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Therapeutic applicability of helminths in atopic and autoimmune diseases

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ABSTRACT

The incidence of atopic and autoimmune diseases has been rising all over the world, so the design of new drugs to prevent and treat these diseases should not be delayed. Epidemiological investigations revealed that the increase also parallels a decrease in infectious diseases, especially helminth's infections. In the past decade, helminth infections became less common due to the developed sanitation. Meanwhile, atopic and autoimmune diseases' incidences were increasing, which cannot be explained by the changes of susceptibility genes. Thus, immune dysregulation may be related to the reduced prevalence of helminths' infections. Helminths' products have been used to prevent the development of inflammatory diseases and reduce their symptoms. Several studies on animal models and clinical trials were conducted to detect the efficiency of helminth molecules in immune-modulating of atopic and autoimmune diseases. Making use of their ability for immunomodulation may lead to the introduction of effective therapies for such diseases.

KEYWORDS: helminth infections, effective therapies, atopic, autoimmune diseases.

INTRODUCTION

Over time, helminths have evolved with humans using different mechanisms to become alive in their hosts, for example, they secrete substances to evade humans' immune systems (1).

The parasites do not seek to destroy the hosts but keep them alive by preserving an equilibrium with them. As they do not stimulate their hosts, causing their removal, or suppress their immune system causing host death (2).

It has been noticed that the prevalence of allergic disorders (like allergic dermatitis and asthma, etc.) and autoimmune diseases (like inflammatory bowel disease (IBD) and Type1 Diabetes (T1D), etc.) were raised, with the decline in helminth infections (3).

Greenwood (1969) recognized the negative relationship between parasites and immune disorders and he observed that infection with Plasmodium in Nigeria was associated with a decrease in the number of rheumatoid arthritis cases (4).

Also, Greenwood *et al.* (1970) determined that immune dysfunction disorders in mice were inhibited when they were infected with Plasmodium berghei (5).

Strachan (1989) assumed the hygiene theory which stated that the patients who were exposed to infectious diseases in childhood, were protected from allergic diseases. So, the rise in the number of cases with allergic diseases can be referred to as the control of infectious diseases particularly the parasitic worms (6).

Also, it has been observed that people infected with worms are more common among the poor populations, while people with atopic diseases and autoimmune diseases are common in rich countries (7).

The current treatments of autoimmune diseases as Long-term glucocorticoid and purine analogs have many side effects therefore it becomes necessary to find more efficient and safe treatment (8).

Several studies have used parasitic worms in the therapy of immune system disorders like IBD, allergy, asthma, multiple sclerosis, and diabetes (9).

Regarding the immune theory, T Helper1/T Helper 17 response is associated with autoimmune disorders and the T Helper 2 response is associated with helminth infections and atopic diseases. Helminth infections enhance TH2 response while suppress TH1/TH17 response, leading to inhibition of autoimmunity. Also, the infections cannot induce allergies due to stimulation polyclonal of IgE which is not specific for allergic diseases (10).

Besides, parasites secrete substances that prevent the inflammation in their hosts to overwhelm their immune system (11).

Furthermore, they can also stimulate regulatory T cells, regulatory B cells, and M 2 macrophages, prohibit type 2 lymphoid cells and dendritic cells, and overwhelm intestinal flora (12).

Helminth therapy in animal studies

The first step of the empirical study is the use of parasitic worms as a treatment in animal models. The efficacy of treatment of IBD in mice with helminths and their eggs was recorded. Several studies documented a reduction in IBD symptoms in mice (13).

As helminths stimulate the immune response sharing in the protection of the hosts from the development of autoimmune diseases. Parasitic infection stimulates IL-4, IL-10, and IL-13 while inhibits INF-γ, INF-α, and IL-12 levels (14).

Also, several animal studies reported that helminth infections decreased the severity of encephalomyelitis in mice with multiple sclerosis. As the infections decreased the activity of Th1 cells, Th17 cells, and INF-γ and stimulated IL-4 and TGF-β (15).

Besides, their infections were effective only as a preventive measure in mice with TID, as the infections protected mice from developing TID before any damage to the pancreas occurred by prohibiting the infiltration of pathogenic $CD4^+$ T cells, $CD8^+$ T cells and macrophages into the islets, or by the infiltration of immune regulatory cells that inhibit islet destruction and by increasing the secretion of IL-4, IL-5, and IL-10 (16).

Moreover, the infections diminished the symptoms and the course of rheumatoid arthritis, as they stimulated IL-4 and IL-10 and inhibit INF-γ to reduce the inflammation in the disease (17).

Helminth therapy in humans

Two parasitic worms were used in the treatment of humans; Trichuris suis (the pig whipworm) and Necator americanus (a human hookworm). T. suis was applied by mouth and infected the gut and could not colonize for an extended duration, while N. americanus was applied to the skin and migrated to the small intestine, and became asymptomatic with no replication abilities for a long duration (18).

Researches began in the treatment of IBD patients with T. suis fifteen years ago. They were treated with the eggs of this worm and treatment appeared effective and the patients tolerated this treatment. The treatment effect was temporary, so it was necessary to repeat the treatment to

improve the symptoms. The promising new therapy was also given for ulcerative colitis and Crohn's disease (19).

Other helminth therapy researches in humans used the Necator americanus. In the clinical study, 9 Crohn's patients were infected with the larvae and 7 patients improved while 2 patients got worse (20).

Helminths products as new drugs

The treatment by excretory-secretory (ES) substances produced by parasitic worms was safer than infection with living worms and was accepted by the patients. The study showed that ES products of Taenia crassiceps decreased the symptoms of multiple sclerosis in mice and the treatment results were better than those results with dexamethasone (21).

However, infection with living worms or their ES products nonspecifically inhibited the host immune system, and they exposed the host to hazards of infection with them as the risk of exposure to vaccines (22).

Therefore, the use of single molecules is the best in modulating the immune response. There are a few studies to extract proteins that yield interesting results. Fasciola hepatica Helminth Defense molecules1(FhHDM-1) protein from *Fasciola* hepatica was used to treat T1D and multiple sclerosis in mice. It had a significant effect in reducing the symptoms of these diseases in mice and decreased the production of proinflammatory cytokines TNF and IL-6 (23).

Omega-1 protein extracted from the antigen of Schistosoma eggs rescued the mice with T1D. This protein protected the mice from the development of TID and stimulated Foxp3 expression and IL-4 in mice (24).

ES-62 is the best parasitic worm' product. This protein is extracted from Acanthocheilonema vitae. It stimulates Th2 cells and inhibits Th1 and Th17 cells. It also stimulates B cells and macrophages to produce IL10 (25).

This substance appeared to improve exacerbations in mice infected with asthma (26). It reduced the severity of symptoms of arthritis in mice. Also, it had a significant decline in the secretion of proinflammatory cytokines by T cells like its effect in mice (27).

CONCLUSION

Helminths accompanied humans for a long time and kept in equilibrium with their hosts. The high incidence of autoimmune and atopic diseases has motivated studies towards the therapeutic use of helminths. Studies on helminths therapy have passed through several steps starting with epidemiological researches, studies on animals, studies on humans, to manufacture of helminths products. Although promising results of helminths treatment have been accomplished however numerous inquiries remain to be verified such as the type of their species used, method of their application, their dose, duration, and their use on a wide clinical scale. So, we recommend that more studies are needed in our way to produce effective and safe therapies for those suffering patients.

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