Mini-review

Strongyloides stercoralis and the immune response

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Abstract

The immune system is a highly evolved network of cells and molecules that can distinguish between invading pathogens and the body's own cells. But helminths, in their complex forms, are capable of down-regulating host immunity, protecting them from being eliminated and also minimizing severe pathology in the host. This review focuses on Strongyloides stercoralis and the immune responses in immunocompetent and/or immunocompromised individuals. It also highlights the implications for diagnosis/treatment and draws attention to an emerging public health disease. The solution to reducing the prevalence of strongyloidiasis remains on the effectiveness of pre-emptive measures in endemic communities, increased awareness, prompt early diagnosis as well as timely treatment.

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1. Introduction

Strongyloides stercoralis, which is the causative agent of strongyloidiasis, is an opportunistic intestinal threadworm parasite that infects man, cats, dogs, and can be passed from man to dog/cat or vice versa. Strongyloidiasis is accountable for about 60–85% mortality rate in immunocompromised persons, affecting an estimated 100 million people worldwide [1,2]. The mortality rate for patients requiring hospitalization with Strongyloides infection is about 16.7%. It is endemic in warm moist tropical and sub-tropical climates and is widespread in Eastern Europe, South and Southeast Asia, Central America, South

America and sub-Saharan Africa. It has also been reported in a non-endemic area [3]. Strongyloidiasis is more commonly found in institutional settings, rural areas and lower socioeconomic groups [4–6].

The Strongyloides life cycle is complicated when compared with other nematodes alternating between a free-living cycle and a parasitic cycle. Strongyloides is the only helminthic parasite that secretes larvae (not eggs) in faeces, appearing approximately 1 month after skin penetration. The transformation of the rhabditiform larvae (L1, L2) into the free-living invasive filariform larvae (L3) is often needed for re-infesting the host through the invasion of the intestinal wall or the perianal skin [7]. The 3 major areas of Strongyloides infection involve the skin, lungs and intestine. Transmission can also be enhanced from increased exposure in occupations that involve handling of contaminated faeces and through increased contact with contaminated soil (e.g. farming, coal mining) [8,9]. The result of infection ranges from an

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asymptomatic condition to multiorgan failure. More commonly, the infection manifests as mild gastrointestinal symptoms with devastating effects in immunocompromised individuals. One significant feature of *Strongyloides* is its asexual autoinfection capacity that explains importunate infections in individuals who have not visited an endemic area or had prior exposure to the infection. Autoinfection occurs predominantly in humans, monkeys, dogs [10,11] but does not occur in immunocompetent gerbils [12]. It only occurs when gerbils are given the non-steroidal immunosuppressant tacrolimus [13]. In contrast, autoinfection has been seen in immunologically immature or immunosuppressed jirds (*Meriones unguiculatus*) [14].

Strongyloidiasis in warm moist climates, rural tropics and sub-tropics where HIV/AIDS prevalence is considerably high, continues to attract the interest of researchers. Furthermore, a condition such as the hyperinfection syndrome complicates clinical presentation in immunocompromised individuals. Factors that determine the risk of occurrence, the understanding of the immunopathology, protective immune response in humans and the biology of *S. stercoralis* are still not fully known. This review focuses on the immunology and immunopathology in immunocompetent/compromised hosts. It also highlights its clinical importance in association with increases in travel histories to endemic and non-endemic countries attributed to globalisation.

2. B-cell immunity against *S. stercoralis*

B lymphocytes are believed to be essential for the acquisition of resistance to larval *S. stercoralis*. Results in severe combined immunodeficiency (SCID) mice indicated that the parasite developed into reproductive adults [15] while in T-cell-deficient hypomorphic mice; *Strongyloides* development was not altered [16]. Data from defective B-cell development [17,18], X-linked immunodeficient [19,20] knockout mice with deficiencies in the B-1 cell population [19,21] illustrated the importance of B cells in the acquisition of resistance to larval *S. stercoralis* and indicated that B-1 cells could play an integral role. However, B cells may not be required in the primary response, but most likely in secondary immune responses to larval *S. stercoralis* [17].

Animal studies have continued to provide us with a better understanding of the molecular and immunological mechanisms of disease development. But, *S. stercoralis* in most animal models may be unrepresentative of natural infection in humans notwithstanding the similar biology of parasite infection of different hosts. Protective immunity in mice to the infective third larvae (L3) of *S. stercoralis* has been shown to involve IgM [17], complement activation [22] and neutrophils [23] in antibody-dependent cell-mediated cytotoxicity (ADCC) type responses [24]. In humans, immunity to L3 is not protective against the autoinfection larvae (L3a), which is the causative agent of strongyloidiasis [25] and L3a seems to have a different antigenic recognition pattern [26]. A previous study showed that both IgM and IgG antibodies were protective against larval *S. stercoralis* but they recognize different antigens and utilize different killing mechanisms [27]. Increased *S. stercoralis*-specific IgG4 antibody titre has been associated with resistance to alendazole treatment in male patients when compared with their female counterparts in a Japanese study [28] and HLA-DRB1*0901 is suggested as a possible genetic marker for resistance to treatment of *S. stercoralis* in this population [29]. In humans, a statistically significant decrease in IgM and IgG antibody levels were found in people with severe Strongyloides when compared with the levels in people with asymptomatic or mild symptomatic infections, signifying the influence of antibodies in defence mechanisms against *S. stercoralis* larvae [30]. Furthermore, infants in endemic areas can acquire IgA and IgG antibodies to *S. stercoralis* from breast milk [31]. Although patients with strongyloidiasis have specific serum IgA responses against filarial larval antigens, the role of IgA antibodies in the disease is still unclear as it correlates poorly with clinical disease [32].

3. The role of eosinophils in protective immunity

Eosinophils are one major component of the immune system responsible for combating infections, specifically parasitic infections. They are commonly associated with helminth infections. In addition, eosinophils have been shown to function as antigen presenting cells (APCs) in allergy [33]. Eosinophils gather anywhere where there is a parasitic infection or an allergic reaction, subsequently releasing toxins that kill the invading pathogen. Their induction is required during immunization [34]. Helminth infections generally induce the activation of Th2 lymphocytes characterized by the production of eosinophilia, IL-5 and IgE [35,36]. IL-5, however, is an essential cytokine for differentiation, activation and proliferation of eosinophils which are cells involved in helminth killings [2,37]. In general, helminths cannot be ingested by phagocytes due to their large size. However, when coated with antibody especially IgE, eosinophils can attack via the high-affinity FceRI.

Eosinophils and antibodies play important roles in defence mechanisms against *S. stercoralis* larvae [28] during innate and adaptive immune responses [34,38]. *S. stercoralis* antigens activate eosinophils; induce the expression of major histocompatible complex (MHC) class II and T-cell co-stimulatory molecules. Activated eosinophils can stimulate T cells for antigen-specific immune responses [39]. Eosinophils are also believed to function as APCs for the induction of the primary and secondary Th2 immune responses to *S. stercoralis* [39,40] indicating an essential role for eosinophils in the interface between innate and adaptive immune responses. Recently, both eosinophils and neutrophils were found to be required in the protective innate immune response while only neutrophils were necessary for the protective adaptive immune response to larval *S. stercoralis* [23]. In individuals with severe strongyloidiasis, eosinophil levels were found to be lower than that of asymptomatic individuals [33]. Thus, eosinophil levels may likely play key roles in preventing *S. stercoralis* infection.

4. *Strongyloides* and Toll-like receptors (TLRs)

The Toll-like receptors (TLRs) are one of the most important pattern recognition receptors (PRR). These PRRs recognize pathogens through pathogen-associated molecular patterns (PAMPs), which are conserved groups of molecules from pathogens that are essential for microbial survival [41]. In humans, 11 TLRs have been identified based on their cellular localization: TLRs 3, 7, 8, and 9 are expressed in endosomes, while TLRs 1, 2, 4, 5, and 9 are present on the surface of many cells. Each TLR activates a distinct signalling pathway and induces specific biological responses against micro-organisms [42]. TLR4 is expressed on B cells and is essential for lipopolysaccharide (LPS)-induced signalling of B-cell activation [43]. Stimulation of TLR4 in dendritic cells (DCs) induces IL-12 production and also enhances surface expression of co-stimulatory molecules [44]. TLR4 has been linked with the activation of Th1 type immune response. Mice deficient in TLR4 are impaired in their ability to recruit neutrophils [45] and exhibit decreased immunity to *Onchocerca volvulus* infections [46]. A recent study established that TLR4 was not required in *S. stercoralis* larval killing during innate immune response, but was required in killing the larva during the adaptive immune response [47]. This adaptive mechanism may require the activation of neutrophils which mediates larval killing whereas TLR4 is not required for T- and B-cell function.

5. *S. stercoralis* and human T-lymphotropic virus type 1 (HTLV-1)

In immunocompetent host, *S. stercoralis* can cause a chronic, well synchronized and occasionally lasting infection since the worm has the unusual ability to multiply asexually [48]. Immediate hypersensitivity is the response of the immune system to *S. stercoralis* infection which could be attributed to protection or pathogenesis depending on the arm of the immune response being activated.
HTLV-1 is a human RNA retrovirus that causes T-cell leukaemia and T-cell lymphoma. It was first isolated from a patient with adult T-cell leukaemia lymphoma [7]. It is rife in Asia (especially Japan), the Caribbean, South America and Africa. The genome of the HTLV-1 virus is diploid and, following interaction with the immune system, HTLV-1 enables the transcription of the viral DNA by integrating into the host genome effectively evading immune surveillance without killing the host.

The human HTLV-1 largely infects T cells and induces spontaneous lymphocyte proliferation and secretion of elevated levels of type 1 cytokines [7]. Exacerbation of S. stercoralis has been correlated with HTLV-1 infection in the human host [49]. HTLV-1 in the infected host incites a biased Th1 response resulting in increased interferon-gamma (IFN-γ) production while decreasing levels of interleukin-4 (IL-4) and IgE antibodies [50,51]. The reduced levels of total serum IgE are characteristic of selective immunosuppression by the retrovirus, creating a lenient environment for the propagation of Strongyloides [2,7,52]. Co-infection with HTLV-1 decreases IL-5 and IgE responses in patients and switches the immune response from a Th2 to a Th1 type [53]. However, the exact mechanism of the immune response to strongyloidiasis is not fully understood. In human helminth infections, Th2 type cytokines, IgE antibodies, eosinophils and mast cells participate in their expulsion and killing of the invading pathogen. IL-4 induces activated B cells to class-switch, differentiate and produce IgE, IgG4 antibodies. Furthermore, both IL-4 and IL-13 increase intestinal fluid content which contribute to parasite rejection [54,55]. The decrease in IL-4, IL-5, IL-10, IL-13 and specific IgE antibodies in patients co-infected with HTLV-1 suggest that a decline in the Th2 type immune response, mediated by high significant levels of IFN-γ, may elucidate the immunological parameter for increased susceptibility of co-infected patients with the development of strongyloidiasis [7,53]. This persistent infection with HTLV-1 increases the expression of IFN-γ and tumour growth factor (TGF-β), decreases the serum levels of specific IgE and IgG4, affects S. stercoralis-specific immunity and reduces therapeutic efficacy [56]. Thus, the HTLV-1 virus is able to impair the host immune response against S. stercoralis in patients [57].

6. Does HIV contribute to widespread strongyloidiasis?

Co-infection with human immunodeficiency virus (HIV) and S. stercoralis have been reported [58–60]. It is thought that immunosuppression in patients due to advancing HIV may favour hyperinfection with S. stercoralis. But, HIV-infection appears not to augment the odds of developing systemic strongyloidiasis [61]. A study conducted among 35 immune adults and the development of S. stercoralis infections showed that in immunocompetent individuals, a direct development of S. stercoralis is favoured whereas in individuals with lesser immune function, an indirect development was observed [62]. The results also signified a significant negative rank correlation between CD4⁺ cell counts and the proportion of free-living male and female worms indicating notably the absence of disseminated strongyloidiasis in advanced HIV disease. Similarly, in Uganda, Schistosoma mansoni, hookworm, S. stercoralis and Mansonella perstans were not associated with higher viral load [63]. Conversely, Olmos et al. [64] reported a case of S. stercoralis hyperinfection in a Spanish patient who had not travelled to an endemic area and in whom HIV-infection and long-term immunosuppressive treatment most likely led to the dissemination of strongyloidiasis. Furthermore, a progressive stage of AIDS in Iranian patients showing severe hyperinfection syndrome has been reported [65]. A similar study in Thailand also indicated a higher risk of S. stercoralis infection among HIV patients [66]. Nonetheless, the immunobiological and immunoregulatory mechanisms involving HIV and strongyloidiasis remain a subject of discussion.

7. Systemic strongyloidiasis

Systemic strongyloidiasis is an unusual but severe complication of intestinal Strongyloides occurring mostly in immunosuppressed patients [61]. It has a life-threatening consequence in immunocompromised patients on corticosteroid medications [67] or in post-transplantation immunosuppression [68]. Systemic strongyloidiasis can be present in individuals for many years subsequent to their departure from an endemic area, emphasizing the utmost need for the collection of patients’ travel history. Chronically infected individuals only have mild or no symptoms but those who are immunocompromised may develop a hyperinfection syndrome [69]. Symptoms include gastrointestinal and pulmonary infiltrates often seen on chest radiography [69,70]. The increased use of immunosuppressive treatments elevates the lethal outcome of this infection. HIV-infection does not appear to increase the risk of developing systemic strongyloidiasis [61] but disseminated strongyloidiasis only arise when HIV-induced immunodeficiency is profound [70]. Glucocorticoid treatment, hypogammaglobulinemia and human HTLV-1 infection are a few other conditions most specifically associated with triggering hyperinfection [2,26,71]. Patients on corticosteroid therapy, hepatic transplantation, renal transplant, systemic lupus erythematosus, asthma, chronic dermatosis, tuberculosis, lymphoma, leukæmia, tumours, and AIDS, are also at higher risk for strongyloidiasis [2,68,71,72]. The increase in ovaiposition is deemed to be as a result of the direct action of corticosteroid on parthenogenenic female thereby hastening their transformation to filaroid larvae [73].

Thiabendazole remains the drug of choice, but due to unacceptable side effects, albendazole and ivermectin are preferred. In particular, ivermectin seems to be the more useful drug for the treatment of strongyloidiasis in immunocompetent individuals [74], immunosuppressed patients [75] and patients co-infected with HIV as the drug is better tolerated [76,77]. The importance of parasitological and serological testing for S. stercoralis, before and during immunosuppressive therapies in patients with gastrointestinal symptoms, especially in areas endemic with strongyloidiasis, has been emphasized in order to improve prompt treatment of patients [78,79]. Moreover, management of strongyloidiasis is a priority and serological monitoring is required to ensure complete eradication following treatment [80,81] given that individuals exposed for many years may have low larval excretion, thus rendering parasitological faecal examination ineffective.

8. Strongyloidiasis: an emerging global disease

In the past few years, the prevalence of S. stercoralis has been on the increase, especially in Southeast Asia and Africa. Poor personal hygiene, insufficient supply of safe drinking water and contemptible sanitary measures have made the spread of infection imminent [82]. The zoontonic transmission capacity makes it even more serious as domesticated small ruminants may act as reservoir hosts. The link between veterinary and medical officers is reportedly weak and the interactive inter-border traffic and migration becomes a big challenge [83]. In a survey to determine the prevalence and seasonal abundance of nematode parasites, Strongyloides species were encountered throughout the year irrespective of the season [84] and arid savannas were found less suitable for helminth transmission than in the forest zone [85]. Furthermore, in randomly selected children below 5 years, S. stercoralis were associated with possible complication of malnutrition in children who presented with diarrhoea [86]. There is also evidence supporting the hypothesis of a possible association between positive S. stercoralis serology and diabetes [87]. Epidemiological studies have also identified endemic rates of Strongyloides infection in developed countries and immigrants/travelers are at particular risks in developing Strongyloides hyperinfection syndrome [88]. A high prevalence of S. stercoralis has been observed among Sudanese refugees in the United States of America and could
persist for prolonged period in the absence of adequate treatment [89]. In a random and representative sample of farm workers in a tourist region of Spain, a high prevalence of S. stercoralis was observed [90]. Infection can in addition be maintained in a temperate climate and may become a hazard for kennel workers [91]. Due to its low incidence, most developed countries place strongyloidiasis patients in iatrogenic danger attributable to misdiagnoses. In addition, there is a risk of medical errors by health care providers resulting from a lack of familiarity with the parasite [92]. Furthermore, S. stercoralis has recently been found in urine, which is a particularly rare occurrence [93]. Clinicians therefore must be aware of this unexpected infectious parasitic disease that is acquired through international travel and immigration which can be potentially lethal [94–96]. Laboratory professionals must also be alerted to the importance of early detection of S. stercoralis in specimens from immigrants at risk and immunodeficient patients to reduce morbidity and mortality [97,98]. New diagnostic methods are needed since the popular Kato–Katz method for the diagnosis of Strongyloides has a low sensitivity with direct faecal smears [99]. Other traditionally employed methods for the diagnosis of S. stercoralis are the Rugai and Baermann sedimentation methods. The more recent agar plate method has been tested and compared with direct smears, formalin ethyl acetate, Harada Mori culture method, Baermann and may be the test of choice, especially in immunocompromised patients [100]. Recently, a real time PCR method targeting the small sub-unit of the rRNA gene was developed for the detection of S. stercoralis DNA in faecal samples, including an internal control to detect inhibition of the amplification process [101]. These emerging methodologies may hopefully enhance routine diagnosis of S. stercoralis infections in the future.

9. Summary

Strongyloides is an emerging global infection that is underestimated in many countries. In humans, it is likely that S. stercoralis L3a down-regulate the host’s protective immunity; the mechanism seen as its survival strategy to evade the immune response. Strongyloides remains an imperative helminth disease due to increases in travel, migration to endemic and non-endemic countries, lack of adequate sewage disposal system especially in endemic countries and the risk of autoinfection which can lead to persistent disease for many years. Therefore, patients with a history of travel to likely endemic areas must be examined for strongyloidiasis before any immunosuppressive therapy. Also, an awareness of an increased predisposition to S. stercoralis is essential when signs of gastrointestinal or pulmonary symptoms are observed in immunosuppressed patients.

Individuals’ resident where strongyloidiasis is endemic or persons with high-risk occupations need to be informed about the risk of infection. Given the increasing number of immunocompetent/immunocompromised individuals worldwide, persistent eosinophilia likely caused by Strongyloides infection, clinicians need to realize the risk factors involved with this neglected helminth disease and additionally have an index of this disease since early diagnosis as well as timely treatment leads to successful resolution. Furthermore, it is worth emphasizing that in warm moist climates in tropical and sub-tropical countries, where strongyloidiasis is endemic, the appropriate practical preventive measures remain stepping up of health education campaigns on the disease, proper sanitation, regular de-worming, behavioural change through proper disposal of faecal waste and the use of protective foot-wear. These measures for disease prevention are all readily achievable and remain important approaches to reducing the prevalence of strongyloidiasis.

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References


