Introduction

It is estimated that parasites currently infect 1.4 billion people worldwide. Parasite infections are of particular interest to studies on pathogenesis and epidemiology of allergic diseases, as they induce strong T helper 2 (Th2) responses, leading to increased production of cytokines such as interleukin 4 (IL-4), IL-5, IL-9, and IL-13, and high levels of immunoglobulin E (IgE) antibodies, resembling responses in allergic individuals. However, chronic infections with parasites can also induce an immune regulatory response, characterized by regulatory T cells, regulatory B cells, and alternatively activated macrophages, with increased levels of IL-10 and TGF-β as well as T-cell hyporesponsiveness, which is thought to enhance survival of the worms within their hosts.

Parasite infections: promote or protect from allergy and asthma?

The issue of whether infections with parasites promote or protect from development of allergy and asthma remains controversial. A recent review by Amoah et al [1], evaluating studies in children 0-18 years-old in the past 5 years, highlights the fact that the interactions are complex as some investigations find an inverse association, but others show no effect or even a positive association. However, most of the studies have come to a few consistent observations: results of cross-sectional studies in humans have generally agreed that helminth infections are often negatively associated with skin prick test (SPT) responses (correlated to IL-10 and T-reg responses); no or even positive associations have been found for lung function or reported clinical symptoms of allergy; repeated anthelmintic treatment of school-aged children for at least one year increases SPT reactivity, but had no effect on reported allergic symptoms; treatment of worms in pregnant women or early in life could lower the risk of developing eczema in the first years of life, but this does not seem to occur to asthma and rhinoconjunctivitis [1]. It is important to bear in mind that species of helminth as well as timing and burden of infection can all contribute to variable findings in population studies, particularly when the study outcome is as complex and multifactorial as clinical allergy.

Although the focus of research on the relationship of parasites to allergy has been on helminth infections, the role of protozoan infections in allergic diseases has been recently investigated [2]. Hagel et al. have shown that infection with the protozoa Giardia duodenalis among Warao Amerindian pre-school children was associated with presence of Atopic Dermatitis, increase in levels of cow’s milk whole blood stimulated TNF-alpha, IL-13, sCD-23 and cow’s milk SPT, and also with increase in hen’s egg (HE)–stimulated TNF-alpha, sCD-23, HE-IgE levels and HE-SPT. These results suggested that gut inflammation caused by G. duodenalis could enhance food allergy, contributing to clinical presentation of Atopic Dermatitis in these patients [2].

Giving intentional parasite infections to treat patients with allergic diseases: is there a role?

Epidemiological and experimental studies which supported a link between infections with helminth parasites and reduced incidence of allergic diseases provided the rationale for clinical trials involving treatment with eggs from the pig nematode Trichuris suis (Trichuris suis ova, TSO), or intentional infection with hookworm larvae (Necator americanus). A double-blind, placebo-controlled, parallel group trial among adults in Denmark has examined the efficacy of TSO therapy in the treatment of grass pollen-induced allergic rhinitis and has demonstrated no therapeutic effect [3]. Likewise, therapy with hookworm larvae showed no benefit to adult patients with asthma [4]. It is important to consider that helminth infections cause significant morbidity in endemic countries, leading to malnutrition, anemia, delays in development, impairment of cognitive functions and decrease in vaccine efficacy. Regular deworming programs are currently strongly recommended by the WHO as a public health priority. Therefore, therapy for allergic diseases with worms would be unacceptable and unethical in most situations. However, it would be of great interest to define and characterize specific helminth molecules associated with consistent and strong immunomodulatory effects as targets for application in the treatment or prophylaxis of allergic conditions.

Parasite molecules with homologues in allergen families

It has been well documented that parasite molecules have homologues in allergen families, including lipocalins, EF-hand proteins, cupin superfamily, profilins, enolase (fungi and latex), albumin (cat), trypsin (group 3 mite allergens), paramyosin (Blomia tropicalis Blo t 11) and tropomyosins, with extensive similarities [5-7].
The role of Cross-reactive Carbohydrate Determinants (CCD) and Alpha-Gal in immune responses to parasites

In addition to IgE to protein antigens, cross-reactive IgE responses directed against N-linked carbohydrates of glycoproteins found in plants and invertebrates including helminths, have been demonstrated [1]. These carbohydrates are known as cross-reactive carbohydrate determinants (CCDs), and include the two major N-glycan motifs, xylose and core-3-linked fucose, associated with cross-reactive IgE responses. In most studies, cross-reactive IgE directed against CCDs was demonstrated to have poor biologic activity, given by increased levels of IgE directed against allergens without SPT reactivity or clinical symptoms (ex. peanut sensitization in Schistosoma hematobium infected children in Africa) [1].

Although the lack of clinical relevance of IgE antibodies against CCDs has been demonstrated, in recent years, IgE directed against the oligosaccharide galactose-a-1,3-galactose (alpha-gal) has been linked to anaphylaxis [9-12]. IgE antibodies to alpha-gal were reported to cause severe anaphylactic reactions in patients treated with cetuximab, a chimeric mAb approved for use in patients with cancer. The reactions often occurred shortly after the first injection, suggesting pre-existing IgE antibodies. In addition, IgE antibodies to alpha-gal have been shown to be associated with delayed symptoms of anaphylaxis, angioedema, or urticaria after eating mammalian meat, which carries the oligosaccharide. Current data strongly suggest that the cross-reactivity originates from tick bites, with the lone star tick Amblyomma americanum as the major species involved [9].

Interestingly, in serum samples from children living in rural helminth-endemic communities in Kenya and Ecuador, positive IgE responses to alpha-gal have been reported, which could be tick-related but could also indicate participation of helminths or other ectoparasites [9]. In addition, a study conducted in Zimbabwe has looked at IgE responses against alpha-gal in rural helminth-infected subjects as well as urban doctor-diagnosed cat-allergic patients [13]. In the parasite-infected group, 85% had IgE against alpha-gal and 66% had IgE against the cat allergen Fel d 5 (cat albumin, which carries alpha-gal) [11]. The IgE to alpha-gal and IgE to Fel d 5 showed strong correlation, whereas only two of 47 of the parasite-infected children had IgE to Fel d 1, which does not carry alpha-gal. By contrast, among the cat-allergic patients, only a few had IgE responses to Fel d 5 and alpha-gal, while 74% had responses to recombinant Fel d 1. These observations suggest that in helminth-endemic areas, the IgE to alpha-gal may not be clinically relevant. However, no information was obtained on reactions to mammalian meat in the helminth-endemic areas, to allow for more definitive conclusions about the relationship between sensitization to alpha-gal and clinical outcomes.

Selected references