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Schistosomiasis: An Association with Autoimmunity

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Abstract

The association between *Schistosomes* infection and autoimmunity has been studied extensively in the medical literature. Schistosomiasis might induce autoimmune activity by several mechanisms: molecular mimicry, production of pathogenic autoantibodies, polyclonal activation of B cells, altered self antigens**.** It has documented the protective effect of *Schistosomes* infection against immune-mediated diseases such as type 1 insulin-dependent diabetes mellitus, multiple sclerosis, and Crohn's disease. This protective effect mediated by Th2 immune response with production of IL-10 which able to inhibit the production of pro-inflammatory mediators such as interferon-γ (IFN-γ), tumor necrosis factor (TNF-α) and nitric oxide and mediate the control of autoimmune disease. Additionally, autoimmune mechanisms might have a role in the pathogenesis of schistosomiasis inducing granulomatous inflammation, glomerulonephritis and visceral fibrosis.

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Introduction

Schistosomiasis is a debilitating disease affecting approximately 600 million people in 74 developing countries, with 800 million, mostly children at risk [1]. It is caused by the platyhelminth worms of the genus *Schistosoma*, that live in the bloodstream of humans. Three species (*Schistosoma mansoni*, *Schistosoma haematobium* and *Schistosoma japonicum*) account for the majority of human infections. *S. mansoni* and *S. japanicum* reside in the mesenteric veins of the intestinal tract causing chronic hepatic and intestinal fibrosis [2]. While, *S. haematohium* worms are found mostly in the venules of the urinary tract causing urinary schistosomiasis manifested by hematuria, bladder calcification, kidney damage and increased risk of bladder cancer [3].

Autoimmune disease occurs when the body tissues are attacked by its own immune system, resulting in destruction of body tissue, abnormal growth of an organ, or changes in organ function. Examples of autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, type 1 insulin-dependent diabetes mellitus. The association between microbiological infection (bacterial, viral and parasite) and autoimmunity has been studied extensively in the medical literature. These infections can act as triggers inducing or promoting autoimmune disease in genetically predisposed individuals [4].

Parasitic Infections may promote the development of autoimmunity by molecular mimicry, epitope spreading, or bystander activation [5, 6]. Molecular mimicry is the concept that antigens of the microorganism closely resemble self-antigens and so when an infection occurs autoimmunity is also induced. Bystander activation may occur when the

immune response is non-specifically stimulated by the infection resulting in activation of autoimmunity in genetically susceptible individuals [7].

Schistosomiasis might induce autoimmune activity by several mechanisms: molecular mimicry, production of pathogenic autoantibodies, polyclonal activation of B cells, altered self antigens [8].

I. Protective effect of *Schistosomes* infection against immune-mediated diseases

Several investigators have documented the protective effect of *Schistosomes* infection against immune-mediated diseases [9, 10]. It is well known that the immune response during the acute phase of *S. mansoni* infection is characterized by a strong T-helper cells type 1 (Th1) inflammatory response with increased production of TNF-α and IFN-γ while in chronic phase the immune response is associated with T-helper cells type 2 (Th2) with elevated levels of interleukin (IL)-4, IL-5, and IL-10 and decreased levels of IFN-γ. This down modulation is mediated by *Schistosoma* eggs' antigen driven IL-10 production [11]. At the same time, the pathogenesis of autoimmune diseases mediated by Th1 immune response. IL-10 cytokine that results from immunomodulatory effects to *Schistosoma* infection able to inhibit the production of pro-inflammatory mediators such as IFN-γ, TNF-α and nitric oxide and mediate the control of autoimmune disease [12].

Experimental studies in mice suggested that infection with *S. mansoni* can protect against autoimmune diseases, including autoimmune encephalomyelitis, multiple sclerosis [13], Graves hyperthyroidism [14], type 1 diabetes and colitis [15-17]. Cooke et al. [15] observed that soluble extract of *S. mansoni* worm or egg completely prevented the onset of type 1 diabetes in genetically susceptible non-obese diabetic mice. Also, La Flammeet al. [13] demonstrated that infection with *S. mansoni* delays the onset of autoimmune encephalomyelitis, a multiple sclerosis like disease and prevents inflammation in the central nervous system. Attenuation of the clinical course of this autoimmune disease was followed by a reduction in the synthesis of pro-inflammatory mediators, such as IFN-γ, TNF-α and nitric oxide, by spleen and central nervous cells. It was found that *S. mansoni* ova immunization leads to production of IL-10, TGF-β and IL-4, by spleen cells in vitro, and decreased IFN-γ synthesis which has been shown to exacerbate multiple sclerosis [18]. Crohn's disease is also mediated by an active Th1 inflammatory response and it is characterized by dysmotility of the gut as a result of chronic intestinal inflammation. In the trinitrobenzesulfonic acid (TNBS) murine and rat model of colitis the colonic inflammation is due to an infiltration of over-IFN-γ-producing CD4+ T cells [19]. Concurrent infection with *S. mansoni* has been shown to significantly attenuate TNBS induced colitis in rats [20]. Moreover, Osada, [21] concluded that *S. mansoni* infection reduced the severity of autoimmune arthritis through systemic and local suppression of pro-inflammatory mediators, indicating the potential of parasite-derived materials as therapeutic agents against rheumatoid arthritis.

Additionally, it has documented the protective effects of *S. japonicum* infection on the development of collagen-induced arthritis, an animal model for human rheumatoid arthritis [9, 10].

II. Pathogenic effect of autoimmune responses in schistosomiasis

Most autoimmune disorders are caused by the involvement of self reactive immune cells such as autoantibodies, mononuclear phagocytes, auto-reactive T lymphocytes and plasma cells (autoantibody producing B cells). Autoantibodies can induce damage to the body by binding to self tissues, activating the complement cascade and inducing lysis and/or removal of cells by phagocytic immune cells. Self-antigen, autoantibodies and complement can combine to form injurious immune complexes that deposit in vessels or joints as is observed in systemic lupus erythematosus, inflammatory heart disease and arthritis [7].

The presence of autoantibodies has been reported during *Schistosoma* infections in man or in experimental models including anti-DNA, rheumatoid factor, anti-sperm, anti-lymphocyte, anti-collagen and anti-cardiolipin antibodies [22]. The presence of rheumatoid factor may represent non-specific polyclonal activation of B-cells.

Glomerulonephritis associated with immune complex deposition consisting of immunoglobulin, complement components and parasite antigens has been documented in patients with schistosomiasis. Immune complexes were found in renal tissue as well as in the circulation. Deposition of circulating soluble immune complexes (SICs) is suggested to account for the most common immunopathologic mechanism of glomerulonephritis. It was found that SICs and anti DNA antibodies are induced by antigens from *S. haematobium* eggs and may be involved in the pathology of urinary schistosomiasis. Arinola [23] found a significant correlation existed between severity of *S. haematobium* infection and SICs or auto-anti DNA antibodies. Also, distinct patterns of glomerular lesions, including membranoproliferative glomerulonephritis and focal segmental glomerulosclerosis, are associated with infection by *S. mansoni* or *S. japonicum*. Evidence suggests that immune complex deposition is the main mechanism underlying the different forms of schistosomal glomerulonephritis and that immune complex deposition may be intensified by portal hypertension [24]. Glomerular lesions are more severe and more common in hepatosplenic schistosomiasis than in hepatic cirrhosis, confirming the role of autoimmune mechanisms in schistosomal nephritis [25]. In addition, the severity of the glomerular lesions and proteinuria is correlated with the impairment of hepatic macrophage function [26]. This macrophage function may involve the clearance of circulating immune complexes and eventually the clearance of other nephritogenic factors. In addition, rheumatoid factor might participate in mononuclear phagocytic clearance of SICs by increasing the size of the complexes and possibly avoiding deposition in the glomerular basement membrane. Rheumatoid factor production might have a protective role in patients with schistosomiasis.

The pathologic hallmark of *Schistosoma* infection is a granulomatous inflammation surrounding *Schistosoma* eggs. Granuloma formation and fibrosis are the major causes of morbidity and mortality in association with schistosomiasis [27]. The formation of granulomas around schistosome eggs is mediated by $CD4^+$ T cells sensitized to soluble egg antigens [28]. Cytokines are important regulators of immune-inflammatory responses and play a major role in the regulation of fibrosis deposition and degradation. In the murine model of schistosomiais, type 1 cytokines such as IFN-γ and activated macrophages have been correlated with immunity. On the other hand, type 2-associated cytokines such as IL-4, IL-13 and IL-10 inhibit classical macrophage activation and have been implicated in granuloma formation and fibrogenesis around tissue-deposited eggs [29, 30]. IL-5 is responsible for the generation of eosinophils in these lesions and IL-4 for the IgE response. TNF-α may participate in the granuloma formation and evolution of the fibrotic tissue process while IFN-γ has a protective effect on severe fibrosis of the liver [31].

Autoimmune mechanisms might have a role in the pathogenesis of the visceral fibrosis in schistosomiasis. In mice infected with *S. mansoni*, autoantibodies and T-cells responsive to collagen have been reported. It is possible that collagen responsive T -cells release lymphokines which recruit inflammatory cells and stimulate fibroblasts to migrate and synthesize collagen. These cells might be important primarily in hepatic fibrogenesis in human [32]. Moreover, T-cells reactive with collagen in connective tissue diseases such as rheumatoid arthritis might have a role in inducing chronic inflammatory state and fibrosis formation. Also, Th2 cytokines and in particular IL-13 and the IL-13 receptors (IL-13Ra2) seem to play a key role in hepatic fibrogenesis associated with schistosome infection [33].

Conclusion

Schistosomes infection were found positively contributing in fight against the autoimmune diseases like type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis and encephalomyelitis by inducing the production of immune regulatory cytokines like IL-10, IL-4 and TGF β. At the same time, autoantibodies such as anti-DNA, rheumatoid factor, anti-lymphocyte, anti-collagen may play a role in the pathogenesis of schistosomiasis.

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