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Hookworm infections in human and laboratory animals – differences and similarities in immune responses

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ABSTRACT: Hookworm infection is one of the most important parasitic infections of humans. About 740 million people are infected with *Ancylostoma duodenale* and *Necator americanus* in the tropics and subtropics. Unlike most other human helminth infections, neither age nor exposure-related immunity develops in the majority of infected people. This review presents the contemporary knowledge concerning the immune response to this complex eukaryotic parasite, recent findings on the human cellular immune responses to hookworms, as well as mechanisms used by the parasite to modulate the immune response in its favor. Also immunological responses in animal models of hookworm infection are presented. Animals in contrast to humans seem to easily deal with hookworm infections and gain protection during re-exposure.

Key words: antibodies, cytokines, eosinophils, hookworm, inflammation.

Over two billion people worldwide are infected with the soil-transmitted nematode helminths *Ascaris lumbricoides*, *Trichuris trichura* and hookworms: *Necator americanus* and *Ancylostoma duodenale*, the last two infecting about 740 million people in tropical and sub-tropical regions of the world [1]. A zoonotic species *Ancylostama ceylanicum* also causes patent human infection but is only of localized importance in Asia [2]. The most widespread of all hookworm species, *Ancylostoma caninum*, parasite of dogs, has been confirmed to develop in human gut, but without maturing sexually [3]. *A. caninum* infection accounts for most cases of human eosinophilic enteritis diagnosed relatively frequently in north-eastern Australia [4]. Clinical symptoms of human hookworm infection include iron-deficiency anemia [5] and protein-losing enteropathy [6] that may lead to physical, mental and cognitive growth retardation effects [7, 8]. Recent findings suggest that hookworms may induce a state of host immunological hyporesponsiveness and could promote susceptibility to the intercurrent viral, bacterial or protozoan infections such as measles or HIV-AIDS [9, 10]. Despite their global importance and the chronicity of infection, very little is known about how these parasites interact with their hosts and tolerate the complex immune responses generated against them [2]. There is little evidence that these responses protect against subsequent exposure and development of hookworm disease [11]. In contrast, dogs become resistant to *A. caninum* and *A. ceylanicum* and acquire immunity to re-infection [11, 12]. Also hamsters, which represent the only suitable rodent model of human hookworm infections, acquire resistance to *A. ceylanicum* [13]. Unfortunately the immunological events responsible for protection in animal models have not been fully understood and the problem of human susceptibility to hookworm infections remains unsolved.

Generally resistance to intestinal nematode infections relates with the ability to mount a CD4+ Th2 type response and is impaired by CD4+ Th1 responses [14]. One of the critical influences in T cell subset polarization is the immediate cytokine environment at the time of antigen presentation, with IL-12 promoting differentiation towards Th1 cells and IL-4 towards Th2 cells [14, 15, 16]. The type of antigen presenting cell (APC) involved is also important, antigen presented by macrophages favors Th1 development, whereas antigen presented by B cells induces Th2 type responses [14, 17].

Antigen load has been shown to be important with low level infection in a normally resistant, Th2 dominated host promoting the development of a Th1 type response and susceptibility to infection [14, 18]. When the immune response is polarized towards Th1 cell subset, augmented production of IL-12 and IFN-γ by APCs and NK cells inhibits the development of Th2 cell development. Th1 type responses induce production of high levels of IgG2a antibodies and activate macrophages. When Th2 responses are promoted by IL-4 and IL-9, Th1 cell polarization is inhibited. Th2 type responses protect the host against intestinal nematode infections and promote mastocystosis, eosinophilia, antibody production and goblet cell hyperplasia [14]. These mechanisms create an environment hostile to worm survival by generation of inflammatory responses in the gut, alterations in gut physiology in which parasites are damaged and forced from their niche within the host.

Primary infections of *A. ceylanicum* in hamsters are chronic and infected animals suffer from anemia and weight loss much as in infected humans [19]. However secondary responses are remarkably effective in reducing worm burdens early during the course of infection and acquire resistance to *A. ceylanicum* [13]. Immunity to hookworms in this system is associated with accelerated mucosal mastocystosis and increased systemic antibodies [11]. Hamsters respond to intestinal nematode infections with a local intestinal inflammatory response, which is probably controlled by CD4+ lymphocytes. The L4 and possibly L3 stages of *A. ceylanicum* are susceptible to such inflammation, whereas adult worms are capable of resisting intestinal inflammatory responses. Also humoral responses are directed against the L4 stage, intense reactivity of secondary infection sera with surface polypeptides of L4 stages of *A. ceylanicum* has been reported [20].

Cytokine profile in hamsters infected with hookworms has only been investigated on molecular level due to lack of immunological reagents. Cytokine mRNA levels were measured using RT-PCR during primary *A. ceylanicum* infection [8]. At patency period highly elevated levels of IL-2 and IFN-γ mRNA were observed and moderate TNF-α mRNA level what suggests that inflammatory response occurs at this period. This Th1 response has a transient nature, levels of mRNA of these cytokines declined after larvae developed to adults. When considering Th2 type cytokines the situation is opposite, low levels of IL-4 and IL-10 mRNA found in the hamster during larval migration increased at patency. Cytokine profile observed in *A. ceylanicum* hamster infections during patency was similar to the peripheral blood mononuclear cell cytokine responses in chronic human hookworm infections in which IFN-γ and IL-12 are suppressed but IL-10, IL-4, IL-5 and IL-13 are elevated [21, 22]. These similarities confirm that the hamster model of *A. ceylanicum* infection could become useful for investigating the mechanism of host-parasite interactions that lead to immunomodulation during human hookworm infection [8].

Although hookworms do not reach maturity in mice and experimental infections in this animal model do not represent natural exposure in humans the findings could provide some valuable information for researchers [23]. Mice rapidly become resistant to L3 stage and this antilarval resistance is thought to be mediated by significant increases of levels of IgM, IgG1 and IgE antibodies [23, 24]. Key effector cells in peritoneal responses in mice orally infected with *A. caninum* L3 are macrophages which adhere to larval surface and facilitate parasite destruction by antibody-dependent cell-cytotoxity (ADCC) [25].

The role of eosinophils during hookworm infections has also been investigated in murine model. These cells can kill infective larval stages but not the adults of most helminth species investigated [26]. However IL-5 knockout mice infected with *A. caninum*, which did not mount blood eosinophilia still had the same numbers of L3 in their tissues as normal mice. This indicates that an absence of circulating eosinophils in mice does not increase susceptibility to hookworm L3 invasion [23].

Previously Girod et al. [27] described complete protection in BALB/c mice vaccinated percutaneously with γ-irradiated *N. americanus* larvae. The data suggest that Th2 responses are responsible for the development of protection. The most important in this process is probably the immunity in the skin, as only few larvae reached the lungs and none reached the intestine. Accumulation of degranulated mast cells was observed in the skin. The degranulation might have been caused by the binding of parasite-specific IgE to Fc receptors on the mast cell surface. Moreover an increased level of mRNA of IL-4, a hallmark cytokine in Th2 responses was observed in skin tissue. Also lymphocytes from axillary lymph nodes specifically stimulated with concanavalin A produced high levels of IL-4 and less IFN-γ (a marker for Th1 cells). The antibody

analysis demonstrated an augmented production of IgG1, a serological marker of the Th2 response. This also confirms that Th2 mechanisms are responsible for protection in mice infected with *Necator* larvae.

In contrast to experimental animals where immunity to human and canine hookworms is rapidly acquired, in humans the development of the same protective immunity is not obvious [23]. In animals mechanisms of immune response act against invading L3 larvae. Larval sheath antigens are also immunogenic to humans. In Papua New Guineans infected with *N. americanus*, strong antibody responses representing all five human immunoglobulin isotypes were formed to larval and adult antigens [28]. But the recognition of larval antigens varied widely between individuals [29]. IgE directed against *Necator* L3 larvae were found to be highly specific and the least cross-reactive of all isotypes [30, 31]. However parasites have a way to protect their potentially susceptible larval surface – antibodies of people infected with *N. americanus* recognize surface antigens of ensheated but not exsheated L3 [32]. When larvae cast their sheath during skin penetration, or later on during their migration through host tissues, it diverts the antibody response away from their exsheated surface.

Antibodies dominating in immune responses against adult nematode parasites are IgG1, IgG4 and IgE, which are under control of Th2 cytokines, typically IL-4 [23]. Levels of IgG and IgM against adult hookworm excretory-secretory (ES) antigens provide the best indicator of current infection with adult parasites and efficacy of chemotherapy [28].

Tissue invasion by helminths is associated with high IgE levels in serum, like in acute allergy, but much of these IgE seem to be directed against heterologous antigens. This observation led to the speculation that helminth parasites secrete proallergic mediators that induce polyvalent, non-parasite-specific IgE, which saturate IgE receptors on effector cells [23, 33]. But in *N. americanus* infections IgE are the most specifically directed against parasite epitopes [31]. Also in human *A. caninum* intestinal infection IgE responses were more specific to ES antigens than IgG [34], and patients infected with *A. duodenale* produce both systemic and jejunal IgE that specifically bind to larval antigens [30].

IgE antibodies can be connected with protection against *N. americanus*. Infected patients with higher levels of IgE had few and less fecund parasites at initial anthelminthic treatment and two years after re-infection [35]. Further research showed that levels of specific antibodies of all isotypes, including IgE, to *N. americanus* ES products were not positively correlated with hookworm weight and fecundity. This suggests that total IgE rather than anti-parasitic antibodies were associated with protection.

Specific IgG4 antibodies have been suggested to be a marker of active infection with *N. americanus* [23, 36]. These immunoglobulins are thought to down-regulate immune responses by competitively inhibiting IgE-mediated mechanisms for example by blocking mast cell activation [37]. This restricts potentially harmful for the host effects of increased IgE response. Another mechanism of this restriction is the production of IgG autoantibodies to IgE [38].

In human infections with both anthropophilic and zoonotic hookworms infiltration by the worm feeding site with eosinophils is an almost universal feature [23]. Eosinophils in the blood and tissues of helminth-infected patients exhibit changes associated with their activation such as enhanced cellular cytotoxicity, release of granule proteins, cytokines, leukotriens and other mediators of inflammation [39]. Eosinophilia in hookworm infections varies according to the stage and intensity of infection as well as individual host factors. In human eosinophilic enteritis associated with *A. caninum*, all layers of the gut, from the mucosa to the serosa can be heavily affected by intense eosinophilic inflammation [3, 40].

Activation of eosinophils, besides cytokines, mainly IL-5 and chemokines [39] is also dependent of mast cell degranulation in response to IgE-allergen interaction [14]. Mast cells are surely important in the host response to hookworms, for example their proteases degrade cuticular collagens of adult *N. americanus* [41], but they had attracted sparse research attention [23].

Protection against gastrointestinal nematodes is usually mediated by Th2 responses, where IL-4 and IL-5 play main roles. While human hookworm infections show some of the hallmark features of Th2 response, these immune responses clearly fail to protect most infected people [2]. To better understand this problem researchers try to establish human cytokine profiles induced by *N. americanus*. Geiger et al. [21] investigated cytokine production in peripheral blood mononuclear cells (PMBCs) from *N. americanus* infected patients. Infected individuals produced higher levels of IL-10 than controls that is non-infected patients and lower levels of both Th1 cytokines: IL-12 and IFN-γ, and Th2

cytokines: IL-5 and IL-13. Also increased levels of TNF-α, multipotential, proinflammatory cytokine were observed in egg-positive individuals. Elevated TNF-α levels may indicate ongoing intestinal inflammation and, on the other hand, elevated IL-10 production may serve to minimize cellular responsiveness and to down-regulate pathogenic processes [21]. During another recent study cytokine responses to *N. americanus* were measured in patients from Papua New Guinea [22]. Before anthelminthic treatment in most cases detectable levels of Th1: IFN-γ and Th2: IL-4 and IL-5 cytokines were produced. Pre-treatment IFN-γ responses were negatively correlated with hookworm burden and significantly increased after treatment. The intensity of re-infection was also negatively correlated with pre-treatment IL-5 responses.

Cytokine levels were also investigated in infected mothers and their new-born children [42]. IL-5 and IL-10 cytokines were equally elevated in both mothers and neonates. However IFN-γ and IL-12 levels were significantly higher in mothers, what suggests a correlation between type I cytokines and presence of live parasites. In conclusion a mixed cytokine response was detected in infected people [21, 42, 43]. These findings suggest that resistance to re-infection may possibly be associated with a parasite-specific IL-5 response.

Human hookworm infections are usually chronic despite many immunological mechanisms induced by these parasites (Table 1). The final effect of these responses is the creation of environment in the intestine that is hostile for the parasite. But hookworms appear to be more resistant to intestinal inflammation than most other intestinal nematodes. Moreover they might protect other parasites during co-infections by generally suppressing host immune responses [44]. Although hookworms secrete significant quantities of antigens into host tissues these secretions might not provoke antibody responses but aid worm survival by many immunosuppressive reactions.

It has been discovered that ES products from *N. americanus* contain factors, which are capable of inducing apoptosis in activated T cells [45]. Culley at al. [46] discovered metalloproteases in *Necator* ES products that can cleave eotaxin. The chemokine eotaxin is a potent eosinophil chemoattractant, it acts in concert with IL-5 to stimulate the release of eosinophils from the bone marrow, and locally, to mediate their selective recruitment to sites of inflammation. Following the action of these proteases, eotaxin can no longer be detected in immunoassays and exhibits no activity on eosinophils in both *in vitro* and *in vivo* assays of eosinophil recruitment [46]. Proteases present in ES products can also cleave IgA antibodies to yield Fab fragments that can block component or phagocyte attack mediated by IgG or IgM [47]. Hsieh et al. [48] described a protein from the ES products of adult *N. americanus* which specifically binds to human and mouse natural killer (NK) cells and stimulates augmented production of IFN-γ. In this way it cross-regulates harmful Th2 immune responses in the host and contributes to the long-term survival of the parasite.

Hookworms also secrete other substances that can impair host immune reactions. One of them is cysteine-rich glycoprotein of adult *A. caninum* – neutrophil inhibitory factor (NIF). NIF potently inhibits neutrophil function by blocking their adhesion to vascular endothelial cells and release of H_2O_2 [49]. Parasites also produce analogs of C-type lectins (C-TLs). Human C-TLs are present on the surface of effector cells including APCs and T and B cells, where they play an important role in regulation of the immune system. Parasite C-TLs, also found in *N. americanus*, compete with host molecules for binding to ligands involved in inflammation [23, 50]. Many other molecules are proposed to

Table 1: Effector mechanisms during hookworm infections in humans, hamsters and mice; possibly significant for protection „+"; not significant „-"; not estimated „?" (based on: [4, 8, 11, 19, 21-23, 25, 27, 28, 30-33, 35, 36, 38, 42])

Effector mechanism	Human	Hamster	Mouse
Antibodies	+ (mainly IgE)	+	+ (IgG1, IgM, IgE)
Mast cells	+	+	+
Eosinophils	+	?	–
Macrophages (ADCC)	?	?	+
Cytokines (Th1 or Th2)	Mixed	Mixed	+ (Th2)
Local intestinal inflammatory response	?	+	?

have a role in immunomodulation such as protease inhibitors, antioxidants, calreticulin and acetylcholinesterase [23].

Although hookworm infections concern millions of people around the world little is known about the details of how the parasites interact with their hosts, about immunological responses they generate and ways in which they can survive in host organism. There is no evidence that infected people gain protection and the reason for ineffectiveness of anthelminthic therapy remains a question. Lack of such knowledge may be due to absence of suitable animal models and available immunological reagents. Still there is a lot to discover about parasite secretions, which play key roles in triggering and modulating host immune responses. Finding new hookworm proteins, unsolving their functions and unraveling the complex cytokine networks involved in host immune responses should contribute to understanding host-parasite interactions and making progress in developing effective human hookworm vaccine.

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