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Review

Current progress toward vaccine and passive immunization approaches for *Strongyloides* spp.

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ABSTRACT

Strongyloides stercoralis is a helminth parasite that can infect millions of people worldwide, particularly in tropical, subtropical and temperate regions with poor sanitation. Several aspects of epidemiology, biology and host-parasite interactions of *S. stercoralis* have been studied, and substantial knowledge has been acquired; however, very few studies on immunotherapeutic control strategies to prevent infection and disease in humans have been conducted. Therefore, this article reviews the current progress and targets toward vaccine and passive immunization approaches for *Strongyloides* spp.

Contents

1. Introduction

According to the World Health Organization, even more one billion people are infected with some species of intestinal helminthes, most of them causative of neglected tropical diseases (NTD), which represent a major public health problem [1]. In this context, human strongyloidosis is highlighted. Strongyloidosis is an intestinal parasitosis caused by nematodes of the *Strongyloides* genus, particularly the following two species: *Strongyloides fuelleborni* [2], whose infection is restricted to some countries of Africa and Asia, and *Strongyloides stercoralis* [3], with a rate of infection that could reach approximately 100 million people, predominantly in tropical, subtropical and temperate regions. Considering only acute infections, strongyloidosis is a major intestinal parasite in humans [4,5].

Strongyloides stercoralis can infect an individual in the following two ways: first, active penetration of infective larvae (L3i) in the skin and mucosa of the host and, second, autoinfection by active penetration of L3i in the perianal area (external autoinfection) or by active penetration of L3i in the intestinal mucosa of the ileum and colon (internal autoinfection) [5,6]. Autoinfection is responsible for chronic conditions because of the long maintenance of the parasite in the host that enables the development of severe forms of strongyloidosis as a hyperinfection and the spread of parasites to other organs because of various immunosuppressive factors [7–9].

Diagnosis of this disease can be performed by parasitological, immunological and molecular techniques. Parasitological diagnosis is routinely used for the detection of the parasite because of the cost; however it has low sensitivity, predominantly because of the limited and irregular release of larvae in feces, requiring the collection of seven samples to obtain 100% sensitivity [10]. Because of the large number of potentially exposed people with undiagnosed or subclinical disease, human strongyloidosis is a neglected condition [11–13]. Intestinal parasitosis by *S. stercoralis* remains a serious public health problem worldwide, and immunotherapeutic approaches may be important and additional tools are needed to prevent and control this disease.

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Strongyloides stercoralis has a unique life cycle, and the interaction between the parasite and the human host is complex because of its intrinsic ability to develop, so infected individuals may experience one of the following three types of disease evolution: eradication of infection, chronicity or hyperinfection, with the possibility of spread to other organs from autoinfection. Infection with *S. stercoralis* is typically self-limited and has low morbidity in immunocompetent individuals; however, infection could become severe if associated with immunosuppression conditions [8,9,14].

Host defenses against helminth infections involve the participation of cellular and humoral immune responses, beginning with antigen presentation to the $CD4^+$ Th2 cells via MHC class II, resulting in the production of specific interleukins of this signaling pathway such as IL-3, IL-4, IL-5 and IL-13 [15–20]. Additionally, there is a T-independent mechanism, which includes activation of macrophages and cytokines such as TNF-α and IL-1 and antigen-nonspecific mediators of inflammation that stimulate mucus production by the goblet glands of the intestine [21]. Mucins act by coating parthenogenetic females to prevent the parasite's establishment in the mucosa and to promote their elimination from the intestine [22].

Cytokines induce a rapid humoral response mediated by IgA and IgM, as well as a cellular response mediated by basophils, mast cells and neutrophils. In this context, antigen-specific IgE and participation of eosinophils, the most rapid immune response effector against parasites, are induced, which is fundamental in the processes of helminth elimination. IgG titers are noted two weeks postinfection (wpi), with a peak at approximately 6 wpi, and persist for up to 20 wpi [10]. Antigens from *S. stercoralis* L3i activate classical and alternative complementary pathways, allowing the adherence of monocytes and polymorphonuclear cells from peripheral blood to the surface of the larvae, resulting in lysis. One of the strategies of immune evasion by this helminth is secretion of proteases by the parasite, which cleave the complement proteins [5,23].

Infected immunocompetent individuals are asymptomatic in most cases or present with abdominal discomfort; such symptoms present as mild clinical manifestations [24]. However, the presence of eggs, larvae and adult worms in the intestinal mucosa may result in inflammatory response, malabsorption syndrome, chronic diarrhea with protein loss and hemorrhage associated with the development of anemia. Another important clinical data from the infection is and eosinophilia. In the pathological changes in which the parasite load is greater, enteritis is ulcerative, resulting in bacterial invasion [25,26].

Migration of larvae can pass through the alveoli capillaries and cause inflammatory infiltration with hemorrhage and, in severe cases, can lead to the development of Loeffler's syndrome, which is characterized by pulmonary edema and respiratory insufficiency [5]. Pulmonary symptoms have varying intensity and are present in most infected individuals, characterized by cough with or without sputum, dyspnea, asthma-like crises arising from larvae and, occasionally, parthenogenetic females [27,28]. Symptoms resulting from these processes are similar to those of other parasitic infections, complicating the clinical diagnosis [29].

Extra-intestinal manifestations can lead to severe and life-threatening cases in immunocompromised individuals suffering from different factors such as severe malnutrition, alcoholism, diabetes mellitus type 2, tuberculosis, sepsis, immunosuppressive treatments in individuals with cancer, autoimmune diseases or post-transplant and in individuals infected by HTLV-1 and HIV [8,30–37]. Therefore, symptoms of human strongyloidosis are related to the parasitic burden and to host factors [38,39]. In these individuals with hyperinfection due to immunosuppression, it is possible to diagnose parasitic forms by examining the secretions of bronchial lavage and alveolar fluid as well as peripheral blood and cerebrospinal fluid [40].

One main control measure for *S. stercoralis* infection is based on anthelmintic treatment; however, due to the possibility of hyperinfection in immunosuppressed individuals with fatal consequences, the development of an effective prevention measure is critical for control of this disease. The majority of studies regarding immunotherapeutic approaches against this parasite were based on the use of *Strongyloides* spp. L3i to obtain antigens that were recognized as being immunogenic and could be used in vaccines or by obtaining antibodies against specific parasite proteins that could be used for passive immunization. This article reviews the current progress and targets toward vaccine and passive immunization approaches for *Strongyloides* spp.

2. Immunotherapeutic approaches

Data were obtained from PubMed-NCBI (US National Library of Medicine, National Institutes of Health). The first article that studied a vaccine perspective for *Strongyloides* spp. was published in 1983 by Conder and Williams [41] and comprised an "immunization with infective larvae of *Strongyloides ratti* (Nematoda) exposed to microwave radiation". From 1983 to February 1986, there were no published articles in this area. For the present review, the inclusion criteria were established considering the keywords "*Strongyloides* spp."; 'vaccine' and "immunotherapy" for the past 30 years (from March 1986 through March 2016). As exclusion criteria; the articles that discuss the search for a better understanding of the immune response without analyzing immunotherapeutic strategies were disregarded of the results.

There were no articles obtained from 1986 to 2001 and from 2013 to 2016. Seven articles were obtained according to these search criteria, including the following: one article in 2002, one in 2004, one in 2005, one in 2010, one in 2011 and two in 2012. Vaccine strategies were conducted using different antigenic preparations derived from the total proteins of *S. stercoralis*, *S. venezuelensis* and *S. ratti* solubilized in deoxycholate (DOC-Ag) and using human IgG-specific antigens, recombinant proteins and DNA vaccines; passive immunization was performed using monoclonal IgM anti-HSP60 of *S. ratti*. Vaccine and passive immunization were applied with different adjuvants, and the challenge was performed by different inoculation routes in different animals (Tables 1 and 2).

Most vaccines studies for the control of *Strongyloides* spp. infection used DOC-Ag. Herbert et al. [42] used DOC-Ag from *S. stercoralis* L3i, eluted after affinity chromatography using IgG from DOC-immunized animals and characterized by molecular weight proteins of 80, 75, 61, 57, 43, and 32 kDa. The proteins were applied to aluminum hydroxide adjuvant and were able to induce protective immunity 5 days after infection at a rate of 83%, supporting the hypothesis of a strong participation of IgG in the protection of DOC-immunized mice. It was found that protective antibodies bound to the muscle and nerve cords of *S. stercoralis* L3i. It was also observed that IgG purified from the sera of animals immunized with DOC was able to transfer passive immunity to naive animals at a rate of 50% compared with total IgG, indicating that there are potential inhibitory components in whole sera removed in the process of purification. The proteins stimulated the production of IL-5 by splenocytes obtained from mice immunized with L3i and promoted eosinophil influx in animals immunized with DOC, showing that the immune protective response was characterized by the Th2 profile.

Kerepesi et al. [43] sought to highlight for the first time the possible transfer of human protective immunity to mice against *S. stercoralis* and to select these human IgG-specific antigens for vaccine purposes. The human IgG used in this study was able to detect antigens on the surface and internal components of the cuticle and