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Where are we on worms?

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Abstract

Purpose of Review—There is something about living in an industrialized country that dramatically increases the risk of acquiring inflammatory bowel disease. Loss of routine exposure to parasitic worms (helminths), due to modern highly hygienic life styles, likely contributes to this risk. This article reviews current understanding on how helminths influence intestinal inflammation and mucosal immune responses.

Recent findings—IBD emerges in populations as regions develop socioeconomically and loose exposure to previously ubiquitous helminthic infections. Helminthic infections provided strong selective pressure for the dissemination of gene variants, many of which predispose to development of IBD. In animal models of IBD, helminth colonization suppresses intestinal inflammation through multiple mechanisms including induction of innate and adaptive regulatory circuits. Trials using helminths like hookworm (*Necator americanus*) or porcine whipworm (*Trichuris suis*) show that they are safe and may be effective therapies for the control of the aberrant intestinal inflammation seen in Crohn's disease and ulcerative colitis.

Summary—Evidence is accumulating that highly hygienic living conditions create risk for developing immune-mediated disease such as IBD. To live in their host, helminths have developed the ability to activate cells of innate and adaptive immunity that suppress inflammation. Therapeutic trials using helminths are in progress.

Keywords

Helminths; intestinal inflammation; IBD; mucosa; colitis

Introduction

Immune-mediated diseases now afflict more than 10% of the population in industrialized Western countries. More than 2 million people in North America and Europe have either Crohn's disease or ulcerative colitis. Inflammatory bowel disease is emerging in other regions of the world as they become more socioeconomically advanced. Loss of routine exposure to parasitic worms (helminths) in highly industrialized countries may explain the emergence of ulcerative colitis, Crohn's disease, and other immune-mediated diseases that now plague modern societies. Helminths are complex multicellular organisms adapted to

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Dr. Elliott and Dr. Weinstock serve on the scientific advisory board of Coronado Biosciences which is developing *Trichuris suis* for possible therapeutic application. Through the University of Iowa, they also have been awarded patents for the use of helminths to treat immune-mediated disease.

living in immune competent hosts. Helminths have developed the ability to induce immune host regulatory cells that suppress inflammation. This review will focus on the effects of helminths on mucosal immunity and intestinal inflammation. The effects of helminths on other emergent immune-mediated diseases are reviewed separately (1). The biological interaction between *Necator americanus* (human hookworm) or *Trichuris suis* (porcine whipworm) and their host currently is being studied for potential medical application.

Epidemiology and the role of environment in IBD

Crohn's disease and ulcerative colitis, collective known as inflammatory bowel disease (IBD), were exceedingly rare conditions prior to the 1900s. During the latter half of the Twentieth Century, both conditions emerged as significant diseases that together now afflict about 1 in 250 people in some locales (2–5). This pattern of increasing disease prevalence is repeating in other countries as they develop socio-economically. IBD is rapidly emerging in Brazil (6), South Korea (7), India (8), and China (9). Previously low prevalence rates in Hungary are now equivalent to those of Western Europe (10). Improvements in diagnostics or access to medical care cannot explain the dramatic increase in disease expression (4). This emergence of disease suggests that an environmental change which occurs with industrialization dramatically increases the risk for acquiring ulcerative colitis or Crohn's disease.

Although many changes occur with industrialization, few have proven direct effect on immune system function. Improvements that prevent spread of infectious disease (heightened hygiene) impact immune reactivity. The "*IBD hygiene hypothesis"* postulates that reduced exposure to infectious agents limits immune system development in a way that causes atrophy of important regulatory circuits. Impaired immune system regulation permits development of immune-mediated diseases like IBD. People living in highly hygienic countries continue to be exposed to viruses and most classes of bacteria. However, one entire class of organism, helminths (also called parasitic worms), have been largely eradicated (11). Previously, exposure to helminths was ubiquitous (12). Helminth infections are exceedingly strong inducers of immune regulatory circuits (1). Thus, lack of these previously ubiquitous infections in children and adults, are likely an important cause for the increased prevalence of IBD.

Genetics and the microbiome

Studies to identify genes that contribute to the risk of IBD support the idea that loss of exposure to helminths may permit immune-mediated disease. Genetic studies have now identified variations in about 160 genes that influence the risk of acquiring IBD (Judy Cho personal communication, (13)) Excepting recognized mutations that result is systemic immune disease (e. g. IPEX syndrome), genome wide association studies have not uncovered a specific gene variant that is sufficient or required for either Crohn's disease or ulcerative colitis. These studies show is that gene variations altering risk occur in pathways involved with the epithelial cell barrier function and stress responses, innate immune cell function and bacterial clearance, immune regulation and the Th17/IL23/Stat3 pathway, and other systems influencing immune cell activity. Furthermore, many of the genes or response pathways that influence risk for IBD have variants that influence risk for developing other organ-specific autoimmune or inflammatory conditions like celiac disease, multiple sclerosis, type 1 diabetes, and rheumatoid arthritis (13). Remarkably, our microbiome including helminths drove development of these genetic variations in many of these immune response pathways (14). Variations in IL18RAP, IL23R, CTLA4, IL10, TLR4, GATA3 and about 800 other genes were selectively favored under the pressure of helminth infection

(15). Gene variants selected to operate under the influence of helminth infection could cause disease when operating without that influence.

Effects of helminths on animal models of IBD

Researchers employ animal models of IBD to determine how different immunologic pathways influence mucosal inflammation (16). These models help identify potential mechanisms through which helminths can suppress colitis. The major models used to study helminth effects include: dinitrobenzene or trinitrobenzene sulfonic acid (D/TNBS) colitis, a model of acute immune-mediated injury that has features of Crohn's disease; interleukin-10 deficient colitis, a murine model of chronic colitis that develops spontaneously in the absence of an important immune regulatory cytokine; and T cell transfer colitis, a murine model of spontaneous intestinal inflammation that occurs in the absence of regulatory T cells. Each of these models can be used to explore aspects of helminth-associated enhanced immune regulation.

To add to the complexity, there are many different helminths. Helminths are divided into three main groups, nematodes (round worms), trematodes (flukes), and cestodes (tape worms). These groups are genetically distant from each other. The survival strategy of parasitism, with the ability to influence immunity, arose independently among members of each group (17). Thus, various helminthic species may utilize different immune modulatory strategies to limited disease in any particular animal model of IBD. Animals as sophisticated as helminths must use various approaches to evade host immunity. It is probable that any one helminth can display a range of responses to limit injury when under host immune attack. This acquired flexibility of response infers that anyone particular helminth possesses a range of distinct approaches to limited disease in different IBD models.

Exposure to the roundworm *Heligmosomoides polygyrus bakeri* (18), fluke *Schistosoma mansoni* (19;20), or tapeworm *Hymenolepis diminuta* (21;22) can protect animals from TNBS-type colitis. Protection is associated with increased production of IL4, IL10 and TGFβ (23) but inhibited IFNγ, IL17 and IL12/23 release by gut-associated lymphocytes, macrophages and dendritic cells. Furthermore, infection with *H. polygyrus bakeri* induces regulatory T cells (24). Blockade of IL10 or IL4 interferes with helminth-associated protection from colitis. Extracts from *S. mansoni* (19) or H. *diminuta* (25) also can protect mice from TNBS-type colitis, in part by inducing alternatively-activated macrophages (26).

Helminths also protect mice lacking IL10 from chronic colitis. Colonization with *H. polygyrus* inhibits development of colitis and will reverse established colitis in IL10-deficient mice.(11;27) Like in wild type mice, helminth colonization of $IL10^{-/-}$ mice inhibits gut-associated immune cell production of IFNγ, IL17 and IL12/23p40 and augments T cell Foxp3 expression (a marker of regulatory T cells) (28). This shows that helminth exposure can modulate inflammation even in the absence of IL10. Indeed, helminths exposure can have wide ranging effects. Colonization with *H. polygyrus bakeri* alters the gut microbiome (29) producing a prominent increase in a family of bacteria called *Lactobacillaceae.* Species within this family can decrease intestinal inflammation.

T cell transfer colitis also is suppressed by helminth exposure. Colonizing immune-deficient mice with *H. polygyrus bakeri* prior to T cell transfer, alters intestinal dendritic cells (30) so that they block colitis and mucosal antigen-induced, IFNγ and IL17 responses upon transfer into colitis-susceptible animals. Thus, in the absence of adaptive T or B cells, helminth exposure can induce innate dendritic cells to become highly regulatory. Furthermore*, H. polygyrus bakeri* colonization after T cell transfer colitis is established will reverse the ongoing inflammation. Reversal of established colitis is associated with enhanced IL4 and IL10 production and suppression of IL17, IFNγ, and IL12/23p40 release by lamina propria

and mesenteric lymph node cells. If transfer colitis is induced with Stat6-deficent T cells that cannot respond to IL4 instead of wild type T cells, colonization with *H. polygyrus bakeri* cannot reverse established colitis (Elliott, unpublished results). Thus, T cell Stat6-signaling is important in this process.

In addition to defining critical immune pathways for helminth-associated protection from colitis, animal models are beginning to identify some of the helminth products that may mediate that protection. Helminths exposure can protect mice from dextran sodium sulfate (DSS) colitis. Extracts from human hookworm (*Ancylostoma ceylanicum*) also suppress DSS colitis (31). Cystatin, a secreted cysteine protease inhibitor made by several species of filarial nematodes, protects mice from DSS colitis (32). Cloned macrophage migration inhibitor-like factor from *Anisakis simplex* can prevent DSS colitis (33). Many of these factors appear to suppress pro-inflammatory responses from macrophages and/or induce T regulatory cell generation.

Suppression of immune-mediated inflammation by helminth exposure is being investigated in other animal models such as experimental autoimmune encephalitis (a models of multiple sclerosis), non-obese diabetes (a model of Type 1 diabetes), collagen-induced arthritis (a model of rheumatoid arthritis), and reactive airway disease (a model of asthma) (1). Like IBD, all these diseases have emerged with industrialization and often share associations in genomic risk (13). Helminths and helminth-derived products appear to suppress these other diseases by mechanisms similar to those in colitis (1). However, specific molecules can have discordant results. A phosphocholine containing product isolated from filarial nematodes called ES-62 suppresses collagen-induced arthritis and reactive airway disease and IL17-type responses (34), but does not induce T regulatory cells and does not suppress autoimmune diabetes in NOD mice (35). Thus, helminthic products that may aid in the control of one disease may prove much less important in the regulation of a different illness.

Clinical studies, case reports, and trials of helminths in patients with intestinal inflammation

Investigators have surveyed populations to determine if groups that are readily exposed to helminths seem protected from IBD. A case control study in Vellore, India reported that healthy controls had greater circulating T cell reactivity to hookworm antigen than did patients with Crohn's disease (36). This suggests that significant hookworm infection, or concomitant exposure to other helminths, may suppress development of Crohn's disease. In contrast, a recent population-based cohort study from Demark found that IBD developed at a similar rate in children previously treated with mebendazole (for presumed childhood pinworm infection) as compared to children never treated with mebendazole (37). This may suggest that childhood exposure to *Enterobius vermicularis* does not protect people from acquiring IBD. This study had series methological limitations, which included among others, that many children treated with mebendazole for anal pruritus frequently do not have pinworm. Also, for those that did, rapid treatment may have limited the duration of exposure to a sub-therapeutic interval. Furthermore, the study design placed children with pinworm, but never treated in the "non-exposed" control group enhancing the risk for a "Type II error". Other epidemiologic studies are in progress to help determine if natural helminth exposure protects individuals from acquiring IBD.

There are two case reports of the effect of natural helminth infection on the course of ulcerative colitis. Bűning reported the case of a 12 year old girl with *E. vermicularis* and histologic evidence for mild ulcerative colitis who developed clinically severe disease after the pinworm eradication (38). The patient's The lamina propria of this patient contained large numbers of Foxp3+ T cell (a marker of regulatory T cells) during helminth infection

than was evident when her ulcerative colitis flared. Broadhurst reported the case of a 35 year old man with severe refractory ulcerative colitis who purposefully acquired *Trichuris trichiura* (human whipworm) and achieved clinical remission (39). His symptoms returned after about three years as his worm carriage declined. He re-acquired *T. trichiura* and again achieved clinical remission. Characterization of his mucosal immune profile showed that helminth infection enhanced mucosal expression of IL4 and IL22. IL22 likely promotes mucosal repair (40). Thus, helminth colonization may suppress ulcerative colitis.

Therapeutic application of helminths is being tested clinically using either human hookworm (*Necator americanus*) or porcine whipworm (*Trichuris suis*). A small open-label trial evaluated *N. americanus* in 9 patients with Crohn's disease.(41) Two patients had moderately active disease and showed improvement in symptom scores after they received 50 larvae. The other 7 patients had inactive or minimal disease, which did not significantly change with helminth exposure. A problem with *N. americanus* is that acute exposure to this organism can cause intestinal symptoms including significant diarrhea, vomiting and abdominal pain in normal volunteers when given in higher doses (50 or greater larvae) (42). However, low dose (10 hookworm larvae) appears well tolerated and resulted in patent colonization (42). Hookworm also has been evaluated in celiac disease. A randomized double blind placebo control trial tested the effect of *N. americanus* colonization (total of 15 larvae) on response to gluten challenge in twenty patients with celiac disease (43). The ten patients that received hookworm had skin rash and mild abdominal pain that resolved without intervention. Gluten challenge (16 g/day for 5 days) produced similar symptoms and duodenal histologic damage in both the control and hookworm colonized groups (43). Although the clinical response to significant gluten challenge was not affected, colonization did suppress duodenal mucosal IFNγ and IL17 production and resulted in a slight, but significant increase in duodenal Foxp3+ T cells (44). These studies showed that low level hookworm infection was safe and could alter mucosal immune responses. It is possible that prolonged colonization and perhaps a higher level of colonization or a more subtle gluten challenge (mimicking inadvertent gluten exposure) could show clinical efficacy.

The majority of helminthic clinical trials used the porcine whipworm *Trichuris suis,* which is closely related to human whipworm (*T. trichiura*). *T. suis* can transiently colonize people (45), but has never been documented to cause human disease. Whipworms are good candidates for clinical use. Whipworms do not migrate beyond the intestines, multiply within their host, or inadvertently transmit from one human host to another. People acquire whipworm infections by ingesting microscopic parasite ova. Colonized primates are the only source of human whipworm (*T. trichiura*) ova making them difficult to obtain for large studies. Porcine whipworm (*T. suis*) ova, obtained from pigs raised in pathogen-free environments, can be mass produced in accordance to good manufacturing practice making them suitable for therapeutic intervention.

The effect of *T. suis* colonization was first studied in a small open-label trial of 4 patients with Crohn's disease and 3 with ulcerative colitis who each ingested one dose of 2500 ova. All had improvement in their symptoms (46). A second study tested repeated dosing (2500 ova every 3 weeks) of *T. suis* in 29 patients with active Crohn's disease (47). At week 24, 79% had a significant reduction in symptoms, and 72% achieved remission as determined by the Crohn's Disease Activity Index. Our third study was a double blind placebo-controlled trial of *T. suis* in 54 patients with active ulcerative colitis (48). The patients received either 2500 *T. suis* ova or placebo every 2 weeks for 12 weeks. Many of the patients given *T. suis* improved compared to those given placebo (43.3% vs. 16.7%, $p<0.04$) as determined by the Ulcerative Colitis Disease Activity Index. The trial also included a blinded crossover limb where patients originally on placebo where switched to *T. suis* and those on *T. suis* were switched to placebo. In the crossover limb, 56.3% of the patients given *T. suis* improved

compared to 13.3% of patients given placebo (p=0.02) (49). These studies showed that exposure to *T. suis* was safe and likely efficacious to treat IBD. More recently, the safety and tolerability of different doses of *T. suis* was tested in a small multicenter placebo-controlled trial of 36 patients with Crohn's disease (NCT01434693). Patients ingested a single dose of 500 ova, 2500 ova, 7500 ova or a placebo and were followed by daily questionnaires. The patient experience no symptoms associated with helminth exposure, and there were no treatment emergent adverse events identified (unpublished results).

Currently, there is a multicenter double-blinded placebo-controlled European trial to test the efficacy and safety of three different doses of *T suis* for active Crohn's disease (NCT01279577). A similar trial (NCT01576471) will soon start in the United States. In addition, an investigator initiated evaluation of *T. suis* exposure on mucosal immune responses in patients with ulcerative colitis (NCT01433471) is currently recruiting subjects.

Conclusion

Evidence continues to mount that loss of exposure to helminths may explain at least some of the increased risk for IBD present in highly hygienic industrialized countries. Helminths are complex multicellular organisms capable of influencing immune responses in their host. Animals with helminths show decreased pro-inflammatory Th1 and Th17 responses, increased anti-inflammatory Treg and innate regulatory cell responses, and protection from intestinal inflammation. Helminth exposure may provide a novel therapeutic approach to treat IBD.

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Key Points

- Something about the environment in countries with high socioeconomic development confers risk for developing IBD and other immune-mediated diseases.
- Residents in highly developed countries are not exposed to helminths and such exposure likely protects against developing IBD.
- Helminth exposures influenced selection of gene variants in many of the same pathways that influence risk for IBD.
- Helminth exposures augment innate and adaptive immune circuits that regulate inappropriate inflammation.
- Therapeutic exposure to select viable helminths appears to be safe.
- Clinical studies are now in process to help determine if helminth exposure is efficacious in the treatment of Crohn's disease.