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# Immunomodulation by helmintos: Possible use as therapy for autoimmune diseases

## Abstract

**Context:** The incidence of autoimmune diseases and allergies has increased markedly in the last half of the 20th century, especially in more developed countries, with an increase in urbanization and hygiene that has led to the elimination of many parasitic infections.

**Objective:** To analyze through scientific bibliographic sources the effects of the parasite load, especially helminthiasis, on the appearance of autoimmune and allergic diseases.

**Methodology:** The documentary analysis of different scientific sources that refer to the theory of immunomodulation by helminths was used.

**Results:** They suggest that the treatment of autoimmune diseases with helminths or products derived from them can have protective and therapeutic effects in these patients.

**Conclusions:** It could be concluded that the immunodulation mechanisms carried out by helminths prevent patients from eliminating the parasites, but have beneficial effects on the course of some autoimmune diseases. Although the causal relationship is not fully proven, studies in animal models and clinical trials carried out in patients with autoimmune diseases suggest that their treatment with helminths or products derived from them may have protective and therapeutic effects in these patients.

**Keywords:** helminths, autoimmune diseases, allergies

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## Introduction

The incidence of autoimmune diseases and allergies has increased markedly in the last half of the 20th century, especially in the most developed countries. With an increase in urbanization and hygiene that has led to the elimination of many parasitic infections, the prevalence of Crohn's disease, ulcerative colitis, type 1 diabetes mellitus or multiple sclerosis has increased at an unjustifiable rate at the level genetic. Various theories try to explain this phenomenon. Among them, the hypothesis of hygiene or the mechanism of old friends. The inverse prevalence between these diseases and parasitic diseases led different researchers to study whether there is a causal relationship. There are epidemiological studies that suggest that a parasitic infection leads to the remission of some of these diseases.[1]

Most of the studies are focused on helminths, a group of metazoans that are evolutionarily different but have common immunodulatory effects. The immunomodulatory effect is characterized by the stimulation of various regulatory cells [regulatory T lymphocytes (Tregs), regulatory B lymphocytes (Bregs), dendritic cells (DCs) and alternative pathway activated macrophages (MAAs)] and an increase in profile cytokines Th2. This mechanism, used by the parasite to try to avoid its expulsion from the body, seems to be responsible for the beneficial effects in patients with autoimmune diseases and / or allergies. Different research groups have studied the possible application of a helminthic therapy. However, due to the risk of helminthic infection, attempts are being made to isolate products derived from these, responsible for the immunomodulatory effects, to try to develop a drug that allows treating these diseases more effectively and safely.[1]

The mechanism that favors the improvement of the disease and even confers protection against autoimmune diseases and allergies is immunodulation. This immunomodulatory effect generates an environment of inflammatory hyporesponsiveness, allowing helminths to establish a chronic infection. Autoimmune diseases are characterized by hyperresponsiveness of the Th1 / Th17 responses and the allergic response and asthma are characterized by an excessive Th2 response. Although the suppression of the Th1 and Th17 pathways and the inclination towards a Th2 immune profile is not clearly beneficial for the parasite, they obtain advantages by creating a hypoinflammatory environment and inclined towards a regulatory immunological profile.[2]

The first reaction of the immune system to infection is the presentation of antigens to T lymphocytes by antigen presenting cells such as dendritic cells. Many parasitic antigens alter this process by stimulating a tolerogenic phenotype of dendritic cells.[2] T lymphocytes can differentiate into helper T lymphocytes (Th) or regulatory T lymphocytes (Tregs). Of the five existing subtypes of Th lymphocytes, it is important to note that the Th1s produce pro-inflammatory cytokines (TNF-α, IFN-γ and IL-12) while the Th2s produce anti-inflammatory cytokines. Immunomodulation produced by helminths is mainly characterized by this induction of the immune Th2 response characterized by an increase in cytokines IL-4, IL-5, IL-13 and immunoglobulins IgE, eosinophilia and mastocytosis and by an increase in anti-inflammatory molecules (IL-10, TGF-β) and cells with a regulatory profile [regulatory T lymphocytes (Tregs), regulatory B lymphocytes (Bregs), dendritic cells (DCs) and alternative pathway activated macrophages (MAAs).[3]

Il-10 and TGF-β can be produced by various cell types, but are associated with regulatory T lymphocytes. These Tregs, which are essential in the control of autoimmune diseases with Th1 / Th17 responses, have also been increased in patients infected by helminths.[3] Bregs lymphocytes also produce anti-inflammatory cytokines (IL-10). They have been shown to be important in the suppressive effect of experimental ulcerative colitis, arthritis, and experimental

autoimmune encephalomyelitis (EEA).[4] The DCs are also stimulated towards a regulatory profile. The alteration of DCs, essential in the innate response and as a link with the adaptive response, prevents the presentation of antigens and therefore reduces the responses of T lymphocytes.[4]

The mechanism by which the response of DCs is modified is the alteration of the expression of pattern recognition receptors (PRR / Patterns Recognition Receptors) [especially Toll-like receptors (TLR / Toll Like Receptors) and lectin-like receptors) and the lipopolysaccharide binding protein (LBP / Lipopolysaccharide Binding Protein).[5] The expression of TLR2 is increased in both DCs and B lymphocytes. These cells, activated through TLR2, inhibit the proliferation of CD4 + T lymphocytes and the production of IFN-γ and IL-17. In normal situations, the stimulation of DCs through TLR4 leads to a cascade of kinases, resulting in the production of IL-12. This process is also modified by helminthic antigens, which interfere with this signaling pathway by inhibiting the production of IL-12.[6]

Basophils are also innate responsive cells capable of producing large amounts of IL-4. They usually do so after cross-linking with surface antigen-specific IgE. Some studies suggest that, after a parasitic infection, which induces a Th2 response, antigen presentation is produced by basophils, which induce a Th2 response and secrete IL-4 independently of dendritic cells and the presence of specific antigen IgE.[6] To confirm the involvement of these cells in helminth-mediated immune suppression, they have been used adored various animal models. The most characterized model is that of mice infected with Heligmosoides polygyrus, a murine intestinal nematode.[7] To confirm the involvement of these cells in helminth-mediated immune suppression, they have been used adored various animal models. The most characterized model is that of mice infected with Heligmosoides polygyrus, a murine intestinal nematode.[8]

Some excretion-secretion products (ES products) of H. polygyrus produce a blockage of IL-33, important in the activation of ILC2, and a lower allergic response is observed.[8] Other studies using Fasciola hepatica show that the prevention of EEA in the murine model is dependent on TGF-β.[9] Due to the complexity of this immunomodulatory mechanism, it would be necessary to continue carrying out studies to understand it in order to develop new therapies in a controlled manner.[9] The possible use of helminths as therapy for autoimmune diseases is being studied more and more. However, it is important to be aware of the pitfalls of this method and to take into account both practical and ethical considerations. In addition, after the great effort that has been made to eradicate these infections, to cause them again on purpose would be a contradiction. For this reason, there is currently a need to isolate the molecules responsible for eliciting this immune response in order to obtain controlled treatments.

The response produced depends both on the parasite and on the moment of the life cycle in which it is found, they do not always have protective effects, so the choice of the species is important. Some parasitic infections commonly generate asthma and allergic reactions such as those produced by Anisakis, Ascaris or Toxocara. In addition, it has been seen that the parasites that can produce benefits in each disease are specific according to the disease; not all parasites produce the same beneficial effects in all diseases. Among the species that have been identified as good candidates for study are species that cause human infections, but with little virulence or animal parasites, unable to complete their cycle in humans. Helminthic antigens produce their effects by different mechanisms, including polarization towards the Th2 response, an increase in IL-10 production, the modification of the macrophage response or the blocking of the Th1 / Th17 response, among others. Some of the most common mechanisms occur through receptors or by intervening in signaling pathways. Research with molecules derived from helminths or the development of molecules that mimic their effects could be the therapeutic future for patients with autoimmune diseases. Although the potential of these molecules still needs to be exploited, advances in their purification and characterization point to the possible development of a new group of immunomodulatory drugs.

As a result of all the above, it could be concluded that the immunodulation mechanisms carried out by helminths prevent patients from eliminating the parasites, but have beneficial effects on the course of some autoimmune diseases. Although the causal relationship is not fully proven, studies in animal models and clinical trials carried out in patients with autoimmune diseases suggest that their treatment with helminths or products derived from them may have protective and therapeutic effects in these patients. Clinical trials have been carried out mainly with eggs of T. suis and larvae of N. americanus and have shown that the treatment can be safe and effective both in ulcerative colitis, Crohn's disease and multiple sclerosis. However, there are still conflicting data and a large number of patients have not been observed, so in the future the goal should be to increase the number of patients in clinical trials.

Studies in animal models with various molecules produced by helminths are encouraging, and therefore the development of products derived from these organisms for their subsequent study in patients should be considered. The potential of these molecules and the synthesis of products that mimic their effects have not yet been exploited. Although a large part of the immunodulation mechanism has already been elucidated, perhaps its better understanding would allow the development or isolation of molecules whose effects are more controlled. The existing data to date suggest that the future development of helminth-derived drugs as immunomodulators or vaccines to prevent autoimmune diseases is possible.

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## Conflicts of interest

There are no personal, professional, financial or other conflicts.

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