

Parasitic Helminths: A Useful Resource for Inflammatory and Autoimmune Disease Therapy

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Helminths are multicellular eukaryotic invertebrates with complex life cycles and development. Nematodes (roundworms) and platyhelminths (flatworms) are 2 groups of helminths that colonize the interior of humans. The nematodes include most of intestinal worms and the filarial worms, whereas the platyhelminths include the flukes, such as the schistosomes, and the tapeworms [1]. Unlike other pathogens such as viruses, bacteria, or protozoa, helminths do not proliferate within their final hosts and the worm burdens in individual hosts depend on the number of initial parasites.

Over the last 40 years, there has been a rapid increase in the incidence of some immune-mediated diseases such as inflammatory bowel diseases (IBD) (e.g., Crohn's disease and ulcerative colitis), asthma, multiple sclerosis and autoimmune (type 1) diabetes in industrialized, highly developed countries [2]. However, these diseases are not as common in less developed countries. The rapid increase in these diseases cannot be explained solely by genetic and/or environmental factors. Interestingly, epidemiology studies indicate that the geographical distribution of these diseases is negatively correlated with helminth-endemic areas [3,4].

Traditionally, parasitism refers to a "hateful" relationship: the parasite benefits at the expense of the health and nutrition of the host for its survival. Indeed, the host could benefit from parasites when colonizing helminths [5]. To some extent, immunological studies theoretically support this notion. Infection with helminth parasites results in a series of immune events that are dominated by T helper (Th) cell type 2 events [6,7]. Considering the reciprocity in immune regulation where, for example, Th2 cell-derived mediators inhibit the activity of Th1 cells, the hypothesis arises that individuals infected with helminth parasites could be less susceptible to the inflammatory diseases induced by the Th1 response [8]. Therefore, infection with helminths could be used to treat diseases driven by Th1 cells.

Studies on animal models [9-18] indicate that the severity of some immune mediated diseases such as Crohn's disease, colitis, type 1 diabetes, asthma, and arthritis (Table 1) can be alleviated or even blocked upon infection with helminth parasites. These results are encouraging with respect to moving clinical trials toward human patients.

Weinstock's group carried out pioneering studies to investigate the effect of infection with helminth parasites on some inflammatory bowel diseases [19,20]. In early clinical trials, they showed that infection with helminths such as *Trichuris suis* can help prevent or even ameliorate Crohn's disease without significant adverse effects [20]. Then, they commenced a randomized double blind placebo-controlled trial of *T. suis* in ulcerative colitis patients. This study indicated a significant improvement over that obtained with a placebo in patients receiving the agent [21,22]. In these studies, they used *T. suis*, a kind of pig whipworm, to consider the safety requirements for future medicine development. However, there are concerns that the deleterious effects due to parasite infection on host health may increase the risk

of emergence of other infectious disease and of potential host-host transmission.

Consequently, the identification of bioactive molecules in helminth parasites that modulate the immune response of the host may provide an alternative strategy for utilizing parasitic helminths in the treatment of immune mediated diseases. Currently, several molecules such as *Ascarissuum* PAS1 [23], *Dirofilaria immitis*-derived antigen (DiAg) [24] and filarial nematode ES-62 glycoprotein [25] have been shown to be involved in immunomodulation in animal models. An inhibitor

Helminths	Effect of infection or injection	Ref.
Nematode		
<i>Ancylostoma caninum</i>	Inhibition of TNBS-induced colitis in mice by injecting <i>A. caninum</i> antigens	[9]
<i>Ascaris suum</i>	Chronic infection reduces eye disease in mice	[10]
<i>Trichinella spiralis</i>	Prevention of colitis in C57BL/6 mice	[11]
<i>Strongyloides stercoralis</i>	Suppression of pulmonary allergy in BALB/c mice	[12]
<i>Heligmosomoides polygyrus</i>	Inhibition of autoimmune type 1 diabetes in NOD mice	[13]
	Protection from colitis in C57BL/6	[27, 28]
Platyhelminth		
<i>Schistosoma mansoni</i>	Inhibition of TNBS-induced colitis in mice by injecting <i>S. mansoni</i> antigens	[9]
	Inhibition of autoimmune type 1 diabetes in NOD mice	[13]
	Inhibition of type 1 diabetes in NOD mice by injecting <i>S. mansoni</i> antigens	[14]
	Prevention of DSS-induced colitis in BALB/c mice	[15]
	Suppression of collagen-induced arthritis in mice	[16]
<i>Schistosoma japonicum</i>	Inhibition of asthma development in BALB/c mice by injecting the egg antigens	[17]
	Protective effects for arthritis in DBA/1 mice	[18]

DSS, dextran sodium sulphate; NOD, Non-obese diabetic; DNBS, dinitrobenzene sulfonic acid; TNBS, trinitrobenzene sulfonic acid

Table 1: Examples of helminth parasites in animal models for inflammatory and autoimmune disease therapy.

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of the apoptosis protein from *Schistosoma japonicum* (SjIAP) was also cloned and molecularly characterized by our group, and the results indicated that SjIAP can inhibit caspase activity and caspase 3 expression in human 293T cells. Although the involvement of SjIAP in immunomodulation in the host remains to be determined, our preliminary study suggests that SjIAP could be a potential agent for treating liver injury, organ transplantation, and other diseases by inhibiting cellular apoptosis [26-28].

Parasitic helminths are a useful resource for inflammatory and autoimmune disease therapy. A deep understanding of the mechanisms of parasite infection and host immune response and of the molecular bases of these mechanisms is critical for developing therapeutic strategies for inflammatory and autoimmune diseases. The utilization of new “-omics” techniques such as secretomics, immunomics and metabolomics need to be accelerated to tap resources that can then be more beneficial for human beings.

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