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TOPIC HIGHLIGHT

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Helminth infections and intestinal inflammation

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Abstract

Evidence from epidemiological studies indicates an inverse correlation between the incidence of certain immune-mediated diseases, including inflammatory bowel diseases (IBD), and exposure to helminths. Helminth parasites are the classic inducers of Th2 responses. The Th2-polarized T cell response driven by helminth infection has been linked to the attenuation of some damaging Th1 driven inflammatory responses, preventing some Th1-mediated autoimmune diseases in the host, including experimentally induced colitis. Helminth parasites (the porcine whipworm, *Trichuris suis*) have been tested for treating IBD patients, resulting in clinical amelioration of the disease. As a result, there is a great deal of interest in the research community in exploring the therapeutic use of helminth parasites for the control of immune-mediated diseases, including IBD. However, recent studies have provided evidence indicating the exacerbating effects of helminths on bacterial as well as non-infectious colitis in animal models. Therefore, a better understanding of mechanisms by which helminths modulate host immune responses in the gut may reveal novel, more effective and safer approaches to helminth-based therapy of IBD.

Key words: Helminths; Innate and adaptive immunity; Intestinal inflammation

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HELMINTH INFECTIONS

Helminths are divided into two major phyla, and all members of each phylum have distinct structural features that separate them from the others. The nematodes (also known as roundworms) include the major intestinal worms and the filarial worms that cause lymphatic filariasis (LF), whereas the platyhelminths include the trematodes (flukes), such as the schistosomes, and the cestodes (tapeworms). Humans and helminths have co-existed throughout our evolution. The history of helminthiases can be tracked back to the earliest record of human beings[1]. Although effective preventive and therapeutic measures have been developed for most parasitic worms, helminth infections are still very common in the developing world today. It has been estimated that one billion people worldwide are infected with one or more helminths. Most of the victims live in regions of sub-Saharan Africa, Asia, and Latin America[2-3]. The most common forms of helminthiasis are infections caused by intestinal helminths, ascariasis, trichuriasis and hookworm, followed by schistosomiasis and LF[4]. Clinical features of helminthiases vary a lot depending on the helminth species, intensity of infection, and host age. *Taenia solium* can cause neurocysticercosis with mass lesions in brain. Ingested eggs of *Echinococcus granulosis* will lead to cysts in the liver and cause life-threatening anaphylaxis if antigens are released from the cysts. Chronic infection with *Schistosoma* causes granulomas, fibrosis, and inflammation of the spleen and liver. Hookworm and schistosomiasis can infect pregnant women, cause neonatal prematurity and increased maternal morbidity and mortality[5]. Children at school-age or younger tend to harbor the greatest numbers of intestinal worms and schistosomes compared with any other age group. As a

result, the young patients suffer from growth retardation and diminished physical fitness, as well as memory and cognition impairment[6]. Most helminth infections, if left untreated, result in multi-year, chronic inflammatory disorders that will eventually cause disability. The chronic, disabling and disfiguring consequences of helminth infections, together with their high prevalence, make them a global problem of significant medical, educational, and economic impact.

HELMINTH INFECTION INDUCES TH2 AND T REG DEVELOPMENT

Since parasitic worms constitute a very heterogenous collection of organisms, a multitude of mechanisms may be expected when they stimulate and modulate host immune responses. However, examination of the immunology of helminth infections reveals a number of characteristics that are generally conserved across all species. Our current understanding of the immune response to helminth infections has largely come from the study of well-defined laboratory models of infection in rodents. Protective immunity to helminths depends on T lymphocytes. It is now well established that the CD4+ subset of T cells plays a major role in the generation of the host protective response that expels the worms, and that CD4+ T cells regulate many of the inflammatory and immune parameters that accompany expulsion of the parasites from the gut. Based on cytokine production profiles, CD4+ T cells can be divided into distinct functional sub-populations, Th1, Th2 and Th17. Th1 cells produce cytokines such as IFN-γ, IL-12 and IL-2 that are involved in controlling of intracellular pathogens. These cells also contribute to inflammatory responses. Recently, a new lineage of Th cells, that selectively produce the cytokine IL-17 (Th17) has been identified, and those cells are thought to be key regulators of inflammation[7,8]. It has also been reported that IL-17 is required for the optimal induction of Th1 and Th2 immune response, although the mechanism has not yet been clarified[9]. IL-17 is a proinflammatory cytokine, which is produced predominately by activated T cells. This cytokine can enhance T cell priming and induces the activation of many cell types including fibroblasts, macrophages and epithelial cells, resulting in the production of multiple proinflammatory mediators by these cells, including IL-1, IL-6, TNF-α and chemokines[8,10]. In the majority of cases, the immune responses of the hosts to worm infections are strikingly dominated by Th2-like T-helper cell responses with a significant production of IL-4, IL-5, IL-10, IL-13, IL-25, and IL-31[7,8,11,12]. Th2 cells contribute to B cell activation and antibody production, eosinophil differentiation and recruitment. Therefore, parasitic worm infection is often associated with high levels of IgE, IgG1 and IgG4, and robust eosinophil and mast cell responses. Th2 immune responses to helminth infections can prevent the survival of invading parasites during a homologous secondary infection[9], expel adult parasites from the gut[10], and allow host survival when the immune responses are not able to clear the parasites. These responses are the basic host protective mechanisms against worms and are highly conserved through evolution. However, Th2 immune responses to helminth infections may also cause host pathology and organ damage. For example, Th2 immunity can mediate pathological fibrotic responses in chronic parasitic infections[13]. This can be understood as the detrimental effects of host immunity to helminths. Cross-regulatory suppression of the Th1 responses by a strong Th2 response has been considered to play a role in modulating diseases that are characterized by a Th1 response. Multiple studies[14-16] have revealed that helminth-induced Th2 responses can attenuate damaging Th1-driven inflammatory responses in the host. However, suppression of Th1 response may also lead to the impairment of host protective Th1 immunity against concurrent infections caused by bacterial, viral and parasitic pathogens, exacerbating the diseases they induce.

In addition to stimulating a vigorous Th2 response, helminth infections are also capable of inducing suppressive T cell populations known as regulatory T cells (Tregs)[17], which may help control morbidity and dampen resistance to re-infection through their potent immune regulatory mechanisms. Several types of Treg cells have been described (natural Tregs, Tr1 and Th3). These regulatory cells constitute 5% to 10% of peripheral CD4+ T cells in naive mice and humans and suppress several potentially pathogenic responses *in vivo*, particularly T cell responses directed to self-antigens. These cells express markers such as Foxp3, CD25, CTLA-4 and GITR, and often secrete IL-10 and/or TGF-β[18-20]. Tregs have been shown to play an important role in regulating immune responses and maintaining homeostasis under various disease conditions including autoimmune disease, inflammation, cancer, and microbial infections. Treg regulate immunity through both cytokine-dependent and independent mechanisms[21]. Th3 cells make TGF-β, which inhibits development of both Th1 and Th2 cells. Tr1 cells regulate immunity through IL-10-dependent mechanisms, which inhibit both Th1 and Th2 responses[22-24]. A recent study has provided a link between the well-established immunoregulatory capacity of Th2 cells and Tregs showing that the Il-4Ra binding cytokines, IL-4 and IL-13 induce FOXP3 expressing Treg from CD4+CD25- precursors[25].

Existing data indicate that helminth infections induce the development of Th2 and/or Treg responses. A polarized Th2 type immune response as well as up-regulated regulatory T cell activity induced by helminths may have a significant impact on the host's ability to cope with concurrent or subsequent viral[26,27], bacterial and parasitic infections[28], by suppressing host protective Th1 responses to microbial pathogens. Consistent with the hygiene hypothesis, helminth-induced responses may also underlie the observed reverse associations between helminthiases and asthma, allergy, IBD, and

other autoimmune diseases[29-31]. A better understanding of immune modulation by helminth infection, therefore, can have significant practical implications for the prevention and treatment of immune-mediated as well as microbial disease.

HELMINTHS AFFECT HOST RESPONSES TO OTHER ANTIGENS AND PATHOGENS

The major importance of helminth infections includes not only the direct pathogenic effect of the worms as described above, but also the modulation of the host immune system, which may alter the response to other pathogens and antigens and cause additional immunopathology. The distribution of several pathogenic helminth infections coincides geographically with many devastating microbial diseases, such as HBV, HCV, HIV/AIDS[26,27,32-34] and malaria[35-37]. Coinfection with helminths increases the transmission of and susceptibility to these infections, and also increases the severity of the associated diseases[27,33-38]. Recently we have demonstrated that an intestinal nematode parasite, *Heligomosomoides polygyrus (H. polygyrus)* infection impairs host Th1 defense against enteric bacterial infection and exacerbates *Citrobacter*-mediated intestinal injury[28,39]. This observation is keeping with a report showing that infection with the helminth *Fasciola hepatica* reduced the protective Th1 response to coinfected *Bordetella pertussis* and exacerbated the bacterial infection[40]. Likewise, infection with *Schistosoma mansoni* downregulated antigen-specific Th1 cytokines and cytotoxic-T-lymphocyte responses, resulting in a delay in vaccinia virus clearance[41]. Moreover, it has been shown that a combined infection with *Trichuris suis* and *Campylobacter jejuni* in immunologically naive, germfree piglets, resulted in an enhanced invasion of the colon by *C. jejuni*, leading to the development of more severe pathology[42]. These observations provide strong evidence to demonstrate that helminth infection can dampen Th1 reactions to other infections and cause impaired immune responses to concurrent viral, bacterial, and parasite infections, as well as to vaccination. The Th2-inducing helminth infection has also been shown to inhibit the development of CD8+ T cell responses[43].

HELEMINTHS MODULATE INFLAMMATORY DISORDERS OF THE HOST

It has been observed that there is an increased incidence of autoimmune disorders and allergic diseases in the developed world. This phenomenon is thought to be the consequence of eradication of major infectious diseases, including helminth infections in this part of the world, a theory termed the hygiene hypothesis. The inverse correlation observed between helminth infection and certain immune-mediated diseases has led to the suggestion that lack of helminth infections favors the induction of Th1 responses, which may, in turn, result in the clinical appearance of gastrointestinal diseases, including inflammatory bowel diseases (IBD)[44-46]. IBD, including Crohn's disease and ulcerative colitis are chronic immune diseases of the gastrointestinal tract with unknown etiology. The current hypothesis indicates that IBD results from an uncontrolled immune response to the normal gut flora[47]. Genetic factors and environmental factors both contribute to the damaging mucosal immune response[48]. The hygiene hypothesis suggests that microbes and worms are important for shaping and tuning the development and function of our immune system[49]. The growing body of epidemiological and experimental data strongly suggest that a reduction in helminth infection is linked to rising rates of autoimmunity and atopy.

The initial work by Elliott *et al*[50] showing a protective response of *Schistosoma mansoni* infection on trinitrobenzene sulphonic acid (TNBS)-induced colitis in mice, a chemically induced Th1-type colitis used as an experimental model of human IBD, have led to several animal studies determining the role of helminth infections in different IBD models. In 2001, Reardon *et al*[51] showed that infection of mice with the tapeworm *Hymenolepis diminuta* ameliorated dextran sodium sulphate (DSS)-induced colitis. Khan *et al*[52] showed that mice that were infected with the nematode, *Trichinella spiralis* are protected from colitis induced by intrarectal challenge with dinitrobenzene sulphate (DNBS). Furthermore, schistosome eggs also provide a protective effect on TNBS-induced colitis in mice[53] and infection with *H. polygyrus* or *T. muris* can prevent or reverse the chronic spontaneous Th1-type colitis in IL-10 deficient mice[46]. A protective effect of infection with *Schistosoma mansoni* on TNBS-colitis in rats was also reported[54]. These observations provide evidence to suggest that helminth parasites (nematode, cestode and trematode) can ameliorate chemically induced colitis in different models. In line with these observations, the Th2 polarized T-cell response driven by helminth infection has also been linked to the amelioration of some Th1-mediated diseases that develop concurrently, such as *Helicobacter*-induced gastritis[14].

Evidence not only suggests that helminths can attenuate experimentally induced IBD in animal models[42,53,54], but also the pioneering work of Weinstock *et al* shows promise using *Trichiuris suis,* a pig helminth, to treat Crohn's patients[16]. Therapeutic potential has also been indicated in CD patients who were infected with the human hookworm *Necator americanus*[55]. The effects of helminth on host intestinal Th1 function could be mediated through several mechanisms, including helminth-induced Th2 response and induction of Tregs. We have shown that infection with the intestinal helminth *H. polygyrus* results in an upregulation of colonic IL-4 expression[28]. Recently Setiawan *et al*[56] have provided evidence to show that *H. polygyrus* infection promotes Th2 cytokine responses (IL-4, IL-5 and IL-13) of colonic lamina propria mononuclear cells. Helminths also induce production of powerful immune modulatory

molecules like IL-10 and TGF-β[57] that can affect both Th1 and Th2 function.

Unfortunately, the anticolitic effect evoked in response to helminths in mice does not extend to all models of colonic inflammation. In a recent study, the ability of the rat tapeworm *Hymenolepis diminuta* to affect the course of oxazolone-induced colitis was determined. A detrimental effect of helminth infection on colitis was detected, as evidenced by the results showing that *H. diminuta* caused a significant exacerbation of oxazolone-induced colitis[58].

Considering the profound and widespread immune activation and dysregulation induced by helminth parasites, the overlapping geographic distributions of helminth and bacterial infections, and the potential to modulate bacteria-associated intestinal inflammation, we have established a co-infection model system to analyze the effect of an intestinal helminth parasite on a concurrent enteric bacterial infection and bacteria-mediated intestinal inflammation[28]. This model involves two murine enteric infectious agents that induce distinct Th-responses: (1) the Th2-inducing helminth *H. polygyrus*, and (2) the bacterial pathogen, *C. rodentium*, which selectively stimulates a Th1-type immune response[59,60]. *C. rodentium* is a mouse pathogen that colonizes the distal colon and causes pathological changes that are similar to those seen in many mouse models of colitis, including transmissible colonic hyperplasia, goblet cell depletion, and mucosal erosion. *C. rodentium* has been used as a model for studying host responses to human pathogens that employ attaching and effacing (A/E) lesion formation for epithelial colonization, such as EPEC, the most important causative agent of severe infantile diarrhea[59,61-64]. We found that mice co-infected with *H. polygyrus* developed a more severe *C. rodentium*-associated colitis. The exacerbation of bacterial colitis induced by helminth co-infection is STAT6 dependent. These results provide evidence to indicate the possibility that helminth infection may have adverse effects on intestinal inflammation (bacteria-mediated as well as inducible colitis). In addition, it has been also reported that *T. suris* ova treatment resulted in infection in the gastrointestinal tract of a pediatric Crohn's patient[65]. These observed deleterious consequences of helminth parasites in intestinal inflammatory responses, therefore, provide a cautionary note for the therapeutic use of helminths in certain forms of IBD. These observations also highlight the need for a more comprehensive understanding of the mechanisms by which helminths modulate host's responses to enteric bacteria and bacteria-associated as well as immune-mediated intestinal inflammation.

IMPACT OF HELMINTHS ON INNATE IMMUNE OF THE HOST

Innate immune cells such as DCs and macrophages are fundamental to directing immune responses along either a tolerating or activating pathway. As master manipulators of the host immune system, helminths have evolved strategies targeting these cells. To effectively control infection, appropriately developed and functionally polarized subsets of Th effector cells are required. DCs, the most competent antigen presenting cells, play an important role in the initiation of both innate and adaptive immune responses to a wide variety of pathogens and Ags, as well as in tolerance[66-69]. DCs can be activated by microbial products through their high-level expression of evolutionarily conserved pattern recognition receptors, such as Toll-like receptors (TLRs)[70,71]. The signals derived from various types of microbial components, such as those from helminth and bacteria, are translated by the DCs into a stimulus for T cells, leading to a productive T cell response. The T cell stimuli derived from DCs include MHC II-peptide (signal 1), the expression or absence of costimulatory molecules (signal 2), and expression or absence of polarizing cytokines (signal 3)[72,73]. Microbial antigens can activate DCs through ligation of TLRs, leading to the up-regulation of functional surface molecules, and the release of cytokines, such as IL-12, IL-18 and IL-27, resulting in the induction of Th1 immunity[70,71,74]. Although it is less clear, there is also evidence indicating that DC function is modulated during helminth infection[75]. Different helminth-derived molecules have been suggested to be able to induce DC activation, and subsequent Th2 and/or T reg responses. Studies have indicated that two *Schistosome* egg-derived components (the glycolipid lysophosphatidylserine and the carbohydrate determinant lacto-N-fucopentaose Ⅲ) can activate TLR4 and TLR2, respectively, in myeloid DCs[76]. Live schistosoma eggs can activate DCs through TLR2 and TLR3[77]. Parasite secreted compounds like ES-62 from filarial nematodes induce the development of DCs and are capable of driving a Th2 response, modulating cytokine production (IL-12 and TNF-α) in macrophages and DCs *via* the TLR4 pathway[78]. A recent report suggests that helminth infection may alter TLR 4 expression in mucosal T cells, and these T cells when stimulated with LPS produce TGF-β[79]. Additionally, murine bone marrow-derived DCs pulsed with the helminth excretory/secretory antigen can, on transfer to naive recipients, prime mice for Th2 responsiveness[80]. Other studies also indicate that the soluble fractions from S. mansoni eggs may alter TLR ligand-induced activation of DCs[81]. These results clearly indicate the possibility that helminth infection may modulate TLR expression of DCs and responsiveness of DCs to TLR ligands.

In addition to Ag-specific MHC-peptide complexes and costimulatory molecules (B7.1 and B7.2, signal 2), other signals derived from Ag-primed DCs have been thought to be required for the differentiation of naive Th cells into Th1 and Th2 cells[72,73,82]. It has been shown recently by us and by others that intestinal helminth infection induces DC activation and up-regulates the DC IL-10 response[39,83], which may provoke a Th2 and/or T reg dominant response.

HELMINTH INFECTION INDUCES THE DEVELOPMENT OF ALTERNATIVELY ACTIVATED MACROPHAGES

The helminth infection induced-Th2 cytokine response has been suggested to affect macrophages[84]. Although macrophages share some functional similarities with DCs, macrophages have distinct functions. As discussed above, DCs play an important role in initiating and regulating host immune responses, whereas macrophages, contribute significantly to the effector phase, i.e. elimination of bacteria, and are also thought to be critical mediators of many chronic inflammatory diseases. Distinct phenotypes of macrophages have also been reported. Activation of macrophages by bacterial products (through TLR engagement) or pro-inflammatory stimuli such as Th1 cytokines leads to the development of the classically-activated macrophages. We and others have shown that helminth-induced Th2 cytokines induce a different phenotype, namely, the alternatively activated macrophages[85-87]. One of the distinctive characteristics of this type of macrophage is the ability to suppress the proliferation of other cells with which they are co-cultured[88,89]. A recent report suggests that alternative activation of macrophages by IL-4 results in impaired nitric oxide (NO) production and increased expression of the transferrin receptor, supporting intracellular growth of bacteria (*Mycobacterium tuberculosis*)[90]. Recently, we observed that the exacerbated *C. rodentium*-mediated colitis that develops in helminth-coinfected mice correlates with the marked accumulation of alternatively activated macrophages in colonic LP *via* a STAT6-dependent mechanism[85]. Functional analysis indicates that these helminth-stimulated macrophages have an impaired ability to effectively control the multiplication of phagocytosed *C. rodentium*. Presumably as a result of the increased bacterial load, these cells also produce increased amounts of TNF-α, a cytokine that has a well-established role in intestinal and other types of inflammation[91,92]. These observations, therefore, provide evidence to suggest an underlying mechanism for the enhanced bacterial infection and exacerbated bacteria-induced intestinal injury in hosts that are coinfected with helminth parasites.

CONCLUSION

In many developing countries, exposure to helminth infections and simultaneous infection with other pathogens, such as enteric bacteria, are quite common. Recent evidence indicates that in the developed world, a complete absence of helminth infection may be a predisposing factor for the development of certain immune-mediated disorders[45]. The emerging evidence indicates the complexity of immune regulation by helminths in host protective immunity and inflammatory diseases. The differences in the effects of helminths on the development and progression of intestinal inflammation observed in various models emphasize the need for a better understanding of the mechanisms by which helminths modulate host mucosal immunity. It is clear that a more thorough understanding of the complex relationship between the human host and parasitic worms will be required to develop safer, novel and more effective treatments for microbial diseases and immune-mediated disorders such as IBD.

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