

ORIGINAL ARTICLE



Parasites: Disease or cure?

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Endoparasitic infections are usually regarded as detrimental to the host causing various diseases in humans and animals especially in tropical and sub-tropical countries. In recent years, the incidence of autoimmune and other inflammatory diseases increase in developed and industrial regions. The entry of any infectious disease is challenged by the body immune system through various branch of immunity among which T-helper branches of immunity (Th1 and Th2) play at the fore-front. However, the uncurbed imbalance of Th immune response where a surge in Th1 (IFN γ and TNF α) over Th2 response is implicated to cause various autoimmune and inflammatory disorders. In general, parasitic helminth infection is fought by the body as up-regulation of Th2 branch of immunity by secreting inflammatory cytokines (Interleukins like: IL-4, IL-5, IL-9 & IL-13) thereby executing antibody-dependent cellular cytotoxicity (ADCC). In recent years, exciting evidences revealed that the uncurbed Th1 surge is brought to balance by administration of parasite or parasite extracts thereby alleviating the clinical manifestation of autoimmune and inflammatory disorders. This paper describes works that have been carried out to control various autoimmune and inflammatory disorders using parasite or parasite extracts.

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Introduction

Parasitic helminths and their hosts have co-evolved therefore; have shared a long line of history. Parasitic helminths are eukaryotic, lower invertebrates which are unable to complete their life cycles outside the human or animal host, i.e., in the environment. Traditionally, parasitism refers to a "hateful" relationship where the parasite benefits at the expense of the health of host and nutrition for its survival. On the contrary, it is not always the intent of the parasite to succumb the host; rather parasite do

needs its host for survival such as for a source of food, a living environment, means of transportation and for completion of their life cycle. In addition, it is the vertebrate host which is required for development of parasite's reproductive organs and therefore, their multiplication and propagation. Over the past many years during their evolution alongside the host, helminths play role in an immune modulation in which they disguise the host immune system and more importantly suppress the host

immune response.¹ Parasites have become remarkably efficient modulators in order to promote their own survival.² Their ability to alter and/or suppress immune responses could be benefited by helping control excessive inflammatory responses. The animal models and pre-clinical trials have all suggested a beneficial effect of parasite infections on inflammatory bowel conditions, multiple sclerosis, asthma and atopy.³ Thus, parasite/helminth therapy has been suggested as a possible treatment method or strategy for autoimmune and other inflammatory disorders.

In recent years, there has been a rapid increase in the incidence of some immune-mediated diseases such as inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis, asthma, multiple sclerosis and autoimmune (type I) diabetes and type II diabetes in developed countries.⁴⁻⁷ There could be multifactorial causes for the increase incidence of the listed allergic related diseases in urban communities especially in developed countries as stated in 'hygiene hypothesis' that the body is exposed more frequently to microbes, allergens and parasites in developing countries and rural communities.⁸ Therefore, the immune systems of people from rural communities are smarter in a way not to develop excessive inflammatory conditions that could harm their own body system. Due to the unwanted excessive inflammatory response of the body there is more chance of development of autoimmune diseases.⁹ Lack of exposure to sufficient benign antigens, particularly during childhood, is sometimes suggested as a cause of the increase in autoimmune diseases and diseases for which chronic inflammation is a major component in the industrialized world.

There is broad agreement that majority of autoimmune diseases are caused by inappropriate immunological responses to innocuous antigens, driven by a branch of the immune system known as the TH1 type immune response. Extracellular antigens like parasite/helminth primarily trigger the TH2 response, as observed with allergies, while intracellular antigens trigger a TH1 response. The T-helper cells can be divided into subtypes based on the characteristic cytokines (chemical messenger) they secrete. Th2 immune response results in the release of cytokines associated with inflammation reduction (IL-4, IL-5, IL-9 and IL-13). These cytokines are thought to alleviate the symptoms of many autoimmune disorders. On the contrary, Th1 immune responses are characterized by release of cytokines like IFN γ and TNF α , both of which are thought to increase inflammation and worsen the progression of autoimmune disease and their symptoms. Considering the reciprocity in immune regulation where, for example, Th2 cytokines lower or suppress the activity of Th1 cytokines, a hypothesis arises that individuals infected with helminth parasites could be less susceptible to the

inflammatory diseases induced by Th1 cytokine responses. Many a times, the immune response of the body is shifted over to Th2 response during parasitic infection from Th1 response for parasite survival in the host hostile environment.

Mechanism of action of helminth therapy

Most of the autoimmune diseases are believed to arise from the imbalance of the two arms of immune responses, such as, Th1 and Th2. In general, when there is a helminth infection, the host body responds by a mechanism employing the Th1 arm of the immune response. During Th1 response, there are secretions of certain inflammatory cytokines like IFN γ and TNF α that mount a lethal action of the parasite, but excessive production of these cytokines are not only harmful to the parasites but for the host body as well. Due to the excessive increase in the level of Th1 cytokines, there could be development of various autoimmune diseases. During parasitic helminth infection, body responses by Th2 branch of immunity (IL-4, IL-5, IL-9 and IL-13) employing antibody dependent cellular cytotoxicity (ADCC). Thus, the immune response of the body up-regulates the Th2 type of immune response and at the same time down regulating the Th1 immune response of the body which is known to caused autoimmune disorders (Fig. 1). Given the down regulation of Th1 immune responses with helminthic therapy, there is alleviation of allergic or autoimmune symptoms.

Ideal characteristics for a therapeutic helminth

- i) Has little or no pathogenic potential
- ii) Does not multiply in the host
- iii) Cannot directly spread to close contacts
- iv) Produce self-limited colonization in humans
- v) Produce asymptomatic colonization in humans
- vi) Do not alter the behavior in patients with depressed immunity
- vii) It is not affected by most commonly used medications
- viii) Can be eradicated with an anti-helminthic drug
- ix) Can be isolated free of other potential pathogens
- x) Can be isolated or produced in large numbers
- xi) Can be made stable for transport and storage
- xii) It is easy to administer

What parasites are mainly used?

Helminth therapy consists of the inoculation of the patient with specific parasite or parasite extracts. A number of such organisms are currently being investigated for their use as treatment including:

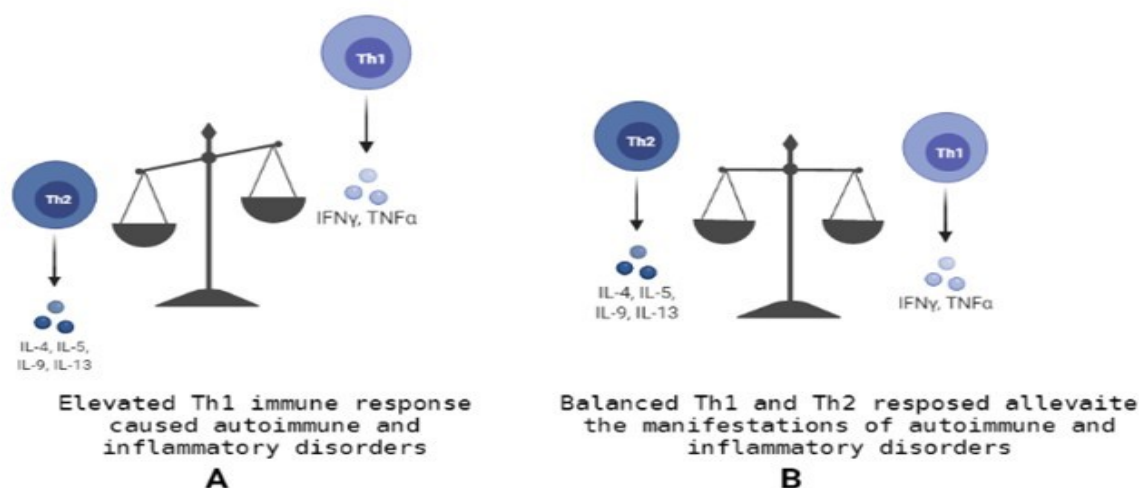


Figure 1. (A) Imbalance of Th1 and Th2 response where the surge of TH1 immune response (IFN γ and TNF α) causes autoimmune and inflammatory disorders (B) Parasitic helminth infection cause balance Th immune response alleviating clinical manifestation of autoimmune and inflammatory disorders

Trichuris suis ova (pig whipworm eggs); *Necator americanus* (hookworms of man); *Schistosoma mansoni* eggs and larvae; *Schistosoma japonicum* eggs; *Trichinella papuae* larvae; *Heligmosomoides polygyrus* larvae; *Trichuris trichiura* ova, (human whipworm); *Hymenolepis diminuta* (rat tapeworm); *Ascaris lumbricoides* (human giant roundworm); *Strongyloides stercoralis* (human roundworm); *Enterobius vermicularis* (threadworm or seatworm); and *Hymenolepis nana* (dwarf tapeworm).

Helminths as therapy for immune mediated disease

Inflammatory bowel disease (IBD) results from chronic inflammation of the small and/ or large intestine which is treated with immune-suppressive medications. IBD was uncommon prior to the 1940s but now it afflicts more than three million people in the United States and Europe.¹⁰ Most of the trials to date have used *T. suis* ova, the pig whipworm which can briefly colonize people for about a week and do not multiply. Due to the fact that being a pig whipworm and its short stay inside the human body, they do not pose a public health threat. Studies in patients with ulcerative colitis (UC) or Crohn's disease, the patients were given viable, embryonated eggs of *T. suis* resulting in significant symptomatic relief although the beneficial effect was temporary; repeated doses of TSO sustained this clinical improvement suggesting a promising new therapy for inflammatory bowel diseases.¹¹ A second approach to helminth therapy has been the slightly more controversial use of the human hookworm *Necator* sp., a pathogen responsible for much of the morbidity associated with intestinal helminth infections around the globe. In a small trial where

Crohn's disease patients were given 25–50 larvae, seven out of nine patients experience improved disease score.¹² Patients with multiple sclerosis, where there is degeneration of sheath around the nerves, which are infected with helminth showed a better clinical picture as compared to those who do not have helminth infection. In follow-up cases, when these patients were given anthelmintic/ antiparasitic drugs, the clinical condition deteriorated.

Helminths secrete a rich mixture of proteins, carbohydrates and lipids, collectively named as excretory-secretory (ES) products and many of these have been found to exhibit a variety of immunomodulatory activities. The best known product to date is the ES-62 molecule from the filarial nematode *Acanthocheilonema vitae* which is a glycoprotein with potent ability to shift towards promoting Th2 and inhibiting Th1 response. In animal studies a variety of ES products can protect against allergen-induced airway hypersensitivity in mice.

Numerous proof-of-concept studies have shown that the severity of concomitant disease in mice (e.g., colitis, airway hyper-reactivity and experimental allergic encephalitis) can be reduced by prophylactic or therapeutic infection with parasitic helminth. The mechanism of the reduction in disease has been, in a species and model-specific manner, ascribed to the inhibition of Th1 cytokine production.

Potential side effect

Helminths are extremely successful parasites capable of establishing long-lasting infections within a host. During this time, helminth competes with the host for nutrients and at the same time possesses

the potential to cause harm, for example *N. americanus* infection can cause harmful association with the host as the parasite is naturally occurring which has the potential to cause anaemia. Therefore, utmost consideration must be given in using this parasite. While the majority of infected individuals are asymptomatic, the administration of live parasite for helminthic therapy does carry a number of potential side effects such as anaemia, abdominal discomfort, diarrhea, weight loss, general malaise etc.

Conclusions

Taken together, all the evidences suggest an exciting potential for new control measures against immune mediated diseases. Without a doubt there is overwhelming evidence from animal studies that helminth infection exerts strong immunomodulatory activity and is able to inhibit, alter and modify other ongoing immune responses. However, many of these are living parasitic organisms; utmost care should be taken not to elicit adverse effects out of the helminth infection. The medication of the patient should address alleviation of the immune disorders. In addition, the use of helminth-derived molecules may offer a less controversial and promising new avenue to anti-inflammatory drug development.

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