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*Review Article*

# Schistosome: Its Benefit and Harm in Patients Suffering from Concomitant Diseases

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Schistosomiasis is an important tropical disease affecting approximately 200 million people worldwide. Because of its chronicity and robust immunomodulatory activity, the effects of schistosomes on other diseases, such as allergies, autoimmunity, and infectious diseases, have been studied extensively in both epidemiological and experimental settings. In this paper, we summarize the beneficial and harmful effects of schistosomes. The importance of controlling schistosomiasis is also discussed.

## 1. Introduction

*Schistosoma* spp., blood flukes, are parasitic helminths found mainly in developing countries with a tropical or subtropical climate and affect 200 million people worldwide [1]. *Schistosoma mansoni*, *japonicum,* and *mekongi* harbor in veins of the portal system and lay eggs in the blood vessels. The deposition of numerous eggs in the intestines and liver results in intestinal and hepatic granulomatous lesions, fibrosis, portal hypertension, and hepatosplenomegaly. In contrast, *Schistosoma haematobium* mainly harbors in the venous plexus of the bladder and/or rectal venous plexus. This worm usually causes bloody urine but is also considered to have an etiological relationship with bladder cancer [2]. Because of the extensive distribution of schistosomes and morbidity due to egg deposition, researchers have been interested in the influences of schistosome infections on concomitant diseases [3]. As mentioned, *S. haematobium* is an important carcinogenic factor of bladder cancer although the worm itself does not have mutagenic activity [4]. This parasite is also suggested to be a risk factor for the transmission of HIV [5]. These effects are attributable to pathological lesions caused by the parasites. On the other hand, most helminthic parasites including schistosomes are known to induce robust Th2-polarization. Especially in schistosome infections, egg deposition in the host tissues was reported to be the major stimulus of Th2 responses [6], and egg proteins (e.g., omega-1, IPSE, and peroxiredoxin) are involved in the Th2-biasing activity [7–11]. In addition, schistosome eggs have immunomodulatory potential inducing the alternative activation of macrophages [12] and regulatory T-cell expansion [13]. Because of its robust systemic Th2-inducing and immunomodulatory ability, this worm has been studied most extensively for its bystander effects on various immunological phenomena *in vivo*. In this paper, we summarize the effects of a concurrent infection of schistosomes on immunological disorders and parasitic/microbial infections.

## 2. Effects of Schistosomes on Immunological Disorders or Infectious Diseases in Mice and Humans

*2.1. Allergy.* Effects of helminths (including schistosomes) on allergic diseases have been studied extensively in both experimental and epidemiological settings. In experimental asthma or airway hypersensitivity models, schistosome infections and antigen administrations have been consistently shown to protect the animals from the diseases (Table 1). In most studies on the antiasthmatic effects of schistosomes, cellular infiltration (including eosinophils) into bronchoalveolar lavage fluid (BALF) was diminished and simultaneously IL-4, IL-5, and IgE levels were reduced. In contrast, an increase in Treg cells and augmentation of IL-10 production

were observed. Fallon and Mangan [14] designated this kind of Th2 response (Treg dominant and IL-10 dominant) a "modified Th2 response" as opposed to the conventional "allergic Th2 response." They demonstrated that in infected mice, IL-10-producing $CD1d^{high}$ B cells induce Treg cells and consequently ameliorate allergic airway inflammation [15]. In the study, IL-10 was indispensable to the effects of schistosomes. The authors also showed the importance of B cells, and IL-10 in the suppression of systemic anaphylaxis by schistosomes [16]. Smits et al. [17] found that in adoptive transfer experiments, spleen cells (especially B cells and $CD4^+$ T cells) from chronically infected mice could confer protection against pulmonary infiltration by white blood cells, especially eosinophils. In addition, administration of anti-IL-10R antibody cancelled out the effects of the cell transfer. These studies seem to support the critical importance of B cells, Treg cells and IL-10 in schistosome-induced protection against airway allergic inflammation. In studies by another group, however, IL-10 signaling was not essential for the antiallergic immunomodulation by schistosomes [18, 19]. The reason for this discrepancy is unclear, but as the authors point out, other immunomodulatory factors may be able to compensate the absence of IL-10 [19].

Antiallergic effects of schistosomes have also been demonstrated in humans. In a study in Brazil, both asthmatic symptoms and skin reactivity to indoor allergens were reduced in *S. mansoni*-infected asthmatics compared to non-infected individuals [42]. In another study, higher expression levels of HLA-DR, IL-10R (in monocytes), CTLA-4 and CD40L (in $CD4^+$ T cells) were observed in *S. mansoni*-infected asthmatics [43]. According to that paper, the main sources of IL-10 were monocytes and Treg cells. A meta-analysis of current parasite infections and atopy [44] revealed that schsitosomiasis was protective against allergic skin sensitization as well as some other helminths (*Ascaris lumbricoides*, *Trichuris trichiura*, hookworm). The same research group also reported a meta-analysis of interrelationships between helminths and asthma [45]. Hookworm infections were shown to be protective, but no beneficial effect was found for schistosome infections, probably due to the insufficient number of studies (only two). Collectively, anti-asthmatic effects of schistosomes have been confirmed in animal models and suppressive effects on allergic skin reactivity have been confirmed in humans. However, more epidemiological (especially intervention) studies are necessary to conclude whether schistosome infections have beneficial or detrimental effects on asthmatic patients.

*2.2. Autoimmunity.* Autoimmune disorders had been considered Th1-mediated diseases for a long time. As the Th2-biasing ability of parasitic helminths and consequent downregulation of Th1 responses have been well known, antiautoimmune effects of such parasites had been attributed to the downregulation of Th1 responses in infected animals. However, some major autoimmune diseases are now considered to be dependent on Th17, a newly found pathogenic T-cell subset that mainly produces IL-17 [46]. With this finding, the antiautoimmune properties of helminths have been revisited. In recent years, downmodulation of Th17 responses by parasitic helminths has been reported [24, 36, 47, 48]. If the suppressive activity on both Th1 and Th17 is common to parasitic helminths, helminths may become ideal sources of drug screening for treatment of autoimmune disorders. That is because both T-cell subsets are involved in the pathogenesis of some autoimmune diseases [49]. Moreover, the unstable nature of Th17 [49] reinforces this idea.

As summarized in Table 1, schistosomes suppress various autoimmunity models in rodents. An upregulation of IL-4 and downregulation of IFN-$\gamma$ responses are almost commonly observed. In addition, responses of IL-17 and/or TNF-$\alpha$, both of which play pathological roles in autoimmune arthritis [24, 26] and hapten-induced colitis [36, 40], were also downregulated by schistosome infections. Moreover, our study in mice with collagen-induced arthritis (CIA) revealed that the disease-associated local augmentation of bone-destructive cytokines (i.e., IL-6 and RANKL) was abrogated in infected animals [24]. These results indicate that schistosomes have suppressive effects on both Th1/Th17 and inflammatory cytokines. In addition, schistosomes suppress other pathogenic mediators such as autoreactive antibodies. Schistosomes decreased levels of anti-insulin IgG [30], anti-TSHR IgG2a [41], and anticollagen IgG [24, 25]. This effect was also observed in humans, as Mutapi et al. recently reported that *S. haematobium* infection intensity was inversely related to autoreactive antinuclear antibody (ANA) levels [50]. The authors also found that antihelminthic treatment increased ANA levels. However, Rahima et al. reported the presence of antinuclear antibodies in *S. mansoni*-infected mice and that sera from patients with systemic lupus erythematosus (SLE) reacted with cercarial antigens [51], suggesting that schistosomes trigger some kinds of autoimmunity. In conclusion, large-scale cross-sectional studies may be necessary to reveal the interrelationships between schistosomiasis and autoimmunity.

It is reasonable to hypothesize that the downmodulation of proinflammatory cytokines and pathogenic antibodies is involved in the antiautoimmune activity of schistosomes, at least partially. As regulatory cytokines are known to downregulate proinflammatory cytokines and pathogenic antibodies, it is important to determine the "essential" regulatory cytokines in each disease models for elucidation of suppressive mechanisms. For this purpose, it is necessary to perform experiments of cytokine neutralization with specific antibodies or experiments using gene-targeted animals. In Th1/Th17-dependent autoimmunity, IL-4, the key cytokine of Th2 responses, may be responsible for the alleviation of the disease symptoms. For instance, by using gene-targeted mice, STAT6 (a key signaling molecule in the response to IL-4 and IL-13) was shown to be indispensable to the *S. mansoni* egg-induced suppression of experimental autoimmune encephalomyelitis (EAE) [28] and of TNBS-induced colitis [35]. In contrast, IL-4 and IL-13 were dispensable to the suppression of DSS-induced colitis (Th2 cytokine dominant and macrophage-mediated colitis) by male worms of *S. mansoni* [39]. In the same study, authors demonstrated that IL-10 and TGF-$\beta$ were also dispensable to the anticolitic effects of schistosome, by using specific antibodies against IL-10R and TGF-$\beta$. IL-10 was not a crucial regulatory cytokine

Table 1: Suppressive effects of schistosome on experimental allergy and autoimmunity in rodents.

| Category of animal models | Diseases | Schistosome | Treatment | Proposed mechanisms | Refs |
|---|---|---|---|---|---|
| Allergy | Asthma/Airway hypersensitivity or inflammation | Sm | Infection (male) | IL-5 ↓, IL-10↑ | [20] |
| | | | Infection, Egg i.p. | IL-4 ↓, IL-5 ↓, IgE ↓, Treg↑, Independent of IL-10 | [18] |
| | | | Infection (chronic) | B cells and $CD4^+$ T cells, Dependent on IL-10 | [17] |
| | | | Infection and Adoptive transfer | IL-10-producing $CD1d^{high}$ B cells → Treg↑ | [15] |
| | | | Sm22.6, PIII | IL-4 ↓, IL-5 ↓, IgE ↓, Treg ↑, independent of IL-10 | [19] |
| | | Sj | Infection (male, mixed) | IL-4 ↓, IL-5 ↓, IgE ↓, IL-10 ↑ | [21] |
| | | | Infection and adoptive transfer | DC → IL-4 ↓, IL-5 ↓, IL-10 ↑ | [22] |
| | | Sj | SEA, Eggs (i.p., p.o.) | Treg↑ | [23] |
| | Systemic anaphylaxis | Sm | Infection | IL-10-producing B cell | [16] |
| Autoimmunity | Collagen-induced arthritis (CIA) | Sm | Infection | IL-17 ↓, TNF-$\alpha$ ↓, IL-6 ↓, RANKL ↓, anticollagen IgG ↓ | [24] |
| | | Sj | Infection | IL-4 ↑, anticollagen IgG ↓ | [25] |
| | Adjuvant-induced arthritis (AIA) | Sj | Sj16 i.p. | TNF-$\alpha$ ↓, IL-1$\beta$ ↓, NO ↓, IL-10 ↑ | [26] |
| | Experimental autoimmune encephalomyelitis (EAE) | Sm | Infection | IL-12p40 ↓, IFN-$\gamma$ ↓, TNF-$\alpha$ ↓, IL-4 ↑ | [27] |
| | | | Egg i.p. | IFN-$\gamma$ ↓, IL-4 ↑, TGF-$\beta$ ↑, IL-10 ↑, dependent on STAT6 | [28] |
| | | Sj | SEA i.p. | IFN-$\gamma$ ↓, IL-4 ↑ | [29] |
| | Type 1 diabetes in NOD mice | Sm | Infection, Egg i.p. | Inhibition of Ab class switch (anti-insulin IgG ↓) | [30] |
| | | | SEA, SWA i.p. | NKT ↑ | [31] |
| | | | SEA i.p. | Treg ↑ | [32] |
| | Streptozotocin-induced diabetes (multiple low dose) | Sm | Infection | | [33] |
| | TNBS-induced colitis | Sm | Infection | IL-2 ↑, IL-4 ↑ | [34] |
| | | | Egg i.p. | IFN-$\gamma$ ↓, IL-4 ↑, dependent on STAT6 | [35] |
| | | | SWA i.p. | IFN-$\gamma$ ↓, IL-17 ↓, TGF-$\beta$ ↑, IL-10 ↑ | [36] |
| | | Sj | Egg i.p. | IFN-$\gamma$ ↓, IL-4 ↑, IL-10 ↑, Treg ↑ | [37] |
| | | | Egg i.p. | IFN-$\gamma$ ↓, IL-4 ↑, TLR4 ↓ | [38] |
| | DSS-induced colitis | Sm | Infection (male) | Dependent on macrophages, independent of Treg, IL-10, IL-4, IL-13 and TGF-$\beta$ | [39] |
| | | | Infection | TNF-$\alpha$ ↓ | [40] |
| | Grave's hyperthyroidism | Sm | Infection | Anti-TSHR IgG2a ↓ | [41] |

↓: down-regulation, ↑: up-regulation, Sm: *S. mansoni*, Sj: *S. japonicum*.

also in other helminthic infections, that is, piroxicam-induced colitis was suppressed by *Heligmosomoides polygyrus* [48], and EAE was suppressed by *Fasciola hepatica* [47], both in IL-10-deficient mice. In the latter study, however, TGF-$\beta$ was shown to be responsible for anti-EAE effects of the worms [47]. Taken together, the involvements of IL-4, IL-10, and TGF-$\beta$ in antiautoimmune effects of helminths depend on the disease models and helminth species. Further investigations using various autoimmunity models and gene-targeted animals would be necessary for comprehensive elucidation of the suppressive mechanisms by regulatory cytokines in schistosome infections.

Regarding the participation of regulatory cell populations in schistosome-induced antiautoimmune effects, Treg cells, macrophages, and other types of cells (e.g., NKT cells) have been suggested. Although Treg cell population is known to expand by schistosome infection or SEA administration [13, 32], their involvement seems to depend on the disease

models. For instance, Cooke et al. have been studying antidiabetic effects of *S. mansoni* using a spontaneous T1D model (NOD mouse) [30], and they demonstrated that Treg cells were essential in the suppression of T1D by cell transfer experiments [32]. The authors (Zaccone et al.) showed that splenocytes from nontreated NOD mice successfully transmitted diabetes into NOD/SCID recipients, whereas splenocytes from SEA-treated NOD mice had a reduced capacity to transmit diabetes. They also showed that SEA had various immunomodulatory effects on dendritic cells (DCs), macrophages, and T cells of NOD mice [12, 32]: for example, increased expressions of TGF-$\beta$, galectins, PD-L1, and so forth. In contrast to this T1D model, Smith et al. showed that depletion of Treg cells did not influence the suppressive effect of schistosomes on DSS-induced colitis [39]. They demonstrated that macrophages (but NOT alternatively activated macrophages) played an essential role in the amelioration of the colitis.

In some of the studies in Table 1, the injection of eggs or SEA was not effective [27, 39, 40]. Likewise, in our study of CIA, SEA injection was not effective [52]. Taken together with findings that mice infected with male worms become resistant to DSS-induced colitis [39], egg-derived substances are not sufficient to explain all of the immunomodulatory activities of schistosomes. Indeed, injection of soluble worm antigens (SWAs) could prevent T1D in NOD mice [31] and TNBS-induced colitis [36]. Therefore, differential effects of worms and eggs should be further elucidated for a precise understanding of the immunomodulatory mechanisms of schistosomes. In addition, further studies on differences between single-sex infections and mixed-sex infections may be necessary.

*2.3. Parasitic Infections.* In tropical developing countries, infections with multiple microbes/parasites are common. Consequently, the immune responses and/or pathological lesions caused by one pathogen may affect the outcome of other infections. Therefore, influences of parasitic infections on concomitant diseases have been studied. In this section, we focus on the effects of schistosomes on other parasitic infections. Malaria is the world's deadliest and most widely distributed parasitic disease. Consequently, there are more than a few experimental studies on the interrelationships between schistosomiasis and malaria (Table 2). The influence of schistosome infections depends on the species of the malarial parasites and mouse strains used in the experiments. For instance, in CBA/Ca mice, *S. mansoni* protected against *P. chabaudi* infection, worsened *P. yoelii* infection, and had no effect on *P. berghei* infection [53]. Even when the same parasite, *P. chabaudi,* was used, schistosomes exacerbated the parasitemia and mortality in C57BL/6 mice but ameliorated the outcome in A/J mice [54, 55]. Although these complicated outcomes should be taken into consideration, in general, schistosome infections seem to exacerbate rodent malaria, that is, increase of parasitemia, mortality, and hepatosplenomegaly [56]. Detrimental effects of schistosome infections on malarial outcome are also reported in humans [57, 58]. In Kenyan school children, even a light *S. mansoni* infection was shown to exacerbate hepatosplenomegaly of malarial patients [57]. In a study in Senegal, heavy *S. mansoni* infections significantly increased the incidence of malarial attacks [58]. However, the modification of antibody responses by concomitant schistosomiasis is controversial [59, 60]. The mechanism responsible for the exacerbation (or amelioration) of malaria is clear in neither mice nor humans. Helmby et al. [54] suggested diminished production of TNF-$\alpha$ in schistosome-infected mice to have contributed to the increase in parasitemia of *P. chabaudi*. Yoshida et al. extensively analyzed possible mechanisms of protective effects of schistosomes against *P. chabaudi* in A/J mice [55]. They observed an enhanced Th1 response to *P. chabaudi* in schistosome-infected mice and that an anti-IFN-$\gamma$ antibody abrogated the schistosome-induced protective effect against *P. chabaudi.* As monoinfection with *S. mansoni* induced a Th2-dominant response, upregulation of IFN-$\gamma$ seemed to derive from the mixed infections of both parasites. They also observed the upregulation of iNOS gene expression in spleen from mice with mixed infections, suggesting an increase of splenic nitric oxide production to have contributed to the protection from *P. chabaudi.* Although the mechanism of the exacerbation of rodent malaria by schistosome is yet to be sufficiently analyzed, Treg cells have been shown to play an important role in the exacerbation of *P. yoelii* infection by preceding *H. polygyrus* infection [61]. Likewise, the induction/expansion of Treg cells by schistosome might be involved in the increased susceptibility to rodent malaria. The Th1 immune response protects against malarial parasites, but it also plays pathological roles in malaria, especially cerebral malaria [62]. Thus, schistosome as a representative Th2-biasing helminth is expected to suppress brain pathology. Indeed, in a model of cerebral malaria using mice infected with *P. berghei* ANKA, *S. mansoni* reduced the incidence of cerebral malaria and delayed death [63]. Moreover, the administration of IPSE/alpha-1, a Th2-inducing schistosomal egg protein [9, 10], also delayed death. Bucher et al. reported that brain pathology was reduced in schistosome-infected mice although they did not observe any beneficial effect on mortality [64].

Influence of schistosomes on other protozoan infections has also been investigated (Table 2). Regarding *Leishmania major*, reports vary, with Yoshida et al. finding no effects of schistosome on the outcome of *L. major* infection [67], and La Flamme et al. reporting an exacerbation of experimental leishmaniasis [68]. The reason for the discrepancy is not clear but might be intensity of the *S. mansoni* infection (20 cercariae in the former versus 70 cercariae in the latter). In the case of *L. donovani*, schistosome-preinfected mice failed to control growth of the protozoa in the liver [70]. In the coinfected mice, hepatic egg granulomas were shown to provide a favorable microenvironment for the growth of the amastigotes. Likewise, *S. mansoni* exacerbated *Trypanosoma cruzi* infection [71] and *Toxoplasma gondii* infection [72]. In general, schistosome infections seem to be detrimental to animals infected with protozoan parasites.

In marked contrast to that for protozoan parasites, protective immunity against intestinal helminths is usually Th2 dependent. Therefore, the Th2-dominant environment

Table 2: Effects of schistosome on other parasitic infections in rodents.

| Category | Parasites | Schistosome | Mouse strain | Effects | Refs. |
|---|---|---|---|---|---|
| Malaria | *Plasmodium berghei* | Sm | CBA/Ca | No effect | [53] |
| | *Plasmodium berghei* ANKA | Sm | Swiss albino | Parasitemia ↑, mortality ↑ | [65] |
| | *Plasmodium berghei* NK65 | Sm | BALB/c | Parasitemia ↑, mortality ↑ | [66] |
| | *Plasmodium chabaudi* | Sm | CBA/Ca | Parasitemia ↓ | [53] |
| | *Plasmodium chabaudi* AS | Sm | A/J | Mortality ↓ | [55] |
| | | | C57BL/6 | Parasitemia ↑, mortality ↑ | |
| | | Sm | C57BL/6 | Parasitemia ↑ | [54] |
| | *Plasmodium yoelii* | Sm | CBA/Ca | Parasitemia ↑ | [53] |
| | | Sm | BALB/c | Parasitemia ↑, mortality ↑ | [56] |
| Cerebral Malaria | *Plasmodium berghei* ANKA | Sm | ICR HSD | Cerebral malaria ↓ | [63] |
| | | Sm | C57BL/6 | Brain pathology ↓, no effect on mortality | [64] |
| Other protozoan infections | *Leishmania major* | Sm | BALB/c | No effect | [67] |
| | | | C57BL/6 | No effect | |
| | | Sm | C57BL/6 | Parasitemia ↑, lesion resolution delayed | [68] |
| | *Leishmania mexicana* | Sm | Outbred | Incubation period shortened | [69] |
| | *Leishmania donovani* | Sm | C57BL/6 | Parasitemia ↑ | [70] |
| | *Trypanosoma cruzi* | Sm | Albino | Parasitemia ↑, mortality ↑ | [71] |
| | *Toxoplasma gondii* | Sm | Albino | Mortality ↑ | [72] |
| Helminthic infections | *Hymenolepis diminuta* | Sm | NMRI | Expulsion ↑ | [73] |
| | *Strongyloides venezuelensis* | Sm | C57BL/6 | Migration ↓ | [67] |
| | | Sj | C57BL/6 | Migration ↓, expulsion ↑ | [69] |
| | *Trichuris muris* | Sm | AKR | Expulsion ↑ | [74] |

↓: downregulation, ↑: upregulation; Sm: *S. mansoni*, Sj: *S. japonicum*.

produced by schistosomes can be expected to protect against intestinal helminths. Indeed, as summarized in Table 2, schistosome infections protected mice from intestinal helminths. Likewise, in a human study in Brazil [75], *S. mansoni* egg counts were inversely correlated with *A. lumbricoides* and *T. trichiura*. (One exception was *Ancylostoma,* which was positively correlated with schistosome infections). Although protection against intestinal helminths is commonly observed in experimental settings, the mechanisms differ in each case. For instance, protection against a lung-migratory parasite, *Strongyloides venezuelensis*, mainly involved eosinophil-mediated killing of larvae in the lungs [76]. In addition, intestinal mucosal mastocytosis induced by *S. japonicum* infection rendered mice resistant to harboring of adult worms [76]. Antigen cross-reactivity between schistosomes and *S. venezuelensis* [67, 76] may have also contributed to the protection. In contrast, in the case of *Hymenolepis diminuta* and *Trichuris muris* (nonmigratory intestinal helminths), the protection seems to be dependent on accelerated expulsion from the intestines [73, 74]. Overall, schistosome infections appear to be beneficial to animals infected with intestinal helminths.

*2.4. Bacterial Infections and Vaccinations.* Prolonged bacteremia in schistosomiasis patients was first reported more than 50 year ago, and the relationship between enterobacteria infections and schistosomiasis has been long studied [3]. The prolonged enterobacterial infection is referred to "prolonged septicemic enterobacteriosis." The schistosome-induced exacerbation of enterobacterial infections has also been observed in experimental settings [77, 78]. As most studies were conducted before the "molecular immunology age," the mechanisms of exacerbation of bacterial infections have not been sufficiently elucidated. However, the mechanisms are likely similar to those responsible for the schistosome-induced increase in susceptibility to protozoan parasites, that is, a reduction in Th1-dependent protective immunity as a consequence of augmented Th2 responses. Indeed, a Th1-inducing protozoan parasite, *L. donovani,* did not affect the growth of *Salmonella paratyphi* A in infected hamsters [78]. Moreover, impairment of the bactericidal function of macrophages from schistosome-infected mice was reported [79]. In addition to the immunomodulation by schistosomes, there are direct schistosome-bacteria interactions providing worm bodies as foci for bacterial multiplication [3, 80, 81]. Another considerable influence of schistosomes on bacterial infections is a reduction in vaccine efficacy. The *Mycobacterium bovis* BCG-induced protective response against *Mycobacterium tuberculosis* in mice was reduced by *S. mansoni* infection [82]. The authors also reported increased susceptibility to intravenous BCG

inoculations and lung pathology in *S. mansoni*-infected mice [83]. In these studies, decrease in IFN-$\gamma$ and nitric oxide in response to PPD were observed.

*2.5. Viral Infections and Vaccinations.* As hepatotropic viruses, that is, hepatitis B virus (HBV) and hepatitis C virus (HCV), cause liver cirrhosis during chronic infections, the synergistic exacerbation of hepatic pathology is expectable outcome of concurrent infections of HBV/HCV and schistosomes. Because of a lack of suitable animal models for infections of these hepatotropic viruses, major findings in schistosome-HBV/HCV coinfections have been obtained from epidemiological studies. Regarding HBV, schistosomiasis (especially the severe hepatosplenic form) was correlated with a higher frequency of HBV infection [3, 84, 85]. This observation could be explained by an increased susceptibility to HBV caused by schistosome infections. On the other hand, there are reports of no relationship between schistosomiasis and HBV [86, 87]. In addition, experiments with animals do not support increased susceptibility to HBV in schistosomiasis. Some evidence comes from an experiment using woodchucks infected with both schistosomes and woodchuck hepatitis virus (WHV) [88]. As HBV and WHV belong to the same family (family Hepadnaviridae), a concurrent infection by schistosomes and WHV in woodchucks is a good model of concurrent infections of schistosomes and HBV in humans. The authors reported no impact of the schistosome infection on WHV serum markers. Another paper on HBV transgenic mice [89] reported an inhibition of HBV replication during schistosome infection. In that study, the antiviral effects of schistosomes were attributed to IFN-$\gamma$ and nitric oxide. Overall, it seems premature to conclude the presence of certain positive or negative effects of schistosomes on HBV infection. Regarding HBV vaccines (both serum derived and recombinant), they were immunogenic in schistosomiasis patients although reduced responses to vaccination were observed in hepatosplenic schistosomiasis [90–92].

In contrast to the controversial effects on HBV infections, detrimental effects of schistosomes on HCV infections have been clearly demonstrated, that is, schistosomes weaken anti-HCV immune responses and worsen liver disease. According to studies in Egypt, patients with coinfections were characterized by a more advanced liver pathology, greater viral burden, higher levels of anti-HCV antibodies, and progression to chronic hepatitis [93–95]. Moreover, schistosomiasis was shown to be inversely correlated with HCV-specific $CD4^+$ T cells, $CD8^+$ T cells, and/or Th1 cytokine responses [95–100]. In addition to the modulatory effects of schistosomes on HCV-specific immune responses, SEA of *S. mansoni* [101] and *S. haematobium* [102] were shown to enhance *in vitro* viral replication in a hepatoblastoma cell line (HepG2) and peripheral blood mononuclear cells (PBMCs), respectively. Likewise, in other viral infections, schistosomes were shown to suppress specific CTL and cytokine responses and to prevent viral clearance [103–107]. It is interesting that the granulomas in *S. mansoni*-infected mice provide a microenvironment suitable for viral expansion [107], as in the case of a hepatic infection with the protozoan parasite *L. donovani* [70].

## 3. Concluding Remarks

Based on the experimental and epidemiological findings reviewed here, it can be concluded that schistosome infections are generally beneficial to patients with intestinal helminth infections and detrimental to patients with bacterial, viral, or protozoan infections. In most tropical or subtropical countries where schistosomiasis is endemic, more serious infectious diseases (e.g., HIV/AIDS, tuberculosis, and malaria) are also endemic. Therefore, control of schistosomiasis (especially infections of *S. mansoni* and *S. haematobium*) has been given low priority compared to control of such infectious diseases. However, if the detrimental bystander effects of schistosomes on concomitant bacterial, viral, or protozoan infections are properly considered, the importance of controlling schistosomiasis should be more emphasized.

In 2002, J. F. Bach summarized epidemiological trends of allergic and autoimmune diseases during recent several decades in developed countries [108]. According to the paper, the prevalence of the immunological disorders such as asthma, T1D, multiple sclerosis (MS), and Crohn's disease (CD) was increasing, whereas the prevalence of infectious diseases such as rheumatic fever, hepatitis A, tuberculosis, mumps, and measles was decreasing. These phenomena may be explained by the "hygiene hypothesis" in which microbial and helminthic infections prevent immunological disorders. Along with this hypothesis, schistosome infections are expected to prevent or alleviate symptoms of immunological disorders. According to the experimental studies until now, antiallergic and antiautoimmune effects of schistosomes are also plausible in humans. However, schistosomes could not be directly used for therapeutic treatment because of their pathogenicity. Instead, purified immunomodulatory products or recombinant proteins could be tested for clinical use. Indeed, considerable numbers of helminths' products have been shown to protect against experimental immunological disorders [109]. The immunomodulators exert their effects via Toll-like receptors (TLRs) and/or C-type lectin receptors (CLRs) [109]. Taken together with the finding that systemic administration of TLR agonists could prevent experimental autoimmunity and allergy [110], appropriately synthesized TLR agonists may be able to mimic or replace the prophylactic or therapeutic effects of schistosomes.

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