American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Research Article

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How does Human Schistosomiasis Jeopardize the Testicular Immune Privilege?

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To Cite This Article: *Kameni Poumeni Mireille*, Mahamat Oumar, Lissom Abel and Kada Sanda Antoine. How does Human Schistosomiasis Jeopardize the Testicular Immune Privilege?. Am J Biomed Sci & Res. 2023 19(2) AJBSR.MS.ID.002576,* DOI: 10.34297/AJBSR.2023.19.002576

Received: June 23, 2023; **Published:** July 03, 2023

Abstract

Human schistosomiasis is a parasitic infection that affects close to a quarter of a million people in 78 nations and the number of people at risk may be projected to 800 million. The disease is caused by Schistosoma parasites, which are blood flukes that infect humans through the skin when they come into contact with contaminated water. Schistosomiasis causes a range of symptoms, including abdominal pain, diarrhea, and blood in the urine. One of the less well-known effects of schistosomiasis is its impact on male reproductive features, germ cells and immune components in the testis. Despite the testicular cells are well equipped with innate and effective local defenses mechanisms against invading parasites. Various pathogens such as Schistosoma parasites, succeeded in hijacking the immune-privileged state of the testis and to evade systemic immune surveillance. Some pathogens can even remain in the testes for long periods of time, disrupting thus local immune homeostasis and affecting testicular function and male fertility. This article presents an overview of the Schistosoma parasites strategies used to jeopardize the testis immune priviledge.

Keywords: Testis, Immune Privilege, Human Schistosomiais

Introduction

Schistosomiasis is a parasitic disease caused by trematode worms that can result in chronic infections, affecting millions of people in developing countries [1]. The global burden of schistosomiasis is estimated at 2.6 million Disability-Adjusted Life Years (DALYs) [2] with a prevalence of at least 236.6 million cases in 78 countries [3]. Although the number of healthy days lost annually is far below those calculated for HIV/AIDS, malaria and tuberculosis, the perceived importance of schistosomiasis is now more realistic than 10–15 years ago. Indeed, due to the inclusion of also mild symptoms, such as anaemia, diarrhoea, dysuria and exercise intolerance [4,5], which were not previously counted by the Global Burden of Disease (GBD) study, schistosomiasis now comes second on the list of 18 Neglected Tropical Diseases (after the intestinal nematodes) published by the World Health Organization (WHO) [2,6]. Moreover, Africa alone accounts for 90% of global mortality and morbidity, i.e., 200,000 deaths recorded each year *WHO* (2021) [7]. Of the six known human schistosome species, *Schistosoma haematobium* (*S. haematobium*) is the main etiological agent affecting particularly the uro-genital tract of human. This species is highly prevalent in the sub-Saharan region [8-10]. Chronic stages of the disease have been shown to be responsible for the damage of bladder, urinary tract and testicles [11,12]. Protecting spermatogenic cells from the immune response of the host is crucial for maintaining male fertility. This protection also encompasses the ability to resist foreign tissue grafts that are introduced into the testicular environment, which is commonly referred to as 'immune privilege' [13,14]. However, this terminology refers mostly to tissues in which the immune response is inhibited or suppressed [15]. Privileged tissues include the brain, eyes, pregnant uterus, and testicles. Testicular immune privilege is a well-documented phenomenon in which the immune

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system is suppressed in the testes to allow sperm to develop without interference [16]. Effectively, the mammalian testis represents an immune privileged organ where both allo- and auto-antigens can be tolerated without evoking immune rejection [17].

The phenomenon of testicular immune privilege involves a complex interplay of various mechanisms aimed at regulating the immune system. These mechanisms include the normal process of immune tolerance, the sequestration of antigens across the blood-testis barrier, reduced immune activation, local immunosuppression, and antigen-specific immune regulation [17,18]. Central to these regulatory processes are testicular somatic cells, particularly Sertoli cells, which play a pivotal role [19]. Furthermore, testicular secretions containing androgens, cytokines, peptides, and bioactive lipids are also involved in the immune regulation within the testicular environment [20]. Failure of these protective mechanisms, caused by factors such as trauma, inflammation, genetic factors or parasites infection, can result in androgen deficiency, infertility, and autoimmunity [21].

Male genital schistosomiasis is well known to pose a significant threat to the testicular immune privilege leading chronically to testicular and epididymal inflammation and hormone levels, steroidogenesis, spermatogenesis disturbance [12,22-25]. The aim of this scoping review is to provide a comprehensive exploration of the mechanisms through which schistosomiasis undermines the testicular immune privilege. By exploring the strategies employed by Schistosoma parasites to breach the testicular barrier, we sought to enhance our knowledge of the pathogenic processes associated with schistosomiasis in the testes. This understanding can potentially contribute to the development of new therapeutic approaches targeting this debilitating condition.

Structural and Cellular Involvements in the Testicular Immune Privilege

The testis is a complex organ with a unique physical structure and many cell types that include immune cells and testis-specific cells. The mammalian testis consists of two distinct compartments: the seminiferous tubules and the interstitial spaces between the tubules with the respective functions to generate germs cells (spermatogenesis) precisely within the Sertoli cells, and to synthesize sex steroid hormones (steroidogenesis) by interstitial Leydig cells. The sex steroid hormones, mainly testosterone in the testis, are critical for normal spermatogenesis. Effectively, during the process of spermatogenesis, numerous newly discovered proteins are synthesized in developing germ cells. This poses a challenge to the immune system, as sperm cells are distinct to the body and emerge long after the immune system has matured. Nevertheless, the testis exhibits tolerance towards these distinct antigens. The testis plays a vital role in safeguarding these antigens, as auto-antigens provoke robust autoimmune reactions if introduced in other parts of the body [21,26]. Thus, the testis is qualified as 'immune privileged site' - with an unique set of mechanisms that prevent immune cells from recognizing and attacking the germ cells within the testis. Many studies reported that systemic immune tolerance and localized active immunosuppression are involved in the regulation of testicular immune privilege [18,21,27]. Therefore, multiple mechanisms are considered to play a key role in the control of the immune privilege of the testis including the special structure of the testis, the immunosuppressive properties of local cells, and paracrine and endocrine cytokines [21,27]. The testicular immune privilege relies on the integrity of the Blood-Testis Barrier (BTB), which consists of three crucial components: anatomical, physiological, and immunological barriers [28]. The anatomical barrier is formed by specialized junctions that tightly regulate the passage of molecules and cells, effectively segregating the testicular microenvironment from the systemic circulation. The physiological barrier encompasses various transporters that control the movement of substances within the testis, creating an optimal milieu for spermatogenesis. Lastly, the immunological barrier plays a vital role in restricting access to systemic immunity and sequestering auto-antigenic germ cells, preventing detrimental immune responses within the testicular environment [20,29,30].

Further, several testis-specific cell types contribute to the immunological functions and maintenance of the testicular immune privilege within the testes. Somatic cells, including Sertoli Cells (SCs), Leydig cells, and Myoid Peritubular Cells (MPCs), play essential roles in supporting spermatogenesis and creating an immunologically privileged niche. SCs form the physical and immunological barrier by forming tight junctions and creating a specialized microenvironment [20]. They can regulate the movement of immune cells and modulate the immune responses within the testis by secreting multiple immunosuppressive factors, such as activin A and transforming growth factor β (TGF-β), that play roles in maintaining the immune privileged status [19]. Testosterone produced by LCs has been reported to be essential for maintaining the testicular immune privileged status [31]. Authors have demonstrated that LCs produce growth arrest-specific gene 6 (Gas6), which inhibits innate immune responses in testicular somatic cells through negatively regulating Toll-Like Receptor (TLR) signaling [32,33]. MPCs, serving as an integral component of the basement membrane's outer layer, actively contribute to the transport of spermatozoa into the epididymis through their contractile activity [34]. Remarkably, human MPCs have been found to possess immunoregulatory capabilities, as evidenced by their production of a diverse array of cytokines involved in immune modulation within the testis. Notably, these cytokines include Transforming Growth Factor-beta (TGF-β), Monocyte Chemotactic Protein 1 (MCP-1), and leukemia inhibitory factor, which collectively orchestrate immune responses and maintain immune homeostasis in the testicular microenvironment [21]. Additionally, the expression of Tumor Necrosis Factor-alpha (TNF-α) receptors on MPCs not only suggests their capacity to respond to pro-inflammatory signals but also implies their involvement in mediating Interleukin-6 (IL-6) production, thus further highlighting their crucial role in the intricate immunoregulation of the testicular immune milieu [19]. These findings collectively em-

phasize the integral role of MPCs in establishing a paracrine immunoregulatory network that finely tunes immune responses within the testis. Macrophages represent a significant population among immune cells in the testicular interstitial space. They exhibit close physical interactions with Leydig cells and have been shown to influence Leydig cell development and steroidogenesis. Moreover, testicular macrophages play a role in regulating SCs functions and spermatogenesis through the secretion of soluble factors [17].

Dendritic Cells (DCs), although present in a minor population, are critical immunoregulatory cells in the testis. They are specialized Antigen-Presenting Cells (APCs) that interact with T cells and orchestrate immune responses [18]. DCs can induce lymphocyte activation, differentiation, and tolerance to autoantigens, thereby modulating immune responses and maintaining immune privilege within the testicular environment. In addition to macrophages and DCs, the testes harbor a small population of T cells, primarily CD8+ cells, and afferent lymphatic vessels that facilitate the trafficking of immune cells [35]. Mast cells, another immune cell population, have been implicated in regulating steroidogenesis and are associated with male infertility [36]. Their precise role in testicular immune privilege, however, remains largely unknown.

Influence of Urogenital Schistosomiasis on Testicular Immune Privilege

Urogenital Schistosomiasis (UGS), caused by *Schistosoma haematobium*, is recognized as one of the neglected tropical diseases that afflict impoverished populations worldwide [37,38]. Within the spectrum of UGS, Male Genital Schistosomiasis (MGS) represents a specific manifestation characterized by schisto some egg-associated pathologies affecting the male genitalia. The pathogenesis involves the migration of larvae from the lungs to the veins, where the adult parasites establish themselves in the genitourinary venous plexus. The excretion of eggs leads to chronic granulomatous inflammation, causing distinct manifestations in the urinary tract for UGS and the liver for intestinal schistosomiasis caused by *Schistosoma mansoni (King, et al., 2018)*.

Rambau, et al., (2011) [24] documented a case of testicular schistosomiasis in a 9-year-old boy, revealing scrotal swelling, atrophic testis, and active granulomatous inflammation with schistosome eggs present in the tunica vaginalis. This finding further confirmed the involvement of *Schistosoma haematobium* in testicular schistosomiasis. The genital inflammation triggered by the schistosome eggs was found to elevate cytokine levels, particularly Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α). Interestingly, these cytokines have been associated with facilitating HIV replication, potentially increasing seminal viral shedding and implying an additional risk of HIV transmission among individuals co-infected with UGS and HIV [24,39]. Furthermore, *Jatsa, et al.,* (2022) [12] reported that MGS contributes to the higher prevalence of genital tract pathologies and may lead to decreased serum testosterone concentrations or increased testis circumferences, indicating potential implications for male reproductive health. These findings highlight the broader impact of UGS on testicular function and overall reproductive well-being. UGS causes morbidity within the genitalia but is underreported and infrequently examined in men [25].

Urogenital Schistosomiasis (UGS), caused by *Schistosoma haematobium*, disrupts the testicular immune privilege through various mechanisms. One such mechanism involving the impairment of the blood-testis barrier is the oxidative stress induced by immune system. It is one of the vital strategies of host defense against intracellular parasites (). Similar mechanism has been reported to be caused by *Toxoplasma gondii* parasitic infection causing oxidative stress in testis tissue. The adverse effects of oxidative stress affected the reproductive system in the rat model [40]. The presence of Schistosoma eggs in the urogenital system will lead to the production of Reactive Oxygen Species (ROS), resulting in damage to the Sertoli cells that constitute the blood-testis barrier [41]. This damage endowed to compromise the integrity of the barrier, might allow immune cells, including CD4+ and CD8+ T cells, macrophages, and neutrophils, to infiltrate the seminiferous tubules and target the germ cells as observed in the testis of rats undergoing autoimmune orchitis [42,43]. In addition to affecting the blood-testis barrier, urogenital schistosomiasis can also modulate the expression of immunomodulatory molecules within the testes. Studies have shown that Schistosoma infections leads to a reduction in the expression of Transforming Growth Factor-beta (TGF-β) and Fas Ligand (FasL) within the testicular environment [44-46]. *Greil and Villunger* (1998) [47] previously reported that Fas (Apo-1/CD95) receptor/ligand (FasL) system plays a key role in complex immunological processes such as the acquisition of self-tolerance in T cells, progression of autoimmunity, clonal deletion of activated T cells, B-cell regulation and the establishment of "immune privileged" sites such as testis. This alteration in the expression of immunomodulatory molecules can participate in the disruption of the delicate balance of the testis environment immune regulation, resulting in heightened immune cell activation within the testes and further compromising the testicular immune privilege. Furthermore, the role of androgens in testicular immune regulation has long been underestimated. However accumulating evidence showed that they orchestrate the inhibition of proinflammatory cytokine expression and shift cytokine balance toward a tolerogenic environment [16]. Testosterone, a key androgen in maintaining the integrity of the immune privileged site in the testes, has been reported to be affected during schistosomiasis infection. Indeed, the infection can induce a decrease in testosterone levels *Jatsa, et al.,* [12], leading to a disruption in the immune tolerance established within the testicular environment. This hormonal imbalance weakens the testicular immune privilege and contributes to the breakdown of immune regulation.

Impact on Male Fertility

Urogenital schistosomiasis disrupts the testicular immune privilege, thereby exerting a profound impact on male fertility. Research indicates that infections with *Schistosoma spp* results in a decline

in sperm count, reduced sperm motility, and an increase in abnormal sperm morphology [48,49]. Furthermore, chronic infection with the parasite can induce fibrosis of the testicular tissue, further compromising testicular function [50]. Generally, the disruption of the testicular immune privilege by Schistosoma parasites has significant implications for male fertility. Inflammation and testicular damage can lead to diminished sperm production and quality, along with the development of testicular fibrosis, which can contribute to irreversible infertility [26,51]. Additionally, the immune response triggered by Schistosoma parasites within the testes can lead to the production of autoantibodies that attack sperm, exacerbating the reduction in fertility [52,53]. Studies have demonstrated a substantially higher risk of infertility among men with schistosomiasis compared to those without the disease [12,26].

Treatment and prevention

There is currently no specific treatment for the disruption of the testicular immune privilege by Schistosoma parasites. However, treatment of the underlying schistosomiasis infection can help to reduce inflammation and damage to the testes, which may improve fertility. In addition, strategies to prevent schistosomiasis infection, such as improved sanitation and hygiene practices, can help to reduce the incidence of infertility caused by the disease.

Conclusion

In conclusion, urogenital schistosomiasis can have a significant impact on the testicular immune privilege, leading to inflammation, tissue damage, and reduced male fertility. The disruption of the testicular immune privilege is caused by the immune response to Schistosoma parasites in the testes, which is characterized by the production of pro-inflammatory cytokines and the interference with immunosuppressive molecules. Treatment of the underlying schistosomiasis infection and strategies to prevent infection may help to reduce the incidence of infertility caused by the disease.

Acknowledgments

None.

Conflict of Interest

None.

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