

ORIGINAL ARTICLE

Effect of parasite infection on allergic disease

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Abstract

Vertebrates and helminths have co-evolved for 500 million years, developing mutual adaptation mechanisms between parasites and hosts. Today, however, helminth diseases are among the most neglected communicable diseases. Epidemiological evidence shows that exposure to helminth parasites is inversely correlated with allergy incidence, and helminths induce immune hyporeactivity in both the innate and adaptive systems. The mechanisms include parasite-derived regulatory molecules, the study of which opens new avenues for the control of allergic and autoimmune diseases.

Epidemiological research shows that allergic disease is becoming more prevalent in developed countries and currently affects several million people. Parasitic infections, for example by helminth worms, are prevalent in developing countries, affecting several billion people. Common parameters exist between parasitic helminth infections and allergic disease, for example levels of IgE, Th2 cytokines, eosinophils, and cytotoxic mediators (Fig. 1). In addition, similarities are seen between allergens and parasitic antigens. Paradoxically, even though both allergy and helminth infection induce a Th2 response, the Th2-type allergic response is decreased in helminth-infected patients (1).

These observations led to the concept of an inverse relationship between parasitic infections and allergic disease. The actual situation is less black-and-white, with more of a gradient relationship observed geographically from north to south between helminth infection and allergic disease (2). Also, the relationship between parasites and disease is not restricted to allergic disease but also applies to autoimmune disease and inflammatory bowel disease. However, these findings do not apply to all parasite diseases, but mainly to those caused by helminths with intestinal migration.

In the last 40 years, we have seen an exponential increase in allergic and autoimmune disorders both in industrial countries and in urban areas of emerging countries. This increase in a short period suggests that an exclusive contribution by genetic factors is unlikely. Instead, environmental factors including infections, specifically parasitic infections, are likely to play a role. This has led to a revision of the hygiene hypothesis in allergy. Studies on parasitic infections contrib-

ute to the understanding of the basis of allergic disorders, specifically asthma, eczema, and rhinitis.

Helminths produce immunoregulatory molecules

The mammalian immune system and helminths have co-existed and co-evolved for 500 million years. This long-term process is not true for all infections, but is unique to the helminths. These parasites induce chronic infections, and schistosome worms can live for more than 40 years indicating that they must have developed systems to protect themselves from the host. This implies that the diminution of parasite infections by environmental control can modify this co-evolved system of balance between parasite and host.

The role of parasite molecules in immunoregulation is best illustrated in schistosomiasis. Infection starts with a low Th1 response for the first 3 weeks and after an enhanced Th2-type response appears when eggs are produced, and a subsequent decrease is observed at about 12 weeks of infection through immunoregulation. Interestingly, there are similarities in the top 10 molecules involved in allergy and helminth infection (3), whereas schistosomes produce many immunoregulatory substances or directly induce interleukin (IL)-10, an important regulatory cytokine produced during parasitic infections. This results in the induction of immunoregulatory cells, including alternatively activated macrophages (AAMs). As an example of parasitic immunoregulation, young schistosomes in the skin can produce prostaglandin D2 that binds to its inhibitory receptor (DPI). This in turn increases cyclic AMP

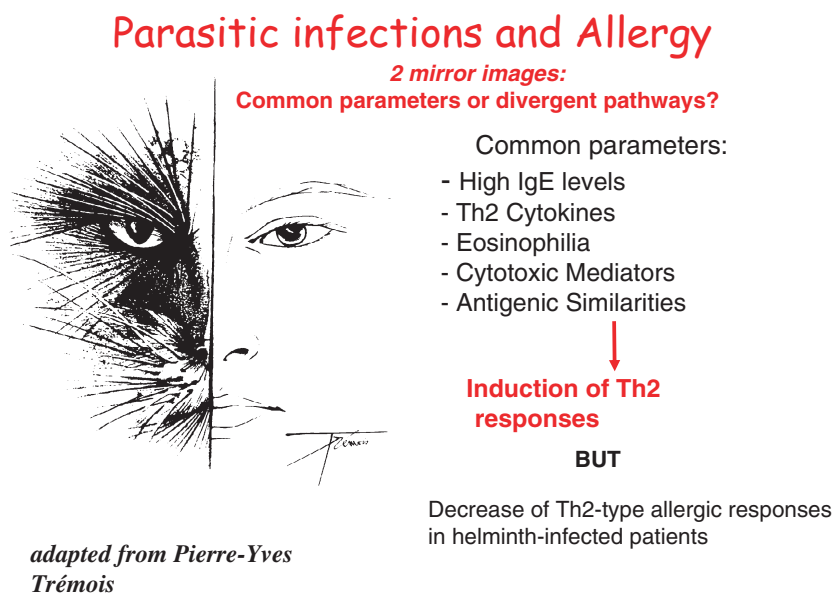


Figure 1 The inverse relationship between parasitic infections and allergy.

levels, inhibition of Langerhans cell migration in the skin and decrease in immune response (4).

Much is already known about lymphoid cells and the two main immunomodulatory cytokines IL-10 and tumour necrosis factor (TNF), so we focus on the influence of IL-4 and IL-13 and the contribution of myeloid cells, especially the population of macrophages called AAMs or M2 cells. These macrophages are immunoregulatory; they control the Th1 response and are anti-inflammatory. Classical M1 macrophages are involved in the immune response against bacteria and viruses. In contrast, M2 cells respond to extracellular pathogens such as helminths and play a role in wound repair together with anti-inflammatory effects.

Another myeloid cell population of interest is eosinophils, which are mainly considered as effector cells in the defence against parasites and in the pathology of allergic disease. However, recent research shows that eosinophils have other functions (5) and can play a role in innate immunity and regulation of the immune response. Our hypothesis is that activated eosinophils induced during parasite infection or allergic disease may be more efficient in innate immunity mechanisms, when compared with normal subjects. These effects enhance eosinophils that exert beneficial or regulatory functions, especially in the tissues. To test this hypothesis, we investigated the antitumour effects of eosinophils from different donors and found a significant increase in the antitumour properties of eosinophils from allergic patients over normal donors. This provides a new view of an effector function of eosinophils in innate immunity, which is not antibody dependent but requires only contact with the tumour cells (6).

Clinical implications of immunoregulation by helminths

These results have several clinical implications. First, it may be possible to translate these findings into the use of helminth parasites as therapeutic agents for allergy. Second, studies in Gabon have shown that mass treatment with anti-helminth drugs may increase sensitivity to allergens (7). Another possible application of these findings is the use of living intestinal nematodes to control asthma or Crohn's disease (8). This has already been used with a pig parasite, but adverse effects have been reported, for example, the iatrogenic effect of development of animal parasites in the patient. Also, producing the live parasite for treatment of patients is currently not possible. Therefore, in our laboratory we recently identified and characterized a schistosoma molecule that plays an immunoregulatory role in intestinal inflammation. (M. Capron unpublished data).

In conclusion, co-evolution and mutual adaptation have occurred between helminth parasites and the human immune system. This model points out the risk of immune dysfunction from environmental control measures reducing exposure to worms, if allergic risks in association with other environmental risk factors are not considered. Studies in this area of immunoparasitology have generated much basic knowledge, especially about Th1 and Th2 polarization.

Conflict of interest

Monique Capron has received honorarium for a talk at ALK-Abelló.

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