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Review article

Infection by *Schistosoma mansoni* during pregnancy: Effects on offspring immunity

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ABSTRACT

About 25 million Brazilians live in areas at risk of contracting the disease caused by the trematoda *Schistosoma mansoni*, the schistosomiasis mansoni. Although the adult parasites inhabit the blood vessels, probably the main element responsible for the pathology of the disease are the eggs, whose deposition in the liver results in formation of granulomas and hypersensitivity mediated by CD4 T cells. In the course of infection, the profile of T helper 1 (Th1) and Th2 cytokines released by immune cells is correlated with the extent of inflammation in the granuloma and with the disease severity. While a Th1 immune response favors the local inflammation and the disease progression, the Th2 immune response has protective character. Also during pregnancy, it is essential a fine adjustment of a Th1/Th2 in the maternal-fetal interface, which ensures the pregnancy progress with peculiar immune characteristics. In particular, the maternal exposure to antigens has been associated with their presence in fetal circulation. The exposure to intrauterine antigens can imply an immune tolerance of the fetus to such components. In turn, the transfer of antigens and antibodies from mother to offspring during breastfeeding is an important stage of maturation and capacitation of immune offspring in future infections against pathogens. This review aims to gather bibliographic data to assist in the understanding of immunological features printed on offspring of mothers infected with *S. mansoni*, which affect latter immune responses to related or unrelated antigens.

1. Introduction

1.1. Schistosomiasis

Schistosomiasis is a parasitic disease caused by trematodes of genus *Schistosoma*, which have different stages of development (adult worms, eggs, miracidia, sporocysts, cercaria and schistosomula), each with peculiar characteristics [1]. It is estimated that at least 200 million people in the world have schistosomiasis and that 42.1 million have been treated in 2012, of which 90% lived in Africa. The disease is prevalent in tropical and subtropical areas where live poor communities that have no access to safe drinking water and adequate sanitation. The trematoda *Schistosoma mansoni* is responsible for 70 million cases of schistosomiasis around the world and in Brazil, it is estimated to be responsible for infecting 2.8 million patients [2].

In its biological cycle, the helminth switches sexual and asexual reproduction stages. After the eggs reach the water collection the miracidia hatch and penetrate susceptible species of *Biomphalaria* — aquatic intermediate invertebrate hosts. Then, the miracidia lose their eyelashes and become primary sporocysts which originate secondary sporocysts by polyembryony. They migrate to the digestive glands, where each unit gives rise to numerous larvae-cercaria — by asexual reproduction. A single miracidia can generate more than 100,000 cercaria. The stage in the intermediate host can last from three to five weeks, after which the cercaria leave the host through the rupture of the seed coat of the shellfish and reach the water during the hottest hours of the day. Since they become free in the water, they actively swim until they are attracted to a definitive host, for example, human host [3].

To reach human cutaneous tissue, the cercaria attach themselves with the aid of their suction cups and actively penetrate the skin, which causes local irritation. After penetration, the larvae are called schistosomula. Noteworthy, although the cercaria may actively cross the skin, just a percentage of them can survive to dermatitis. Schistosomula are adapted to the physiological conditions of the inner environment and migrate through the subcutaneous tissue being passively taken by the

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bloodstream until the right side of the heart, lungs, pulmonary veins, left side of the heart, and intrahepatic portal system, where the schistosomula develop in adults. This course is conducted in approximately 7 days [4]. When males and females are present, the parasites mate and migrate to the venules of the superior hemorrhoidal plexus and the finer branches of the lower mesenteric veins draining the large intestine. The females produce and lay eggs in these localities, which pass from the lumen of the vessels to the lumen of the intestine causing an inflammatory reaction in the tissues involved, being finally released through feces. The first eggs are seen in the stool about 40 days after the definitive host infection. It is, therefore, the biological cycle of intestinal worms. The eggs can also stay in the host tissues and cause immune reactions [2].

The clinical manifestations of schistosomiasis are intestinal disorders, with the presence of blood in the stool, abdominal pain, splenomegaly, abdominal hypertension and possibly death [5]. The eggs of *S. mansoni* are eliminated in the feces of infected individuals or remain in the bloodstream, being dragged by the liver via portal vein, which establish and cause an inflammatory process and fibrous tissues surrounding the egg, resulting in a hepatic granuloma [6]. The eggs may still be scattered across various systems through circulation, causing other less frequent pathological forms, such as pulmonary vascular lesions or neurological dysfunctions by the deposition of eggs in the spinal cord [7–9].

1.2. Immune response to infection by S. mansoni

The immune system of infected hosts must recognize hundreds, if not thousands, of antigenic motifs expressed in the parasite along the various stages of its life cycle (cercaria penetrating, the schistosomula, the adult worms and the eggs). Many of these antigenic motifs are strong and easily detected by the humoral and cellular immune response. Likely experimental models, the morbidity during human schistosomiasis results from the immune stimulation by eggs chronically trapped in the tissues, formation of granulomas, and fibrosis [10]. The immune response is triggered by recognizing of PAMPs in surface of the eggs of *S. mansoni* adhered in the wall of the small intestine, liver or other organs [11]. The response mechanisms are initiated through the accumulation of polymorphonuclear leukocytes, with subsequent recruitment of macrophages and lymphocytes to the tissues where the eggs are deposited. In this reactive environment, the immune system employs efforts to eliminate the parasite infection. The immune response to the eggs of *S. mansoni* deposited in the tissues, especially in the liver, generates a hypersensitivity mediated by CD4 T cells [12].

The penetration of *S. mansoni* cercaria through the epidermis and the dermis causes an immediate hypersensitivity reaction with activation of components of innate immune response, including polymorphonuclear leukocytes, mononuclear cells and Langerhans cells, in addition to the local production of chemokines CCL3 and MIP-1a, and cytokines IL-1β, IL-6, IL-12p40 and IL-10 [13]. Four to five days after penetration, the influx of CD4 T lymphocytes and production of IL-12p40, IFN-γ and IL-4, can be observed, decreasing in the second week. In the passage through the lungs and liver, the schistosomula can cause outbreaks of arteritis and necrosis, likewise acute hepatitis and infiltration of neutrophils, lymphocytes, and eosinophils. The transformation of the schistosomula in adult worms occurs between 30 and 60 days after infection, coinciding with the onset of clinical manifestations of acute schistosomiasis [3].

The acute phase of infection is divided into two periods of evolution: the pre-patent (before the egg) and the post-patent (after the egg). In murine models, the response to infection with *S. mansoni* is manifested as a moderated Th1 response (in the pre-patent period) – until the 6th week of infection – followed by an exacerbated chronic response Th2 (post-patent) until the 9th week. Subsequently, the immune response acquires regulatory characteristics with the production of IL-10 and TGF-β [14,15]. Briefly, the Th1 immune response is polarized by the cytokine IL-12, produced by cells of innate immunity, being characterized by the production of large quantities of interferon gamma (IFN-γ) and tumor necrosis factor (TNF). These cytokines empower the innate immune cells to eliminate the parasite by stimulating the production of microbicides molecules, such as nitric oxide (NO), phagocytosis and formation of multinucleated giant cells. The immune response is polarized toward Th2 by the cytokine IL-4 and has a cytokine profile that includes IL-5, IL-6, and IL-13, mediating mainly activation of B lymphocytes and antibody production, while inhibits the synthesis of microbicides molecules in innate immune cells via arginase induction [16].

It is believed that the Th1 immune response promotes tissue injury and the clinical manifestations of the acute phase. In murine experimental model infected with *S. mansoni*, the balance between the expression of Th1 and Th2-types cytokines is correlated with the extent of inflammation in the granuloma and with the disease severity. In general, the Th2 immune response favors the presence of large granulomas, while the Th1 response is associated with minimal lesions [17]. The inflammatory mediators involved in the Th1 immune response will inhibit the formation of mediators of Th2 response and vice versa. Evidence supports that the maintenance and control of axis Th1/Th2 are critical for the formation of a protective granuloma without leading to excessive pathology during schistosomiasis mansoni [18]. IL-12-deficient mice infected with *S. mansoni* presented an intense Th2 response after infection, which culminates in mortality [19]. It demonstrates the protective character of Th1 response in this experimental model.

Studies of the immune response in cases of reinfection by *S. mansoni* demonstrated that, contrary to what has been observed in mice, the protective immune response in human infection is linked to Th2 immune response. The correlation among specific IgE, eosinophils and resistance to reinfection was observed during the infection by *Schistosoma* in epidemiological studies [20,21]. In contrast, susceptibility to infection has been associated with the production of IgG4 [20], which can act as a neutralizing antibody, inhibiting the action of IgE. Regarding the cytokines involved in immune response to human infection by *S. mansoni*, it is suggested that IFN-γ, as well as IL-10, is more often (but not exclusively) connected with the susceptibility to reinfection after treatment. Interestingly, the level of IL-10 correlates with increased production of IgG4, confirming the observations that responses mediated by IgG4 are linked to disease susceptibility. In a murine model of reinfection with *S. mansoni*, the blockade of IL-10 receptor is required to induce protection during the treatment [10].

The role of adult worms in immune response and pathology is not clear, although they eliminate antigens which could modulate the immune response. They also have developed different mechanisms to hide from the immune system. Among them, the ability of the parasite attach antigens of the vertebrate host to its surface, avoiding the recognition of their own antigens by the host immune system; the shedding of the tegumental outer layers, replacing them by new layers; and the release of proteases that cleave immunoglobulins and components of the complement system [22].

1.3. Immune response during pregnancy

Pregnancy is a paradoxical physiological condition because it implies in tolerance due the generation of a fetus antigenically distinct from the mother and that is not rejected by the maternal immune system from the moment of conception until the delivery. In this sense, CD4 T cells are essential for the establishment of a favorable environment for pregnancy, in which the Th1 and Th2 immune response are finely regulated. A Th2 response is essential for pregnancy and ensures the negative regulation of inflammatory mediators related to Th1 profile [23] (Fig. 1).

According to Wegmann and colleagues, cytokines of Th1 immune profile exert deleterious effect during pregnancy, inducing inflammatory reaction and placental necrosis, and may compromise the