

In-Depth Analysis of Schistosomiasis and Human Immunity: A Comprehensive Study of Host Immune Response and Pathogenic Immune Mechanisms

Tianchuan Liu

*College of Animal Science, Fujian Agriculture and Forestry University, Fuzhou, China
dididada7923@126.com*

Abstract: Schistosomiasis is a neglected tropical disease that is widespread throughout the world. In this paper, the complex relationship between schistosoma and the human immune system is discussed. Based on the existing literature and data, this paper reviews the prevalence of schistosomiasis, parasitic characteristics of schistosomiasis, human immune response, immune strategies of schistosomiasis and related pathological changes. The complex relationship between schistosoma parasites and human immunity was discussed comprehensively and deeply from the aspects of parasitic characteristics and damage to human organs, the hindering of self-healing caused by pathological changes, and the response and limitation of the human immune system. The research results indicate that schistosomes parasitize in the portal vein of the human body and cause damage to organs such as the liver and intestines. The human immune system initiates an immune response, including innate immunity and adaptive immunity, but schistosoma escapes attack through antigenic variation, camouflage, immune molecular simulation, immune regulation, and other strategies. In addition, pathological changes such as liver fibrosis and portal hypertension caused by schistosomiasis also hinder the self-healing of infection.

Keywords: schistosomiasis, human immune response, schistosome immune mechanisms, immune evasion

1. Introduction

In humans, several flukes of the genus schistosomiasis can induce schistosomiasis, categorized as a "neglected" tropical disease. Schistosomiasis is a significant parasitic illness in humans regarding morbidity and mortality. The World Health Organization (WHO) believes that schistosomiasis is endemic in over 78 countries, spanning extensive regions of the tropics and subtropics [1]. Schistosomiasis is not only a threat to human life and health, but also a huge obstacle to social and economic development. In the process of terminal host infection, the main pathogenic factors are eggs. The soluble antigens of cercaria, child worms and adult worms or can also be used as antigenic substances to trigger host immune response and cause damage to the host to a certain extent. Schistosomiasis can be roughly divided into gastrointestinal, hepato-splenic (*Schistosoma japonicum*, *Schistosoma Mansoni*) and urogenital (*Schistosomiasis Egypti*) types according to the different laying sites and egg distribution of different schistosomiasis in the terminal host [2]. After schistosoma infection, the host's immune system initiates a series of complex immune responses.

However, the schistosoma skillfully evades the host's immune attack, making it difficult for the infection to heal on its own. Schistosomiasis can survive in immune hosts for more than 30 years. In this paper, the relevant cases and experimental research methods of schistosomiasis were analyzed, and the mechanism of mutual immunity between schistosomiasis and the terminal host was discussed.

2. Parasitic characteristics of schistosomiasis

The parasitic reproduction of schistosoma in the portal vein of the human body has caused serious damage to human organs, and the disease infected by schistosoma is difficult to heal itself. After penetrating the skin, the schistosoma cercaria invade the host and remove the tail in the skin to form child worms. The juvenile worm infiltrates the veins, is conveyed to the lungs via the right heart, then arrives to the left heart, enters the arterial circulation, and ultimately reaches the portal system, where it matures into an adult worm. The maximum invasion time of schistosoma is 10 seconds.

2.1. Lung

After laying eggs, the eggs can circulate through the lateral branches of the hepatic vein or portal vein into the lung and deposit in the lung tissue, causing congestion in the lung tissue. The child worm is constantly moving through the vasculature, and this movement makes it more difficult for patrolling immune cells, such as neutrophils, to locate local immune responses. In addition, observation of schistosomiasis infected mice showed that it takes 30-35 hours for schistosomiasis to pass through the capillary bed in the lungs, while it takes only 6-16 hours to pass through the capillary bed in the whole body and intestine, suggesting that the pulmonary blood vessels may provide a migration barrier for schistosomiasis. To avoid obstacles, the 18mm wide schistosoma must narrow and elongate once it reaches the lungs, bypassing thin-walled and 6mm wide pulmonary capillaries. Schistosomiasis must remain completely inside blood vessels to migrate successfully, as ruptures into the alveoli put them at risk of being swept by the respiratory tract, swallowed, and digested [3]. In addition, child worms entering the lungs can promote the expression of arginase in the host lungs, thus interfering with the production of nitric oxide as a signal for immune cell activation, inhibiting the activation of macrophages and T cells, and weakening the host immune response. These escape routes make it difficult for the host's lungs to clear the infection.

2.2. Liver

Adult schistosoma larvae are enclosed in the portal vein and females lay a large number of eggs, with each adult female reported to lay 300 eggs per day [1]. Some of these eggs enter the liver in the bloodstream, and some are expelled in the feces. Eggs that enter the liver can deposit in small blood vessels in the liver, triggering an immune response that can lead to liver disease. The soluble antigens released by the eggs stimulate the body to produce immune cells, such as eosinophils and macrophages, which gather around the eggs to form granulomas. Granulomas form as part of the body's immune defense against the eggs, but they can also cause damage to liver tissue. With the continuous deposit of eggs and the gradual increase of granuloma, liver tissue will be seriously damaged, and fibrosis and cirrhosis will occur. Cirrhosis can cause damage to the normal structure and function of the liver, affecting its metabolic, detoxification and synthetic functions.

2.3. Intestine

Intestinal schistosomiasis symptoms arise from the passage or entrapment of parasite eggs in intestinal tissue, resulting in mucosal granulomatous inflammation, microulcers, superficial

hemorrhaging, and occasionally, pseudopolypoidosis. False polyps are significant aggregates of inflammatory tissue that arise during the reparative phase of recurrent ulcerative episodes [4]. Patients will have abdominal pain, diarrhea, mucus, pus, blood stool and other symptoms, seriously affecting the intestinal digestion and absorption function. Long-term intestinal lesions will lead to intestinal mucosal damage difficult to repair, the normal function of the intestine is seriously affected, further increasing the burden on the body, making it difficult for the body to rely on its own immunity to eliminate schistosoma.

3. Pathological changes hinder self-healing

Schistosomiasis is difficult to heal after infection, mainly because it causes a series of pathological changes on the body caused by many serious effects. On the liver side, the deposition of schistosomiasis eggs in the liver stimulates the production of immune cells that surround the eggs and form granulomas. With the passage of time, the granuloma increases and fuses, destroying the normal structure of the liver tissue, and a large number of fibrous tissue hyperplasia, and eventually develops into cirrhosis. Cirrhosis can seriously impair the metabolic, detoxification and synthetic functions of the liver, and can also hinder blood circulation to the liver. At the same time, the deposit of schistosomiasis eggs in the portal vein system leads to the thickening of the wall of the portal vein, the narrowing of the lumen, and the increase of blood flow resistance, which leads to portal hypertension. Portal hypertension can lead to serious complications such as esophageal and gastric varices and ascites [4]. Furthermore, adult schistosoma worms deposit eggs in the mesenteric veins, with some eggs traversing the intestinal wall into the gut, resulting in irritation of the intestinal mucosa. In this condition, the immune system is impaired, rendering it incapable of successfully eradicating schistosoma and obstructing the self-healing process of the infection.

4. Responses and limitations of the human immune system

4.1. Innate immunity

After the human immune system recognizes the invasion of schistosoma, it quickly initiates a series of complex immune responses. In the non-specific immune phase, macrophages, neutrophils and other innate immune cells are activated. Macrophages engulf the larvae and eggs of schistosoma worms and kill pathogens by releasing reactive oxygen species and cytokines. Neutrophils, on the other hand, chemotaxi to the site of infection to defend against schistosomiasis invasion by releasing antibacterial substances and forming neutrophilic extracellular traps (NETs). Natural killer cells (NK cells) are also involved in the immune response, recognizing and killing cells infected with schistosomiasis and releasing cytokines such as interferon- γ (IFN- γ) to regulate the immune response [5].

4.2. Adaptive immunity

In the adaptive immune phase, T lymphocytes and B lymphocytes play a key role. T lymphocytes are divided into helper T cells (Th), cytotoxic T cells (Tc) and regulatory T cells (Treg). Th1 cells can secrete IFN- γ , tumor necrosis factor- α (TNF- α) and other cytokines, activate macrophages, enhance their ability to kill schistosomiasis, and promote cellular immune response. Th2 cells secrete interleukin-4 (IL-4), IL-5, IL-13 and other cytokines, which mainly participate in humoral immune response, promote the activation of B cells and the production of antibodies. These antibodies can work in a variety of ways, such as neutralizing the toxins of schistosoma, agglutinating schistosoma larvae, and promoting phagocytosis.

4.3. Limitations of the human immune system

Schistosoma has a complex mechanism of antigenic variation, and the amino acid composition of its surface antigens constantly changes, making it difficult for T cells and B cells to recognize and attack. Studies have shown that schistosoma express different antigens at different stages of development, and these antigens mutate to evade the memory and recognition of the host immune system, allowing the schistosoma to survive in the host. Schistosoma also secretes some immunosuppressive factors. Exosomes secreted by schistosoma encompass various molecules capable of modulating the host immune response, inhibiting T lymphocyte activation and proliferation while diminishing immune cell activity. These immunosuppressive factors can disrupt normal immune system function and attenuate the body's immune response to schistosoma. In addition, proteases secreted during the cercaria stage promote host molecular cleavage and molecules released by adults to reduce blood clotting in specific areas, and many different families of proteases help promote host molecular cleavage when cercaria penetrate the skin. Through the observation of mice with schistosomiasis in their blood, it was found that the blood coagulation function of these mice was decreased, and it was inferred that the adult worms contained anticoagulants [6].

The immune complexes formed after schistosoma infection can also negatively affect the immune system. When schistosomiasis antigens combine with antibodies to form immune complexes, they may be deposited in tissues, triggering an inflammatory response that can lead to tissue damage. This immune complex-mediated damage not only worsens the disease, but also interferes with the immune system's clearance of schistosoma. In addition, the extracellular vesicles (E-EVs) secreted by schistosoma eggs and their Sja-miR-71a can up-regulate the expression of IL-10 and inhibit the formation of NETs, which is conducive to the survival of schistosoma eggs in the host and escape immune attack [5]. These factors make the human immune system in the fight against schistosoma infection faces a great challenge, difficult to completely eliminate the schistosoma, resulting in the infection is difficult to heal.

5. Immune strategies of schistosomiasis

5.1. Evade the attack of the body's immune system

5.1.1. Antigenic variation

Schistosoma can escape the attack of the human immune system through antigenic variation, which is one of the important mechanisms of immune escape. Studies have shown that schistosoma surface antigens are highly polymorphic, which makes it difficult for the immune system to continuously and effectively recognize and attack them. For example, in *Schistosoma mansoni*, there are multiple variants of the membrane protein antigen on its surface that differ in amino acid sequence and structure, making it difficult for the antibodies produced by the immune system to bind to all the variants, allowing the schistosoma to evade the neutralization of the antibodies. The antigenic variation is also reflected in the alteration of the epitope of the schistosoma antigen. An epitope is a specific region of an antigen molecule that can be recognized by the immune system. Schistosoma can change the structure of antigen epitope through gene mutation and gene rearrangement, so that it cannot be recognized by the original immune cells. Some studies have found that schistosoma successfully evade the recognition of the immune system by changing the amino acid composition of the antigen epitope and utilizing the heterozygote advantage brought about by its diploid characteristics. This mechanism makes it difficult for T cells and B cells to mount an effective immune response, thus helping schistosoma survive in the host [7].

5.1.2. Camouflage and immune molecular simulation

Schistosomiasis also uses camouflage, a strategy of obtaining molecular components of the host to cover its surface, making it look like the host's own tissue, in order to evade recognition by the immune system. A large number of experiments, especially the experiment of host-to-host transfer, have fully confirmed the existence of antigen camouflage in schistosoma [8]. Schistosoma camouflage is achieved by acquiring host molecular components and simulating host antigenic determinants.

On the one hand, schistosoma parasites disguise themselves by absorbing various substances from the host's blood and tissues, such as gamma globulins, liver proteins, and red blood cell antigens. In addition, it can also ingest host blood group glycoprotein, serum protein, low density lipoprotein (LDL), serine protease inhibitor Contrapsin, etc., and integrate these substances into the body surface membrane. These host-derived molecules can mask the schistosoma's own antigens, interfere with the immune system's recognition of them, and make it difficult for immune cells to distinguish between schistosoma and the host's own tissues, reducing the risk of attack [8]. On the other hand, schistosoma itself synthesizes substances similar to host antigens, and its genes are highly homologous to mammalian genes in some sequences, which makes it difficult for the host immune system to mount an effective immune response to it. Immune molecular simulation is also an important way for schistosoma to escape immune attack. Experiments were conducted using mouse serum, immunized rabbits and schistosoma mansoni, and it was found that schistosoma can synthesize some substances similar to host immune regulatory molecules, which can interfere with the normal function of the host immune system [8].

5.2. Regulates the body's immune response

Schistosoma produces, releases, or eliminates many immunomodulatory chemicals that disrupt the functionality of the human immune system, facilitating evasion of immune response and ensuring prolonged survival within the human host. At the innate immune level, schistosoma inhibits the function of macrophages and neutrophils. The former blocks the signaling of macrophages and inhibits their phagocytosis by secreting proteins. The latter interferes with chemotactic signals by releasing factors and inhibits the release of bactericidal substances. In terms of adaptive immunity, schistosoma enhances Th2 immune response, inhibits Th1 and Th17 immune response, induces IgE antibody production to cause tissue damage, and weakens immune defense. At the same time, it induces the production and activation of regulatory T cells (Treg), and Treg cells secrete immunosuppressive factors, down-regulate the immune response, inhibit the function of effector T cells, and impede the self-killing [9].

5.3. Molecular mechanism of immune escape

Studies have shown that schistosoma can evade the attack of the human immune system through a variety of molecular mechanisms, which involve the regulation of multiple signaling pathways.

Schistosoma secretes a variety of protein molecules, which help schistosoma achieve immune escape by interfering with cytokine response, affecting antigen presentation, regulating immune cell signaling, and simulating or binding immune-related molecules. For example, the phosphoglycomutase (PGAM) secreted by schistosoma can bind to Toll-like receptor 4 (TLR4) on the surface of macrophages, block the downstream signal transduction pathway, inhibit the activation of macrophages and reduce their immune function. In addition, schistosoma secretes protein molecules such as smCKBP, IPSE/ α 1, Omega-1, and SmSP2. smCKBP can bind chemokines, inhibit immune cell migration and activation, and contribute to egg excretion. IPSE/ α 1 can induce the release of various cytokines, promote the development of regulatory B cells and T cells, and regulate the

immune response; Omega-1 can promote the polarization of dendritic cells towards Th2 cells, affect their maturation and function, and enhance the production of some cytokines. SmSP2 can inhibit blood coagulation, promote parasite migration, invasion of host and escape host immune surveillance, and participate in nutrient processing. These protein molecules work together to enable schistosoma to survive and reproduce in the host and evade the attack of the host immune system [10].

Extracellular vesicles (EVs) also play a significant role in immunological escape of schistosoma. Schistosoma can release EVs carrying a variety of physiologically active chemicals, which can penetrate host cells and control the host immune response [11]. The study found that mirnas (short non-coding RNA molecules that play an important regulatory role in the cell) play a regulatory role in maintaining the balance of the immune response, which can inhibit liver fibrosis, including granulomatous formation and schistosomiasis induced fibrosis, by targeting Sema4D. In the development of liver fibrosis, transforming growth factor β (TGF- β) is regarded to be the most effective fibrogenic cytokine. TGF- β facilitates the phosphorylation of SMAD2/3 via the receptor, subsequently interacting with SMAD4. Upon translocating the impacted complex to the nucleus, it can persist in stimulating the production of the pro-fibrotic gene (type 1 collagen). Nonetheless, SMAD7 can inhibit the entire process [12].

Autophagy signaling pathway also plays an important regulatory role in immune escape of schistosoma. A self-degrading process within autophagy that removes damaged organelles and proteins and maintains cell homeostasis. It has been found that Schistosoma japonicum egg antigen (SEA) can trigger macrophage autophagy, which can limit the pathological development of the host liver. However, IL-7 induced by Schistosoma japonicum infection binds to the IL-7 receptor (IL-7R/CD127) on macrophages and activates AMP-dependent protein kinase (AMPK), thereby inhibiting SEA-triggered macrophage autophagy. Inhibition of autophagy resulted in reduced apoptosis of macrophages and increased cell numbers, which favored schistosoma survival and reproduction within infected cells, while enhancing pathological changes in the liver, including the development of granuloma and collagen deposition. This suggests that the autophagy signaling pathway may limit liver immunopathological changes induced by schistosoma infection and inhibit immune escape by promoting macrophage autophagy under normal conditions. However, the action of IL-7 breaks this balance, inhibits autophagy signaling pathway, helps schistosoma achieve immune escape, and exacerbates the development of liver diseases [13].

6. Conclusion

After infection with schistosoma, it is difficult to heal itself, mainly because of the parasitic characteristics of schistosoma, its parasitic reproduction in the portal vein of the human body will cause serious damage to the liver, intestine and other organs. Although the human immune system initiates immune response to fight schistosoma infection, schistosoma has immune escape mechanisms such as antigenic variation, camouflage and immune molecular simulation, which makes it difficult for the immune system to completely eliminate schistosoma. Pathological changes such as liver fibrosis, portal hypertension and intestinal mucosal damage caused by schistosomiasis further hinder the self-healing of infection. Schistosoma has a complex immune strategy, through antigen mutation, constantly change the surface antigen, to evade the human immune system recognition and attack. Camouflage and immune molecular simulation are used to cover up self-antigens and interfere with the normal function of the immune system. It can also regulate the human immune response, inhibit the activity of innate immune cells, regulate the subgroup differentiation and function of T lymphocytes in adaptive immunity, and induce the production and activation of regulatory T cells, so as to survive in the human body for a long time. The molecular mechanism of schistosoma immune escape involves the regulation of several signaling pathways, such as phosphoglycolate mutase inhibiting macrophage activation, miR-71a inhibiting liver fibrosis in extracellular vesicles, and

autophagy signaling pathway providing nutrients to schistosoma and inhibiting host cell apoptosis. An in-depth examination of the interplay between schistosomiasis and the human immune system is crucial for formulating effective preventative and control strategies. This paper concentrates on the ultimate host of schistosomiasis; however, the intermediate host, specifically the oncomelania snail, has not been sufficiently examined. Future studies will utilize genetics to investigate the interaction mechanisms between *Schistosoma* and its intermediate host, *Biomphalaria*, and will employ proteomics to identify the critical proteins that facilitate *Schistosoma*'s evasion of detection by the definitive host. Metabolomics will be employed to identify critical chemicals that modulate immunity, offering insights for the therapy of this disease.

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