



Review article

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## Schistosomiasis with special references to the mechanisms of evasion

Nawras M. El-Saghier Mowafy<sup>1,2</sup>, Ekhlas Hamed Abdel-Hafeez<sup>1\*</sup><sup>1</sup>Department of Medical Parasitology, Faculty of Medicine, Minia University, Minya 61519, Egypt<sup>2</sup>Department of Medical Parasitology, College of Medicine, Umm Al-Qura University, Makkah, KSA

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### ABSTRACT

Schistosomiasis is a disease caused by infection with *Schistosoma* spp. It affects 200 million people worldwide, especially in the developing countries. There are five known species of *Schistosoma* which currently infect humans in various geographical locations. Infection with *Schistosoma* spp. leads to two forms of the disease: acute and chronic. Chronic infection can affect various organs within the human body including the brain, lungs, gut and the reproductive organs, which leads to neuroschistosomiasis, pulmonary schistosomiasis, hepatointestinal schistosomiasis and urinary genital schistosomiasis, respectively. All *Schistosoma* spp. have a common denominator that they have the ability to infect, invade and evade the host's immune mechanism. *Schistosoma* sp. is a very complex organism that requires two hosts, mollusk and mammalian, to survive, propagate and complete its life cycle. Hence, it has developed specific immune evasion mechanisms for each of them. Once *Schistosoma* sp. has infected and established itself within its mammalian host as an adult worm, it evades the immune mechanism of that host. However, the antigens released by the eggs can elicit an immune response with formation of granuloma around eggs. Granuloma formation is the main characteristic lesion in schistosomiasis, which in the liver can cause hepatomegaly in hepatointestinal schistosomiasis. This paper will summarize various immune responses against the parasite as well as varieties of strategies which developed by the *Schistosoma* spp. to persist within human hosts.

## 1. Introduction

*Schistosoma* is a name derived from the Greek words (*schisto* means split and *soma* means body), because the body of male appears splitting longitudinally to produce a canal. *Schistosoma* is one of a trematoda but with separate sexes. Male is broader than the female and its lateral borders are curved ventrally forming long groove called gynaecophoric canal in which the female is held[1].

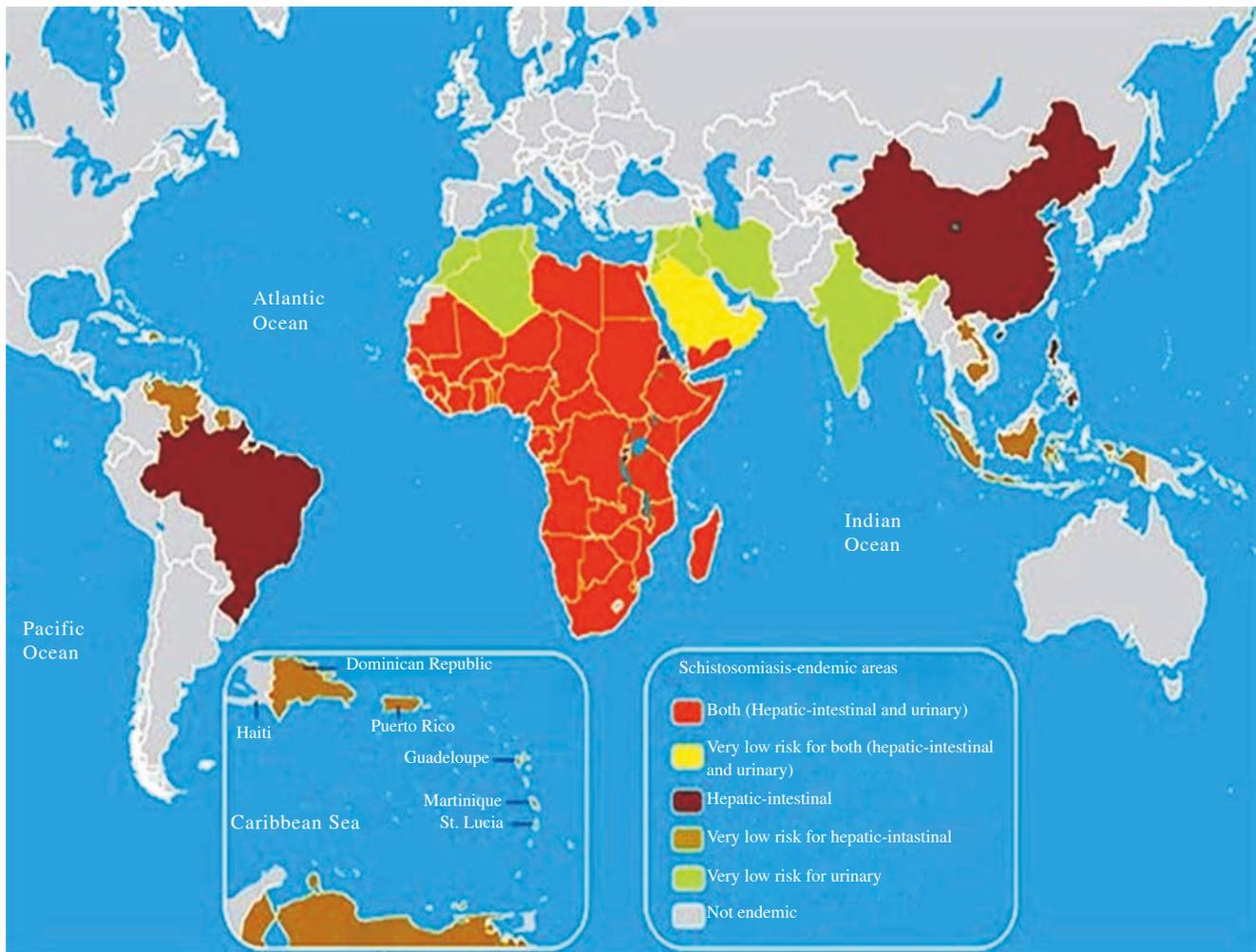
Schistosomes were formerly called bilharzia before Dr. Theodor Bilharz observed the worm firstly in the mesenteric veins of an Egyptian patient in 1851. The disease caused by this parasitic infection called bilharziasis or schistosomiasis. The disease is also called snail fever after its intermediate host, the fresh water snail[2]. Eggs of *Schistosoma haematobium* (*S. haematobium*) have been found in the renal pelvis of an Egyptian mummy dating back to the time of the 20th Dynasty (1250 to 1000 BC). *Schistosoma* antigens have been also identified by ELISA in Egyptian mummies of the Predynastic period (3100 BC)[3]. Schistosomiasis is a chronic parasitic infection which has been prevalent in the world for over

5000 years. It is responsible for nearly 280000 deaths per year with 200 million people worldwide being infected[2,4-8]. The geographical distribution of different species was shown in Figure 1.

## 2. History

Theodore Maximilian Bilharz (1825–1862), the German pathologist who was the first person describing schistosomiasis in humans. Autopsies had been done on infected Egyptian patients. He discovered male and female *Schistosoma* worms in portal system and bladder. Moreover, he described the eggs with their terminal projection. He named the worm Distomum (*S. haematobium*) [9,10]. In 1847, Yoshinao Fujii (1818–1895) was the first person who described the symptoms of schistosomiasis in Japan. He was a practitioner of Chinese medicine who worked in the rice fields in the Katayama region of Japan. Yama meant mountain and referred to an isolated hill in the middle of surrounding low-lying wet rice fields. The villagers who worked in them developed a rash on their legs and followed by fever, diarrhea, and bloody stools. Even today, these early acute symptoms are still known as Katayama fever. Many of his patients eventually became emaciated, developed ascites and leg edema, and then died. Dr. Fujii suspected that something in the water was causing the disease and wrote about the illness, hoping that a cause could be found through the

\*Corresponding author: Ekhlas Hamed Abdel-Hafeez, Department of Medical Parasitology, Faculty of Medicine, Minia University, Minya, 61519, Egypt.  
Tel: 01095796664  
E-mail: ekhlasha@yahoo.com



**Figure 1.** Diagrammatic representation of the geographical distribution of different species.

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analytical methods of “Western medicine”[9]. On the other hand, Manson in 1902 discovered eggs with lateral spines in the faeces of a West Indian patient and recognized this second species of human schistosomiasis. It was therefore named *Schistosoma mansoni* (*S. mansoni*)[1]. There are two major forms of schistosomiasis: intestinal and urogenital forms. These are caused by five main species of blood fluke as shown in Table 1[11].

**Table 1**

Parasite species and geographical distribution of schistosomiasis.

Type	Species	Geographical distribution
Intestinal	<i>S. mansoni</i>	Africa, the Middle East, the Caribbean, Brazil, Venezuela and Suriname
	<i>S. japonicum</i>	China, Indonesia, the Philippines
	<i>S. mekongi</i>	Several districts of Cambodia and the Lao People’s Democratic Republic
	<i>S. intercalatum</i>	Rain forest areas of central Africa
	<i>S. haematobium</i>	Africa, the Middle East

*S. japonicum*: *Schistosoma japonicum*; *S. mekongi*: *Schistosoma mekongi*; *S. intercalatum*: *Schistosoma intercalatum*.

The five species of *Schistosoma* that are involved in the pathogenesis of human schistosomiasis include: *S. mansoni*, *S. japonicum*, *S. mekongi*, *S. intercalatum* and *S. haematobium*. Clinically, every species is characterized by having a different form of the disease. All species affect the hepato-intestinal organs except *S. haematobium* that affects the urinary tract[12]. Furthermore, every species has different geographical distribution: *S. mansoni* occurs in most African countries, parts of Arabia, in northern and eastern parts of South America and

in some Caribbean islands; *S. japonicum* occurs in the pacific side of the world and includes countries such as Japan, Philippines, Chinese mainland and Thailand and *S. haematobium* is present in most African and in some Middle Eastern countries[4]; *S. intercalatum* was first recognized in 1934 in West Central Africa. The eggs have terminal spines, but are passed in stools; *S. mekongi* also recognized for the first time in 1978 in Thailand and Cambodia along the Mekong River. It is closely related to *S. japonicum*[1]. Currently, the largest number of cases of schistosomiasis occurs in Egypt, Yemen, and Algeria[13].

### 3. Morphology and life cycle

Schistosomes are trematoda that belong to the phylum Platyhelminths (flatworms). Most trematodes usually require two intermediate hosts and one definitive host to complete their life cycle whereas Schistosomes require only one intermediate host (snails) and one definitive host (humans or other mammals). Unlike other trematodes, the schistosomes show distinct sexual dimorphism. Schistosomes are blood flukes *i.e.*, the coupled schistosomes live within the perivesical or mesenteric venous plexus feeding on blood and globulins through anaerobic glycolysis with the waste being regurgitated into the host’s blood stream[14,15]. The morphology of different *Schistosoma* spp. was illustrated in Figure 2[10,16]. The life cycle of all schistosomes is similar with few modifications and consists of both asexual and sexual reproductive stages. The sexual stage of these dioecious parasites is where the interactions between male and female worms occur within their definitive hosts, whereas the asexual stage takes place within the

aquatic intermediate mollusk host that leads to production of clonal larvae (cercariae). This facilitates exposure and potential infection of any mammal that comes in contact with the water. Once infected, the transmission of the infection would occur through excretion of the *Schistosoma* eggs through stool (*S. mansoni* and *S. japonicum*), or via urine (*S. haematobium*)[2,11].

#### 4. Pathogenesis and clinical picture

##### 4.1. *S. haematobium*

Clinically, schistosomiasis can be classified according to the stages in the evolution of the infection as follows: skin penetration and incubation period, egg deposition and extrusion and tissue proliferation and repair[1,16]. The clinical features during the incubation period may be local cercarial dermatitis or general anaphylactic or toxic symptoms. Cercarial dermatitis consists of transient itching petechial lesions at the site of entry of the cercariae. This is seen more often in visitors in endemic areas than in locals who may be immune to them because of repeated contacts[1,16]. Anaphylactic or toxic symptoms include fever, headache, malaise and urticaria. This is accompanied by leukocytosis, eosinophilia, enlarged tender liver and a palpable spleen. This condition is more common in infection with *S. japonicum* (Katayama fever) [1,16]. Clinical manifestation caused by egg laying and extrusion is painless terminal hematuria (enteric hematuria). Initially hematuria is microscopic, but in heavy infection it becomes gross. Most patients develop frequency of micturition and burning. The prostate gland may also be affected leading to the alarming symptom of hematospermia, or more frequently, brown lumpy semen. Cystoscopy shows hyperplasia and inflammation of bladder mucosa with minute papular or vesicular lesions[1,16]. In the chronic stage, there is generalized hyperplasia and fibrosis of the vesical mucosa with a granular appearance (sandy patch). At the sites of deposition of the eggs, dense infiltration with lymphocytes, plasma cells and eosinophils leads to pseudo-abscesses. Initially the trigon is involved, but the entire mucosa becomes inflamed, thickened and ulcerated. Secondary bacterial infection leads to chronic cystitis. Calculi is form in the bladder due to the deposition of oxalate and uric acid crystals around eggs and blood clots. There may be obstructive hyperplasia of the ureters and urethra. Many years of untreated urinary schistosomiasis may lead to squamous cell carcinoma of the bladder[1,16].

##### 4.2. *S. mansoni*

Skin penetration and incubation periods are similar to that caused by *S. haematobium*. During the stage of egg deposition, the symptoms are mainly intestinal (known as intestinal bilharziasis or schistosomal dysentery). Patients suffer from colicky abdominal pain and bloody diarrhea. Deposited eggs in gut wall cause inflammatory reactions leading to micro-abscesses, granulomas, hyperplasia and fibrosis. Ectopic lesions include hepatosplenomegaly and portal hypertension[1].

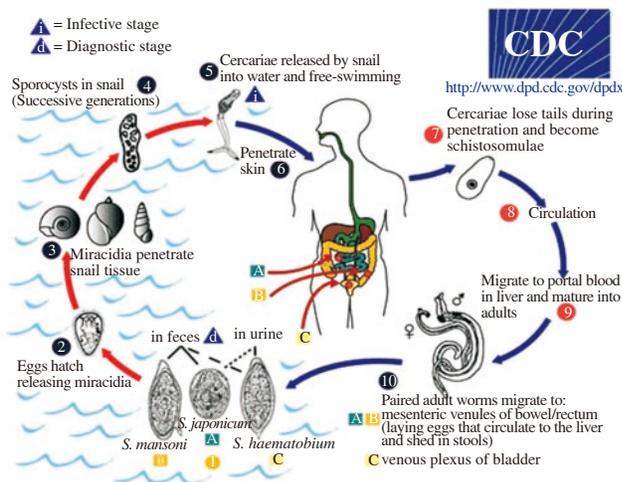
##### 4.3. *S. japonicum*

Schistosomiasis japonicum is also known as oriental schistosomiasis or Katayama disease. Its pathogenesis is similar to that of other schistosomiasis, but probably because of the higher egg numbers, its clinical manifestations are more severe. The acute illness manifested by fever, abdominal pain, diarrhea and allergic manifestations (Katayama fever). It is an immune complex disease caused by antibodies to the schistosomula, adult worms and eggs. In the chronic stage, liver is the most affected organ. There is initial hepatomegaly followed by fibrosis. Portal hypertension leads to esophageal varices that may bleed spontaneously causing dramatic hematemesis and gastrointestinal bleeding. The spleen is secondarily enlarged. Cerebral and pulmonary involvement may occur in some cases. In prolonged heavy infection when ova reach pulmonary circulation, pulmonary hypertension and core-pulmonale may result. This is seen occasionally in all types of schistosomiasis. In heavy infection, there may also be involvement of female genital tract resulting in menorrhagia and a degree of infertility[24].

**Figure 2.** Diagrammatic representation of the morphology of different *Schistosoma* spp.

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These trematodes undergo striking morphological and physiological changes with individual life-stages displaying distinct adaptations both to parasitic life, and also to free-living life that permits movement between definitive-vertebrate and intermediate snail hosts. Those adaptations include cilia or tails for swimming, secretory glands for host penetration, a tegument and glycocalyx for parasite protection/host immuno-modulation, a gynaecophoric canal for sustained pairing between sexes, muscular suckers for attachment/feeding and highly organized reproductive systems for efficient fertilization and egg production[17-23]. Schistosomes are characterized by having two sexes of different shape. Females are long and slender, while males are flattened behind ventral sucker, but folded ventrally to form gynaecophoric canal to carry females[16]. The life cycle of different *Schistosoma* spp. was illustrated in Figure 3[1,16].



**Figure 3.** Diagrammatic representation of the life cycle of three primary species of human schistosomes.

This figure has been cited from <http://www.cdc.gov/parasites/schistosomiasis/biology.html>

## 5. Diagnosis

### 5.1. Clinical diagnosis

In an endemic area, a patient complaining of terminal hematuria is suggestive of his infection with *S. haematobium*. Dysentery is suggestive for infection with *S. mansoni* or *S. japonicum*[1,16].

### 5.2. Laboratory diagnosis

Laboratory diagnosis includes direct methods and indirect methods. Direct methods are used for detection of eggs, while indirect methods are used for detecting specific antibodies and antigens.

#### 5.2.1. Direct methods

Microscopically in schistosomiasis haematobium, eggs could be found in terminal urine by nuclepore filtration or after centrifugation. Eggs may also be found in semen and also in faeces directly by using formalin ether concentration, rectal scrapings or biopsies. In schistosomiasis mansoni, eggs with lateral spines could be detected microscopically in stools. Concentration methods may be required in light infection. Proctoscopic biopsy snips of rectal mucosa reveal eggs. Although there are several different methods which are available for preparing the wet mounts, the Kato-Katz method is usually recommended. In this technique, an aliquot of stool is smeared onto a glass slide through a plastic template[25].

#### 5.2.2. Indirect methods

##### 5.2.2.1. Antibody detection

Antibody detection methods have been shown to be more sensitive than direct examination for eggs. Many different methods have been developed to test *Schistosoma* antibodies. Some reference laboratories use the Falcon assay screening test, which is a specially designed kinetic-based ELISA technique for rapidly screen sera[26]. Two special tests are circumoval precipitation (globular or segmented precipitation around *Schistosoma* eggs incubated in positive sera) and “cercarien-hullen” reaction (development of peri-cercarial membranes around cercariae incubated in positive sera). Animal schistosomes can be used as antigens in these tests[1]. Skin tests are specific and give positive results in all schistosomiasis. Intradermal allergic test is useful. The used antigen is from infected snails and cercariae and eggs and adult worms are from experimentally infected laboratory animals.

##### 5.2.2.2. Antigen detection

There are two major circulating glycoprotein antigens associated with the gut of adult schistosomes (circulating anodic antigens and circulating cathodic antigens) which can be detected by ELISA using monoclonal antibodies and sensitizing sheep erythrocytes with mouse immunoglobulin M monoclonal anti-schistosomal antibodies[27]. An indirect hemagglutination assay has been used to establish the levels of circulating anodic antigens and circulating cathodic antigens in infected humans[28]. ELISA tests using monoclonal antibodies to circulating anodic antigens have also been shown to have a high sensitivity, capable of detecting < 1 ng of antigen/mL of serum[29].

### 5.3. Molecular studies

The term “molecular” implies for the studies involving parasitic molecules mainly DNA and RNA which are involved in the storage and expression of genetic information that is required for the organism to grow, function and to reproduce its life[30].

#### 5.3.1. DNA probes and PCR

Molecular approaches can be used to detect DNA of different life cycle stages of *S. mansoni* by analyzing different biological samples: feces, snail tissues and infested water bodies, resulting in diagnosis of vertebrate and invertebrate host infections and identification of transmission sites. The detection of specific DNA sequences by PCR has proved extremely valuable for the analysis of genetic disorders and the diagnosis of a variety of infectious disease pathogens[31-34]. In 1993, the World Health Organization initiated a parasite genome project for six parasites, including schistosomes. One of the goals was to catalog new parasite genes. To date, approximately 20% to 25% of the total schistosomal genome has been discovered[35]. Molecular diagnostic techniques have only relatively recently been applied to the detection of *schistosoma* infections. Species-specific probes have been developed which bind to a 640-bp segment of *S. mansoni* DNA[36]. Pontes used PCR to detect *S. mansoni* DNA in human serum and in fecal samples of patients living in endemic areas and reported that this technique has been shown to be more sensitive than the Kato-Katz direct examination[37]. The sensitive and accurate identification of human infection and the precise monitoring of *schistosoma* transmission sites may be important tools for the long term control of the disease.

## 6. Treatment

Praziquantel (PZQ) is the drug of first choice for treatment of all types of schistosomiasis. It is given in a dose of 40 or 60 mg/kg in the case of *S. japonicum*. It should be taken with or shortly after a meal and usually has minimal side effects. Patients who are heavily infected may experience some abdominal pain and diarrhea. The mechanism of its action is unknown, but it only kills adult worms[38]. Thus, it may be necessary to repeat treatment after several months in patients who give a history of recent exposure to fresh water. Treatment with PZQ may reverse changes in the liver and renal tract identified by ultrasound over several months. Interestingly, the anti-malarial artemisinin will kill immature worms and have been used to prevent *S. japonicum* infection. They are unlikely to find widespread use against schistosomiasis, because of worries of inducing anti-malarial resistance. They may have a limited role in the treatment of severe early infection[39]. Patients with Katayama syndrome who are treated with PZQ often temporarily become more symptomatic as a result, and may benefit from corticosteroids. Corticosteroids should also be administered to those with central nervous system schistosomiasis in tandem with PZQ. Central nervous system schistosomiasis is treated with several days of PZQ at standard dosage, because it is important to be sure that the parasite is completely eliminated and the drug is well tolerated. Corticosteroids should be gradually tailed off after a week. It is important to treat promptly if neuro schistosomiasis is suspected. The treatment is not toxic, so it is not vital to have a proven diagnosis first. Attempts to perform central nervous system biopsy are dangerous and unnecessary, unless there is no response to treatment[24].

## 7. Evasion of the host's immune response

The schistosome-induced pathogenesis evades the host immune system by cercariae, schistosomulae, adults and the eggs during different stages (penetration through the skin, migration through the circulation, incubation of the adult, production and then excretion of the eggs). Most immune responses are widely observed in chronic schistosomiasis as compared with acute stage. During the earlier stages of the pathogenesis, schistosome excretory/secretory (ES) products are involved in modulating the immune response while soluble egg antigens are involved in the later stages of immune modulation[2].

### 7.1. Skin penetration by cercariae

The penetration through the primary defense layer *i.e.*, the human skin is the first step of invasion by the cercariae. The penetration is facilitated by serine proteases which are packaged in the acetabular glands of the cercariae[40,41]. These proteases degrade epidermal and dermal protein components including keratin, elastin, collagens, fibronectins and laminin. It also disrupts cell-cell contacts within the epidermis. Once the cercariae have invaded the primary physical barrier, it progresses toward the next step of evasion. Schistosomal ES products are released or secreted from epithelial surfaces of the gut and/or tegument as well as other specialized ES organs throughout almost all life stages of the parasite. The production and secretion of these products might be induced by factors presenting in the host fluid, such as blood cells, phagocytic cells, hormones and complement proteins. Due to the complexity in collection and harvest of ES products from host tissue and the inability to mimic *in vivo* environment and *in vitro* environment, studies on the immune modulation by ES products is a daunting challenge for researchers. In the adult worms, ES products are mostly secreted by the excretory cells and co-localized to the tegumental and sub-tegumental regions along with the gut epithelium[42,43]. Six of these ES products have been suggested as potential vaccine targets (paramyosin, glutathione s-transferase, IrV-5, triose phosphate isomerase, Sm23 and Sm14[44]. Female schistosomes then start to deposit viable, active and highly antigenic eggs. These eggs can attach to the endothelium of mesenteric blood vessels and cause inflammatory response in order to find their way into the intestine to be excreted in the faeces. These eggs can then hatch and the released miracidia can infect snails in a species-dependent manner in order to complete the asexual life cycle. Few eggs may get trapped into liver, intestine or elsewhere and induce granuloma formation. This granulomatous inflammation is the cause of most pathological features in schistosomiasis and mortality due to *S. mansoni*[2].

### 7.2. Immune response against cercariae and schistosomula

Penetration of cercariae and entry of schistosomula through the skin do not go unnoticed by the host immune system. Inhibitory molecules are produced followed by stimulation by the cercarial ES products. These molecules include prostaglandins such as prostaglandin E2 (PGE2) and parasite-derived prostaglandin D2 (PGD2) in all *Schistosoma* spp.[45]. The production of the prostaglandins leads to an increased production of IL-10 in the skin[46]. The cercariae penetrated into the skin turn themselves into schistosomulae. This change of stage is also concomitant with the production of PGE1, PGE2 by the parasites[47,48]. Schistosomula elicits an inflammatory response due to infiltration of polymorphonuclear and mononuclear cells which is followed by the localized production of pro-inflammatory cytokines (IL-12, TNF- $\alpha$ , and IL-6) as well as immunoregulatory mediators such as IL-10 and PGE2 and D2[49-51]. The invasion and consequent infection by the schistosomes leads to a predominantly Th2 immune response, which is in contrast to the expected pro-inflammatory Th1 response. This skewing of the cytokine response is a rather complex and intriguing process by the virtue of which the parasite thrives and survives within the host immune system. One of the main immunomodulatory cytokine induced following exposure to cercariae is the anti-inflammatory IL-10[45,49]. Studies have demonstrated the ability of schistosomula to induce PGE2 production by human keratinocytes[52]. The schistosomula might be favoring the induction of increased production of PGE2 in the skin for various reasons. First, schistosomula-induced overexpression of PGE2 plays a role in the production of IL-10 by host cells[49]. Second, PGE2 acts as a potent vasodilator which might facilitate the easy

passage of the parasite into the circulation[52].

The *S. mansoni* schistosomula, following entry into the skin, remains in the skin for up to 3 days after it gets into the circulation and progresses toward the other organs. Cytokine analysis shows a rapid increase in the levels of IL-10 within a few hours of the parasite entry into the skin, along with significant reduction in the levels of IL-1[53,54]. Parasite-derived PGD2 has been reported to inhibit migration of epidermal Langerhans cells to the site of invasion[50]. Physiologically, Langerhans cells are found anchored to neighboring keratinocytes and when the skin is penetrated by parasites, both keratinocytes and Langerhans cells produce pro-inflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$ . The expression of these cytokines, in turn, leads to the diminished expression of E-cadherin and stimulates actin-dependent movements of the Langerhans cells[55]. However, during a schistosomal infection, the migration of Langerhans cells is inhibited due to the parasite-induced production of PGE2 by the host cells and parasite-derived PGD2 which both lead to an increased production of IL-10. IL-10 impedes migration of Langerhans cells by down regulating the production of IL-1 $\beta$  and TNF- $\alpha$  by epidermal cells[55]. Thus, the purpose of the schistosomula-induced IL-10 production is to create an anti-inflammatory cytokine environment which can down regulate the host immune response against the invading parasite[49,56]. The interruption of the migration of antigen presenting cells from site of exposure to the draining lymphoid tissue is another strategy adopted by the parasites to modulate the host's immune response. The schistosomula also adopt additional strategies to evade the host immune response. The ES products from the schistosomula can induce *in vitro* mast cell degranulation, and therefore lead to production of IL-10, release of histamine and 5-hydroxytryptamine in an immunoglobulin E-independent manner[57]. One of the components of the ES products, termed *S. mansoni* apoptosis factor, has been shown to induce apoptosis specifically in the CD4+ lymphocyte population. The CD4+ lymphocyte population apoptosis allows the schistosomula to escape detection by the host immune system[58]. Once the schistosomula has evaded the immune response, it gains entry into the portal veins and remains in the circulatory system. Within 1–3 weeks, it turns into a sexually active adult that adheres to the inner lining of the veins. The male and female adult schistosomes form a pair and can reside adhered to their chosen vein lining, escaping the host's immune response for decades. *S. mansoni* and *S. japonicum* adhere to the inferior and superior mesenteric veins, respectively, while *S. haematobium* adheres to the venous plexus of the bladder. The adult pairs then produce 300–3000 eggs depending on the species. The eggs are the second stage in the schistosomal life cycle, which elicits an inflammatory response within the host body[58].

### 7.3. Immune responses triggered by the adult worm[59]

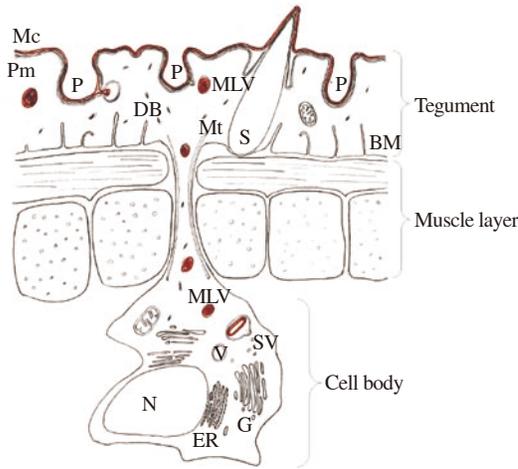
#### 7.3.1. Molecular mimicry

The schistosome host-parasite relationship was revealed through the innovative experiments undertaken by many researchers in which they demonstrated that schistosomes can acquire blood group antigens on their outer surface. The demonstration of such fascinating experiments which included transplanting adult schistosomes from mice into monkeys immunized against mouse antigens[60,61].

#### 7.3.2. Tegument

In hostile environment, the parasites are constantly exposed to host immune responses, yet their ability to thrive for several decades testifies the possession of effective evasion mechanisms[62]. Schistosomes are covered by a living syncytium called the tegument. This tissue is bounded at its basal surface by a conventional invaginated plasma

membrane, whilst its apical surface has an unusual heptalaminate appearance as shown in Figure 4[63]. This latter structure was interpreted as a normal plasma membrane overlain by a membrane-like secretion termed the membranocalyx[64].



**Figure 4.** Diagrammatic representation of the *S. mansoni* tegument and an associated cell body (not to scale).

BM: Basal membrane; DB: Discoid body; ER: Endoplasmic reticulum; G: Golgi apparatus; Mc: Membranocalyx; Mi: Mitochondria; MLV: Multilaminar vesicle; Mt: Microtubule; N: Nucleus; P: Pits; Pm: Plasma membrane; S: Spine; SV: Shuttle vesicles; V: Vacuole; This figure has been cited from <http://www.scielo.br/img/revistas/mioc/v101s1/v101s1a32f01.gif>

**7.3.3. Antioxidant proteins**

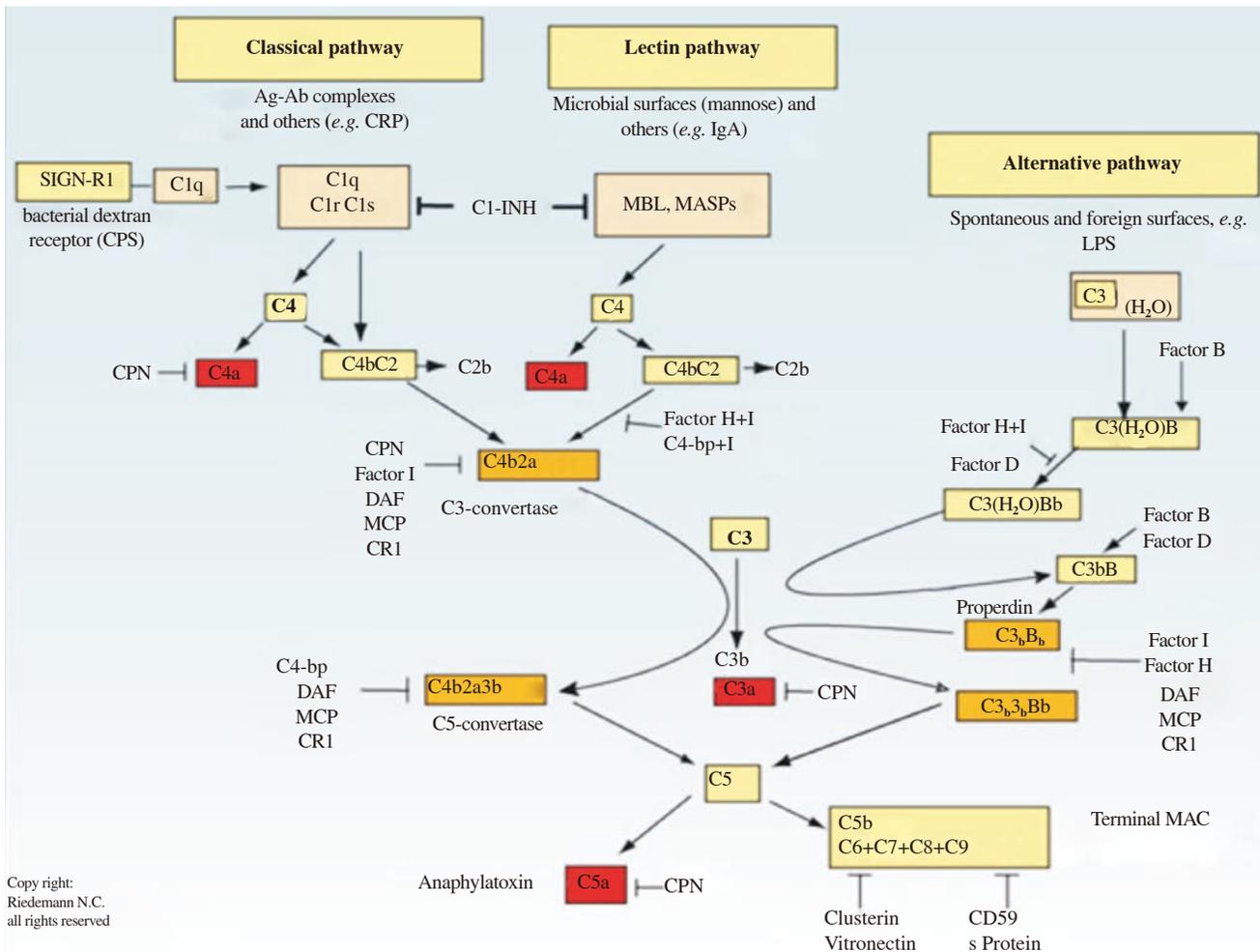
Host immune defenses are capable of producing superoxide, which has tremendous detrimental effects on the worm. However, worms are able to produce a number of antioxidant proteins which block the effect of superoxide. Schistosomes have four superoxide dismutases, and levels of these proteins increase as the schistosomes develop and mature. Antioxidant pathways were first recognized as a chokepoints for schistosomes and later extended to other trematodes and cestodes[65]. Targeting this pathway with different inhibitors of the central antioxidant enzyme thioredoxin glutathione reductase results in reduced viability of worms[66].

**7.3.4. Defenses against host membrane attack complex (MAC)**

Schistosomes have evolved ways to block host complement proteins. Immunocytochemistry techniques have found decay accelerating factor protein on the tegument. Decay accelerating factor is found on host cells and protects host cells by blocking formation of MAC. It has also been found that the schistosome genome consists of human CD59 homologs. CD59 inhibits MAC[64].

**7.3.5. Complement evasion by schistosome paramyosin**

Schistosomula and adult worms evade the immune system by developing resistance to complement attack. Complement system comprises of three different pathways: the classical pathway, the lectin pathway and the alternative pathway. All the three pathways involve cascades of events which eventually attempt to the lysis of the target cell or opsonization and phagocytosis. The three complement activation pathways converge on the formation of C3 convertase



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**Figure 5.** Diagrammatic representation of the three complement activation pathways. This figure has been cited from <http://www.humphath.com/spip.php?article1388>

(Figure 5)[2,67,68]. The alternative pathway is initiated by low-level activation of C3 by hydrolysed C3 and activated factor B. The activated C3 binds factor B that is cleaved by factor D to form C3 convertase. The alternative pathway amplifies the effects of the classical complement pathway through bound C3[69]. In mannose-binding lectin pathway, complement activation occurs following the binding of mannose-binding lectin to repetitive carbohydrate patterns on pathogen surfaces *i.e.*, pathogen-associated molecular patterns through the mannose-binding lectin-associated serine protease[70]. The eventual assembly of the MAC and its insertion into the pathogens cell membrane leads to lysis of the pathogen. *Schistosoma* evades the complement attack and survives within the host system for years and the complement evasion mechanisms are yet to be fully understood. However, studies have been performed understanding how the parasite escapes from or offers resistance to the complement-mediated killing at every step of its life cycle within the mammalian host[2]. Following host skin penetration by the schistosomal larva, it undergoes a change from being sensitive to complement attack to gain resistance to the complement system. This is made possibly by the shedding of the glycocalyx coat by the larva, which otherwise contains strong complement activators[71,72]. Once inside the host, the other life stages of the parasite employ several strategies to evade the hosts' complement attack system. Parasitic proteins have been shown to bind to complement proteins such as C1, C2, C8 and C9[73-75].

Paramyosin (Pmy) is an important schistosomal protein which has been studied extensively as a complement pathway evader. Pmy is a 97-kDa protein that forms a major core protein of thick filaments of invertebrate muscle. Immuno-labelling studies in adult schistosomes have localized the detection of Pmy in regions just below the parasitic surface *i.e.*, either the tegument or muscle layers of the male and female adult schistosomes[76]. Earlier studies identified a schistosome complement inhibitor, SCIP-1, on the surface of *S. mansoni* larvae and adult worms which was later shown to be the exogenous form of Pmy[75,77]. Pmy binds to C1q, the initial subcomponent of the classical complement pathway, in solution and this interaction fails to activate C4 and the MAC formation on sheep red blood cells[73]. This suggests that the inhibition of the complement-mediated killing of the parasite is modulated by Pmy at the initial phase. Pmy has also been shown to bind to other complement proteins such as C8 and C9[77,78]. Thus, Pmy appears to inhibit complement activation, and hence complement-mediated killing of schistosomes by binding to at least three complement proteins. Pmy also shows binding ability to the Fc portion of IgG which might possibly mask the surface of the parasite and block the binding of specific antibodies[79]. Thus, Pmy is an attractive candidate for developing a potential vaccine against schistosomiasis. Trials in various animal models have demonstrated that immunization with native or recombinant paramyosin can substantially reduce the worm burden and liver/fecal egg counts in the infected animals[80-82].

#### 7.4. Immune responses triggered by schistosome eggs

The onset of egg production by the adult schistosomes is associated with the skewing of the CD4 response toward the Th2 polarization characterizing by the production of IL-4, IL-5 and IL-13. IL-4 is one of the key cytokine which plays a role in the regulation of the development of the Th2 response. IL-4 is produced in small amounts by naive CD4 cells. This IL-4 in turn acts in an autocrine manner to induce GATA-3 (GATA-3 belongs to the GATA family of transcription factors) expression, and hence establishes the Th2 phenotype. The resultant IL-4/IL-4R/Stat6 signaling

pathway plays an important role in stabilizing and expanding the Th2 cell populations[83]. Dendritic cells, as the most potent antigen presenting cells, are known to play a central role in initiation and polarization of T-cell responses. *S. mansoni* eggs preparations have been shown to prime Th2 cells through the functional modulation of dendritic cells[84,85].

##### 7.4.1. Granulomas formation in acute schistosomiasis

Acute schistosomiasis, also called Katayama syndrome, is due to primary infection by the parasites and is observed in travelers visiting affected places and non-immune people[86]. Acute toxemic schistosomiasis by *S. mansoni* and Katayama syndrome by *S. japonicum* are systemic reactions against the first cycle of eggs laid by the adult schistosomes usually after 28–90 days of infection. Granulomas are formed around eggs which are trapped in the intestinal and liver wall leading to hepatosplenomegaly and leukocytosis with eosinophilia[86,87].

##### 7.4.2. Granulomas formation in chronic schistosomiasis

Chronic schistosomiasis with complications occurs in infected individuals living in endemic areas. Intestinal schistosomiasis is the most frequently diagnosed form of chronic schistosomiasis. Schistosome eggs that have entered into circulation reach different organs including the intestinal wall. The eggs which get trapped in the intestinal wall provoke inflammation. Hepato-intestinal schistosomiasis is due to the embolization of schistosome eggs in the liver and is the leading cause for hepatomegaly. In patients with severe longstanding infection, periportal collagen deposits lead to progressive obstruction of blood flow and portal hypertension (hepatosplenic form). *S. haematobium* eggs, on the other hand, cause inflammation in the bladder and ureteral wall, which can lead to hematuria and dysuria. With progressive involvement, fibrosis and calcification can occur and result in obstructive uropathy. Chronic disease caused by schistosome species is due to the immune response against entrapped eggs within tissues[87].

Liver is the main organ which gets affected in *S. mansoni* and *S. japonicum* infections as the sinusoids of the liver are too small for the eggs to pass by. Contrastingly, in *S. haematobium* infections, the bladder is affected as the eggs traverse across the bladder wall. Once they are trapped within the sinusoids, death of the eggs can cause the stimulation of the host response against the egg antigens. Granulomatous lesions, which comprise of collagen fibers and cells like macrophages, eosinophils and CD4+ T cells, are formed around the live eggs. Once the eggs die inside the granuloma, the resolution of the granuloma occurs leading to the formation of fibrotic plaques. The liver can become fibrotic, congested and harder to perfuse due to the granuloma-induced fibrotic plaques and this can in turn lead to an increase in the portal blood pressure[88].

Ascites and portal-systemic venous shunts are also caused and lead to excessive bleeding which could be life-threatening. Infection with *S. haematobium* can lead to very serious diseases such as bladder cancer and genital schistosomiasis. Genital schistosomiasis is very common in women infected with *S. haematobium* and women affected can have some degree of inflammation in the genitalia. This inflammation is due to the egg migration through the urinary system that can lead to localization of the eggs in the womb or vagina. The most serious morbidity associated with genital schistosomiasis is infertility because of excessive tissue fibrosis[89].

Thus, the causative factor for the hepatosplenomegaly and fibrosis is the immunopathology of the uncontrolled inflammatory response involving granulomatous formation induced by the trapped eggs in the tissues. The eggs generate a typical Th2 response that also includes infiltration of eosinophils, mast cells and alternatively

activated macrophages, followed by fibroblasts leading up to fibrosis[90,91]. It is unclear whether granuloma formation is beneficial for the human host as the egg sequestration may reduce further tissue damage. For instance, mouse models which were tolerated against *S. mansoni* egg antigen did not develop granuloma but had severe hepatotoxic liver damage, which may be due to hepatotoxins secreted by the eggs[92]. Granulomas along with egg-antigen specific antibodies are likely to sequester these hepatotoxins away from the hepatocytes. However, what is evident via murine experiments is that the parasite uses host immune response for its proliferation, survival and excretion of eggs[93]. The egg antigen induces production of IL-4, IL-5 and IL-13, and elevated IgE levels and eosinophilia[94].

There appears to be a direct correlation between the intensity of the Th2 response against egg antigens and severity of granulomatous inflammation in murine models, which declines in the chronic phase (3 months). Thus, mice genetically deficient in IFN- $\alpha$  or IL-12p40 show no changes in granuloma formation following infection whereas IL-4-deficient mice generate impaired granuloma and develop severe pathology[95].

The modulation of T-cell polarization from Th1 to Th2 response is due to secretory egg protein (soluble egg antigens) which can suppress maturation and subsequent cytokine production by dendritic cells co-pulsed with microbial and helminth antigens undergone modified maturation, segregate the antigens to distinct intracellular compartments, and concurrently induce microbe-specific Th1 and helminth-specific Th2 responses[96,97]. Although granulomatous inflammation is principally triggered by CD4+ cells, cytotoxic D8+ T lymphocytes, B cells, alternatively activated macrophages, eosinophils and mast cells are also engaged in the development and maintenance of granuloma. Tissue eosinophil infiltration is aided by IL-5 and IL-13 in the granuloma[98,99]. However, transgenic mice deficient in eosinophils and infected with *S. mansoni* show no apparent defect in parasite load, granuloma formation and fibrosis[100]. The role of eosinophils as well as mast cells in *S. mansoni* induced immunopathology remains unclear. T-cell-deficient mice show impaired granuloma formation leading to mortality due to infection within 4–6 weeks[101]. Regulatory T cells with CD4+CD25+Foxp3+ phenotype have been shown to suppress IL-4 in the murine chronic stage that is reflected in the reduction in the size of granuloma[58]. Thus, regulatory T cells may play a role in limiting the pathogenesis in the chronic stage of the disease[102].

### Conflict of interest statement

We declare that we have no conflict of interest.

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