entwickeln. Die Resultate dieser Untersuchungen ergaben, dass bestimmte Helmintheninfektionen (nicht humanpathogen) eine sichere und effektive Alternative zur Behandlung von unkontrollierten Entzündungsreaktionen darstellen können. Nichtdestotrotz bleibt es vorrangiges Ziel, nur jene Bestandteile der Parasiten, die für die schützende Wirkung verantwortlich sind, zu identifizieren (und zu isolieren) und für künftige Behandlungsmodelle zu verwenden.

Schlüsselwörter Helminthen · Allergie · Immunomodulation

There is something wrong with urban life: allergy, hygiene hypothesis and worms

Allergy

Epidemiological studies from different parts of the world have shown that the prevalence of allergic diseases such as asthma, allergic rhinitis or atopic dermatitis, has been increasing exponentially in the recent decades, reaching currently epidemic proportions [32]. This trend was clearly demonstrated in a study of the population in Greenland, where the frequency of atopy, (measured as levels of specific immunoglobulin E (IgE) against most common inhalant allergens), doubled between 1987 and 1998 [55]. This increase has been observed particularly in western industrialized countries and in urban areas of emerging countries, where approximately 15–30 % of the population is affected [15]. The same trend can also be seen in the Austrian population, where a 2-fold, 3.6-fold and 4.6-fold increase in the prevalence of hay fever, asthma and atopic eczema, respectively, has been observed between 1986 and 2005 among 18-year-old men [31]. While genetic factors contribute significantly [39, 72, 107], they cannot solely explain the dramatic rise in allergies. Rather environmental factors such as reduced or altered exposure to microbial stimuli and infections especially during childhood as a consequence of improved hygiene have been suggested to account for the increasing prevalence of allergies over the past decades in the Western society.

Hygiene hypothesis

According to the original “hygiene hypothesis”, the early-life exposure to Th1-driving microbial infections might protect against allergic diseases by deviating the immune response from a Th2 to an anti-allergic Th1 response [95]. However, the parallel increase in Th1-associated autoimmune diseases such as type 1 diabetes, multiple sclerosis or inflammatory bowel disease cannot be explained by a Th2-Th1 cytokine shift paradigm. In this respect, the importance of exposures to helminths in the induction of an immune regulatory network that can control both Th1- and Th2-mediated inflammation has been recently emphasized [67, 115].

Helminths

Helminths, commonly referred to as parasitic worms, are multicellular organisms that adopt a parasitic life in humans and they live in locations such as the gut, blood stream or muscles. Helminths, such as *Ascaris lumbricoides*, *Toxocara canis*, *Trichinella spiralis*, *Trichuris trichiura*, *Ancylostoma duodenale*, *Necator americanus*, *Schistosomes* or filarial worms infect more than two billion people world-wide, affecting the poorest and most deprived human communities with the greatest prevalence in tropical and subtropical areas [20]. Numerous palaeoparasitological investigations of fecal samples have shown that helminthes such as the pinworm have been around for at least 10,000 years. Interestingly, in the colon of the Neolithic iceman “Ötzi”, found in Tyrol in 1991, the presence of *T. trichiura* eggs was shown [9]. A modern and extremely hygienic life style in industrialized countries leads to a dramatic reduction of helminth infections. The prevalence of ascariasis in Costa Rica, for example, dropped markedly between 1953 (9.5 %) and 1996 (2 %), likely due to improved hygienic conditions and intense anthelminthic treatment [51]. In the United States during the late 1940s, about 16 % of the population was exposed to *T. spiralis* and recently, fewer than five cases are recorded on an average each year, mostly as a result of eating undercooked exotic meats [33]. Studies on helminths infestation in Austria have shown that 26 % investigated fecal samples were positive for helminths in 1945 and only 0.24 % were positive in the time span between 1990–2000 [102]. Mutual adaptation mechanisms between helminths and their hosts developed through coexistence and coevolution over many thousands of years. Parasites have learned to modulate and suppress the host's immune responses and prevent excessive inflammation [65–67]. The interaction with helminths might be an important component of the normal development/maturation of the host's immune system [52, 90] and therefore eradication of helminths by environmental control might have caused unforeseen consequences.

Worms and allergy: hate and love relationship?

Th2-driven paradox

Both allergic diseases and helminth infections have common parameters, such as induction of Th2-polarized immune responses with high levels of IgE, up-regulation of cytokines IL-4, IL-5, IL-13, eosinophilia, as well as

mast cell degranulation [3, 42]. In addition, structural and immunological similarities have been observed between allergens and parasitic antigens [75, 103]. Paradoxically, even if both diseases are typically associated with Th2 polarization, epidemiological and experimental evidence shows that Th2-type allergic immune response such as sensitization to aeroallergens, airway hyperresponsivenes, eczema, rhinitis and asthma are reduced in subjects infected with helminth parasites [35, 58]. However, the concept of an inverse relationship between helminth infections and allergic disease is by no means clear-cut, with some studies showing no or even a negative association. Several factors such as parasite species, timing of infection, acute vs chronic infection, and intensity of infection have been suggested to influence whether the infection prevents or enhances the development of allergy [94].

Examples of positive or no association between helminth infections and allergy

Sensitization to *Ascaris* has been strongly associated with airway hyperresponsiveness and aeroallergen sensitization in African subjects living in a periurban environment [59]. There was a dose-response relationship between the levels of *Ascaris*-specific IgE and sensitization to grass or house dust mites [59]. Similarly, a study in rural China in a large sample of children from asthmatic families has shown that *A. lumbricoides* was associated with an increased risk of childhood asthma, increased airway responsiveness to metacholine, and sensitization to common aeroallergens [80]. A systemic review and meta-analysis of 33 epidemiological studies indicated that *A. lumbricoides* is associated with significant increased odds of asthma [58]. A positive association between *Ascaris* seropositivity and asthma was found in a population of 4-year-old children in the Netherlands [84] as well as in Germany in a cohort of school children [30]. In a Costa Rican population, the positive association between sensitization to *A. lumbricoides* and indicators of asthma severity (e.g. increased airway responsiveness) and asthma morbidity (e.g. asthma exacerbation) was reported [51]. The Netherlands, Germany and Costa Rica are countries where the prevalence of helminthiasis is low and it has been suggested that a low-grade infection with helminths, characteristic of industrialized countries, elevates reactivity to specific allergens by the polyclonal induction of IgE synthesis. In a population of adult individuals in a country with low to moderate intensity of *A. lumbricoides* infections, anthelminthic treatment dramatically reduced total serum IgE levels as well as specific IgE antibody levels and positivity in skin tests [63]. Another helminth parasite which has been positively associated with an increase of atopy and asthma-like symptoms in humans is *T. canis*. *T. canis* is an intestinal parasite of dogs which may infect humans by accidental ingestion of embryonated eggs. *Toxocara* infection is the most prevalent helminthiasis in industrialized countries and occurs mainly in young children [38, 108]. In Austria, epidemiological studies reported a seroprevalence of 3.7 % among the normal population and up to 44 % among people at risk, such as farmers or hunters [29]. Chan et al. have shown that *Toxocara* seropositivity was associated with an increased predisposition to the development of allergic diseases in Malaysian children [19]. Tissue-dwelling larvae can survive in humans for many years, migrating through different organs including lungs. This might cause damage leading to pulmonary inflammation, eosinophilia or airway hyperactivity [5, 38, 79]. Two consecutive cross-sectional surveys in the Netherlands have shown that *T. canis* seropositive school children had higher serum IgE levels and higher prevalence of allergic sensitization than *T. canis* seronegative individuals [16, 17]. In an adult population, *Toxocara* exposure was associated with an increase in both total serum IgE levels and blood eosinophil counts in non-atopic individuals (negative SPT) and an opposite effect was observed in atopic subjects (positive SPT especially to mites) [46]. These data are in line with the hypothesis that the allergic state may modulate the host immune responses to helminths [60, 62].

However, not all studies support a positive association between *T. canis* infection and allergy. For example, a study carried out in Austria has shown no association between *Toxocara* seropositivity and bronchial hyperreactivity [116].

Examples of negative association between helminth infections and allergy

Several epidemiological studies support a link between helminth infections and protection against allergic skin sensitization to environmental allergens. Most of the evidence is based on cross-sectional studies. Epidemiological studies from Ecuador [21–23], Ethiopia [25, 28], Vietnam [40], Gambia [77], Brazil [6] and Gabon [105] show protective effects on skin prick test (SPT) for helminth parasites such as *A. lumbricoides*, *T. trichiura*, hookworm or *Schistosoma*. A study conducted in a schistosome-hyperendemic region has shown that an on-going infection with *A. lumbricoides* was protective against asthma, however, the authors did not rule out the role of *Schistosoma mansoni* in the protection [18]. A recent systemic review and meta-analysis of 21 epidemiological studies demonstrated strong evidence that helminth infections are associated with reduced risk of allergen skin sensitization and in a species-specific analysis a protective effect was also found for *A. lumbricoides* [35]. Discrepancies observed between effects of *A. lumbricoides* on asthma (increase) and skin sensitization (reduction) raise the question about the interaction of parasites and hosts in different allergic diseases/settings as well as the connection between allergic sensitization and clinical symptoms [35].

Along these lines, several studies indicate that *T. canis* infection can in fact reduce allergic disease. A prospec-

tive case-control study found a negative association between *T. canis* infestation and allergic rhinitis [64]. Similarly, a recent study performed in children living in Brazil showed that *Toxocara* infection was associated with a reduced prevalence of SPT reactivity to common aeroallergen [70]. These data are in discrepancy with data discussed above, where *T. canis* was positively associated with allergy. One of the possible explanations might be that the timing of infection in relation to the exposure to an allergen plays an important role. To address this, Pinelli et al. combined a mouse model of allergic airway inflammation with an experimental model of *T. canis* infection [83]. Mice were infected with *T. canis* eggs and exposed to an ovalbumin (OVA) sensitization/challenge protocol at 3 or 20 days post-infection. The data show that the infection 3 days before sensitization resulted in an exacerbation of airway responsiveness. In contrast, no airway hyperreactivity was observed in mice infected 20 days prior to the sensitization.

A positive effect of helminths on allergy might be more important during the early life phase, when the maturation of the immune system takes place. A prospective study with children in Brazil investigated the effects of early vs late childhood intestinal helminth infection on allergen skin test reactivity measured in late childhood [89]. The data showed that early heavy infections with *T. trichiura* reduced the prevalence of allergen skin test reactivity in later childhood, and this protection was independent of the presence of the live worm at the time of skin testing. These data indicate the existence of a so called "window of opportunity", where early helminth infections may programme the immunoregulation in early childhood [89].

Proof of principle of the causal relationship between helminth infections and reduction of allergic diseases

There is considerable evidence from epidemiological studies pointing towards an inverse relationship between allergy and helminth infections, but this does not prove a causal relationship between a lack of helminth infections and an increase of allergic diseases [78]. In order to solve this task, several clinical intervention studies were performed. It has been shown that the elimination of intestinal helminths (reduction in *Ascaris* and/or *Trichuris* infections) resulted in a significant increase in the rate of developing skin sensitivity to house dust mite in Gabonese school children [104]. Similarly, reduced worm burden in helminth-infected children living in the rural area of Vietnam [41] or Venezuela [61] led to an increased risk of allergen skin sensitization. The effect of long-term periodic and community-based treatment of children living in rural tropical Ecuador with a broad-spectrum anthelminthic drug reduced the prevalence of *T. trichiura* which was associated with an increased allergen skin reactivity and an increased prevalence of eczema symptoms [34]. Similarly, a significant worsening in the clinical scores of asthma as well as in pulmonary function have been observed in asthmatic individuals living in an endemic area of schistosomiasis after repeated anthelmintic treatment in a randomized, double-blinded and placebo-controlled trial [1]. Thus, the inverse association between allergic disease and helminth infections in a high-prevalence population has been interpreted to require an active suppression by present/active worms [22]. Interestingly, a study conducted in Uganda found that treatment against helminths during pregnancy was associated with increased risk of infantile eczema [74] and eczema in childhood [76]. These data suggest that allergic disease may be programmed *in utero* or very early in the postnatal life and perinatal exposure to helminths may be beneficial and protect against allergy in infancy. On the other hand, a trial that followed school children in Ecuador showed no effect of anthelmintic treatment on the prevalence of atopy or clinical allergy [24] or even an improvement of asthma and reduced positivity in SPT [62]. It is difficult to explain these conflicting observations, which may relate to the age and immunological status of the subjects, differences in an anthelmintic drugs and treatment regimens (incomplete and/or short-lived helminth eradication), nature of parasites, intensity of infection, co-infections, reinfections, geographic variation or acute vs chronic infections.

Immunological mechanisms of helminth-induced suppression of allergy

Regulatory network

There is strong evidence from human and animal studies revealing that helminth infections induce several independent regulatory pathways. These pathways encompass cellular components of both innate and adaptive immunity and regulatory cytokines such as IL-10 and transforming growth factor beta (TGF-beta) [67].

Regulatory T cells (Tregs) are an essential component of the immune system and maintain homoeostasis by the suppression of exaggerated immune response against environmental allergen as well as pathogens [91]. It has been shown that Tregs are compromised in numbers and activity in patients with allergic diseases [57, 82]. Interestingly, a successful allergen specific immunotherapy (SIT) in allergic patients has been associated with the induction of Tregs during grass pollen SIT [87], venom SIT [81] or during house dust mite immunotherapy [109]. Tregs represent the most noticeable cell population in the regulatory network acting during helminth infections [101]. An infection with hookworm in areas endemic for *N. americanus* in Brazil induced an augmentation of circulating Tregs in comparison to non-infected individuals [88]. Furthermore, infection increased levels of Tregs expressing CTLA-4, GITR, which are markers associated with regulation. In different mouse models it has been demonstrated that certain helminths can suppress experimental allergic airway inflammation and

Tregs have been shown to play an essential role in this process. Studies with *T. spiralis*, for example, have demonstrated that chronic infection reduced an allergic airway inflammation associated with increased numbers of $CD4^+$ $CD25^+$ $FOXP3^+$ Tregs with suppressive activity [4]. A similar suppression of airway allergy was demonstrated by an infection with the rodent nematode *Heligmosomoides polygyrus*. [112]. The protective effect could be transferred with $CD25^+$ Tregs [112] or by B cells [113]. Correspondingly, an infection with *S. mansoni* suppressed lung inflammation by inducing the recruitment of natural Tregs to the lungs [2]. Human field studies of the relationship between helminths and atopy have focused mainly on the measurements of IL-10 levels. IL-10 plays an important role in helminth induced regulation and may be produced by several different cell types, including regulatory T cells and B cells. Parasite-specific IL-10 was inversely associated with allergen skin sensitization in populations infected with *Schistosoma haematobium* [105] or in children living in a rural area of Vietnam, where hookworm (mostly *N. americanus*) is the predominant gut parasite [41]. In a population of Gabonese children, the infection with *S. haematobium* induced the development of IL-10-producing regulatory B cells in peripheral blood, which decreased after anti-schistosome treatment [106]. Importantly, the suppressive capacity of those cells was confirmed by a mouse model of allergic airway inflammation. However, a study in a group of Ecuadorian school children, where *A. lumbricoides* and *T. trichiura* are the most prevalent parasites, does not support the concept that helminth-induced IL-10 plays an important role in the modulation of atopy.

IgE saturation hypothesis

Helminth infections stimulate polyclonal total IgE production in much higher levels than detected in uninfected allergic patients and according to the "IgE saturation hypothesis", high levels of helminth-induced polyclonal IgE may saturate high-affinity IgE receptor FcεRI on basophils and mast cells thereby preventing allergen-specific hypersensitivity reaction [11]. This hypothesis was supported by findings that *in vitro* sensitization of mast cells with serum containing grass pollen-specific IgE was blocked in the presence of high total IgE levels [45]. More recently, chronic infection with *Litomosomoides sigmodontis*, a filarial nematode, and *S. mansoni*, a blood fluke, led to suppression of basophils responsiveness to IgE-mediated activation in mice. In order to verify these data in a clinical situation, the basophil function in children infected with intestinal helminths (*A. lumbricoides*, *T. trichiura* and *Hymenolepis nana*) was investigated before and after anthelmintic treatment. The findings have shown that helminth infections suppress basophil responsiveness to both IgE-dependent and IgE- independent activation and this suppression required the on-going helminth infection [56]. However, Mitre and colleagues investigated the basophil function in a population infected with the filarial parasite *Brugia malayi* and they have shown that high polyclonal to specific IgE ratios did not attenuate basophil sensitization to dust mite *Dermatophagoides pteronyssinus* as measured by *D. pteronyssinus*-specific histamine release. The authors suggest that a saturation of IgE binding sites by polyclonal IgE in filarial-infected patients might be possible, but not the crucial mechanism of helminth-induced allergy prevention [71]. Similarly, Pritchard and colleagues have reported that individuals living in the area where hookworm infection is endemic maintain stable basophil responsiveness. Given that basophils and mast cells are central effector cells in allergic inflammation and have been shown to be important in the development of type 2 immunity to allergens and helminths [86, 44], further studies are needed to investigate the impact of helminth infection on the function of these cells with respect to protection against allergic disease.

Has the time come to treat allergic patients with helminths or helminth-derived immunnomodulators?

Trichuris suis

There is considerable interest in taking an advantage of the beneficial effects of helminth parasites and to use controlled helminth infections, so called "helminth therapies", to treat immune-mediated diseases, such as allergy, autoimmunity and chronic inflammatory intestinal conditions [8]. It has to been pointed out that the selection of suitable parasite species is crucial. Clinical trials have been performed mainly with whipworm *Trichuris suis*, a natural parasite of pigs which is closely related to human parasite *T trichuira*. *T. suis* is non-pathogenic in human subjects. Eggs of the *T. suis* (TSO) are not infective until they have embryonated in the soil. They hatch within the human gut, where they remain for several weeks [111]. *T. suis* does not multiply in the human host and there is no host-to-host transmission. To maintain the infection, repeated dose of live TSO has to be performed. Reducing the risk of an inadvertent transmission of diverse infections or contamination by bacteria or endotoxins, which might directly cause harm or may influence the outcome of the study, *T. suis* can be harvested from animals kept under pathogen-free conditions [110]. TSO are produced under Good Manufacturing Practice (GMP) conditions and are commercially available (OvaMed GmbH). TSO have been shown to be safe in multiple studies for the treatment of allergic disorders and in inflammatory bowel disease [53]. The first clinical trial was performed on patients with inflammatory bowel disease and was based on oral application of 2500 live TSO [96]. This study demonstrated that treatment with TSO is safe and well tolerated and led to improvement in the common clinical manifestations. The benefit was temporary in some patients with a single dose, but it could be prolonged when the treatment schedules

contained repeated administration every 3 weeks. Two following clinical studies showed that TSO suppressed significantly both the Th1-mediated Crohn's disease [97] and Th2-mediated ulcerative colitis [98]. Currently, there are two multicentre double-blinded placebo controlled trials in the United States (Trial identifier NCT01576471) and Europe (Trial identifier NCT01279577) testing the efficacy and safety of different doses of TSO (500, 2500 or 7500) in patients with Crohn's disease [110]. Although there is a substantial preliminary evidence for beneficial effects of the helminth therapy in patients with IBD, there is currently insufficient evidence for the therapeutic effect of worms in allergic diseases. A first randomized double-blind, placebo-controlled study of TSO in the therapy for grass pollen-induced allergic rhinitis showed that repeated treatment with TSO induced substantial clinical and immunological responses (increased eosinophil counts, elevated plasma IL-5 and parasite-specific IgE, IgG, IgG4 and IgA and Th2-polarized cytokines with high levels of IL-10) consistent with the helminth infection [10, 14]. However, the therapy had no therapeutic effect on grass-pollen-induced allergic rhinitis and did not affect allergen-specific cytokine responses. Several explanations for the lack of clinical efficacy of TSO on allergy have been suggested. First, patients received TSO relatively late with respect to the onset of the tree pollen allergy season. It might take time to establish the immune regulatory network and induce beneficial clinical effect on pollen allergy [49, 99]. Individuals with natural infections living in the endemic areas are exposed to parasitic infections early in life, thus strategies preventing the development of allergic disease rather than the therapy of already sensitized patients may be more beneficial for the prevention of allergic disease. Second, it was proposed that the therapeutic benefit of gut-dwelling helminths on diseases where the target organ, such as airways, is distant from the site of infection might be achieved by higher or multiple doses of TSO [85].

Hookworms

Hookworms are gastrointestinal parasites infecting currently almost 800 million people in developing countries [12]. While high levels of hookworm infection can cause morbidity and mortality, there is strong evidence from epidemiological data that hookworm infection is associated with a protective effect against allergic sensitization and asthma [40, 58]. These findings provided a rationale that experimentally induced hookworm infections may have a therapeutic effect in allergy.

Hookworm *N. americanus* is the second candidate used in clinical trials. Adult worms live in the gut, producing fertile eggs which hatch into larvae. Third stage larva penetrates skin, enters the circulation, then lungs and migrates via the trachea and oesophagus to the gut, remaining here for years [85]. *N. americanus* is soil-transmitted and cannot be propagated in a modern sanitary environment. Short-term trials were designed to verify the safety of larval migration through the lung in healthy and allergic individuals [13, 36, 73]. When given at high dose (25–100 larvae), an acute exposure can cause intestinal syndromes including diarrhoea, vomiting and abdominal pain. Low infection intensity with 10 worms, however, was well tolerated and did not cause clinically significant exacerbation of airway responsiveness [13, 36, 73]. *N. americanus* has also been used in a randomised double-blind, placebo-controlled clinical trial in an attempt to test the potential of helminth infection to suppress the immunopathology induced by gluten [27]. Although an infection with *N. americanus* suppressed gluten-specific inflammatory Th1 and Th17 responses in the mucosa, no significant reduction in symptom severity was observed in infected individuals [27, 65]. The suppression of mucosal IL-23 and upregulation of IL-22 during an established infection have been suggested as a potential mechanism of suppression of proinflammatory Th17 responses [43].

The first randomized double-blind placebo-controlled study on the effects of experimental hookworm infection in individuals with allergic asthma reported that cutaneous application of 10 *N. americanus* larvae were well tolerated and improved airway responsiveness, however, the difference between infected individuals and placebo group was not significant [37]. This study provided proof of the concept that experimental hookworm infections are feasible and well tolerated, supporting their use in a therapeutic context. The administration of repeated low-dose infection, which mimics the pattern of natural infection, might further boost immune modulation and generate significant clinical benefit.

Parasite-derived molecules

As mentioned above, therapeutic applications of live helminths such as *T. suis* or *N. americanus* are now being studied in several clinical trials for diseases such as Crohn's disease, ulcerative colitis, asthma, allergic rhinitis, autism and multiple sclerosis. Although helminth therapy has shown to be well tolerated, several safety concerns such as side effects, especially in immunocompromised patients, have been voiced [110]. Hence, there is a great interest in the identification, characterization and production of parasite-derived therapeutic molecules. Total whole body extracts, secretory/excretory products, isolated fractions or recombinant produced proteins or chemically synthetized glycoconjugates from a broad spectrum of parasites were used in animal models [48, 66, 115]. In our lab, we have recently shown that whole body extract derived from the swine nematode *Oesophagostomum dentatum* prevents airway inflammation in a mouse model of birch pollen allergy [92]. Remarkably, *O. dentatum* extracts inhibited the development of allergen-specific responses and at the same time induced parasite-specific Th2/regulatory responses. These data suggest that *O. dentatum* prevents the allergy without evoking general suppression of the host immune

system. The suppressive effect of *O. dentatum* was heat-stable, suggesting that non-protein components, such as carbohydrates, may play an important role in allergy suppression. Recent structural data on glycan decorations of *O. dentatum* indicates the presence of galactosylated fucose epitopes [114] and it is of interest to investigate whether such structures have an immunomodulatory potential. Similarly, the application of *H. polygyrus* excretory/secretory products (HES) during sensitization to ovalbumin suppressed the allergic airway response with a reduced eosinophilia and IgE production and the heat-treatment did not compromise its protective ability [68]. This study replicated the therapeutic effect observed in the same model with live *H. polygyrus* infection [112]. In a setting, where already sensitized mice are treated with parasite products, HES also prevented the allergic airway inflammation and heat-treatment compromised its ability to suppress recruitment of eosinophils [68]. Cystatins, cysteine protease inhibitors, are among the best-characterized secreted helminth molecules, associated with immunomodulation [50, 54, 100]. Cystatin from the filarial nematode *Acanthocheilonema viteae* (AvCystatin, Av17) suppressed allergic airway hyperreactivity in mouse model of OVA-induced allergy when applied during or after sensitization before challenge with OVA [92]. More recently, Av17 was shown to suppress allergic responses in a clinically relevant mouse model of grass pollen allergy [26]. Interestingly, Av17 modulated allergen-specific responses of human PBMC derived from timothy grass pollen allergic patients [26]. Interestingly, another *A. viteae* product, ES-62 was found to supress the severity and progression of airway hyperresponiveness, as peribronchial inflammation, mucosal hyperplasia, eosinophilia and IL-4 release were markedly reduced in ES-62-treated mice in comparison to controls [69]. ES-62 is a 62-kDA glycoprotein, containing phosphorylcholine (PC), which is well tolerated in humans (evidence comes from tropics, where tens of millions of people are infected, some of them for their entire lives). PC has been shown to be responsible for the modulatory effects of ES-62 [47] and thus there is currently an interest to develop small PC-based analogues of ES-62 molecule as a drug to treat allergic airway inflammation. PAS-1 is a 200-kDa protein component derived from adult *Ascaris suum* extract. PAS-1 reduced the lung allergic inflammation in a mouse model of OVA-induced allergy and this effect was mediated by IL-10 [7] and was associated with expansion of regulatory cells.

Conclusions

Allergy and helminth infections represent major public health problems with inverse global distribution, where the first is a growing problem of developed and industrialized countries, while the latter affects rural developing countries. Epidemiological and experimental data indicate that helminth infections can suppress the development of allergic disorders. Helminth therapy has been already used in several clinical trials for the treatment of allergic disorders and live parasites are now available commercially. Nevertheless, there is currently insufficient evidence to support the use of helminth therapy in routine management of allergic disorders and more preclinical studies need to be performed. Although no parasite derived molecules have been used as a treatment in clinics yet, experimental data from animal studies strongly indicate that the products derived from different helminths have immunomodulatory properties. Thus, the identification, characterization and production of synthetic equivalents that mimic the effect of helminth infections as well as identification of the mechanisms of their action may offer new strategies for the prevention and treatment of allergic diseases.

Conflict of interest

The authors declare that there are no conflicts of interest.

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