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Progress on Immunopathogenesis of Hepatic Fibrosis by Schistosome Infections

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Abstract: Schistosomiasis is a widespread zoonosis. It seriously threats human health. Schistosomiasis is caused by schistosomes, which belong to *Schistosoma* genus, a kind of blood-dwelling fluke worms, mainly living in the venus portal-mesenteric system of human by digenetic intravascular parasite. People who infected by schistosomes may appear the symptoms with abdominal pain, diarrhea, anemia, and splenomegaly, progressing from egg-granulomas eventually to hepatic fibrosis. This review describes hepatic fibrosis caused by schistosomes, *Clonorchis sinensis* and *Toxoplasma gondii*, *Capillaria hepatica* and hydatid, mainly focused on the hepatic fibrosis caused by *S. mansoni* and *S. japonicum*. T helper (Th) cells (Th1, Th2, Th17 and Treg cells) play an important role in the process of anti-schistosomiasis infection and immune regulation. Especially, the balance of Th1/Th2, Th17/Treg is closely related to the development of hepatic fibrosis. Th2 and Th17 cells can promote the granuloma formation by the secretion of IL-4 and IL-17 respectively; while Th1 and Treg cells can suppress the granuloma formation. These $CD4^+$ T cell subsets are in complicated cross-talk in schistosomiasis immunity. Hepatic fibrosis caused by these parasites are also the key and difficult points of prevention and treatment of parasitic diseases, with further study about their molecular mechanism will provide us more thinking about parasitic effective prevention and treatment.

Keywords: Hepatic Fibrosis, *Schistosoma mansoni*, *Schistosoma japonicum*, Other Parasites, Th1 and Th2, Th17 and Treg

1. Introduction

Schistosomiasis is a widespread zoonosis, it seriously threats human health [1, 2]. Schistosomes (*Schistosoma* genus) are blood-dwelling fluke worms. The main pathogenic species are *Schistosoma haematobium* (*S. haematobium*), *Schistosoma mansoni* (*S. mansoni*), and *Schistosoma japonicum* (*S. japonicum*) [3-5], they may lead to urinary system disease (caused by *S. haematobium*) or intestinal disease, hepatosplenic inflammation, and hepatic fibrosis (caused by *S. mansoni* and *S. japonicum*). In the early phase, ova laid by adult parasites trap in the portal vein of the liver [6, 7], leading to dramatic egg-granulomas, that chemotactic eosinophils, neutrophils, macrophages, hepatic stellate cells (HSCs) and lymphocytes are infiltrated around the eggs [8-10]. As granuloma accumulated in liver, the elasticity of the veins decreased, and portal blood flow obstructed, resulting in portal hypertension [11-14], eventually lead to hepatic fibrosis. Hepatic fibrosis is the result of the imbalance of synthesis and degradation of extracellular matrix (ECM). It seriously damages the structure of liver tissue and makes connective tissue abnormal. Persistent hepatic injury make hepatocytes be replaced by abundant ECM, including collagen I, collagen III, collagen IV, fibronectin, hyaluronan, laminin, and proteoglycans etc.

Hepatic fibrosis is a way of wound-healing response [15]. The immunological mechanism of hepatic fibrosis caused by schistosomes is the result of the joint participation of cellular immunity and humoral immunity, predominantly by cellular immunity [16, 17]. T helper (Th) cells are one of the important components of cellular immunity, they play an important role in schistosomal hepatic fibrosis [18-21]. There are four subsets of Th cells,, namely Th1, Th2, Th17 and Treg. Recent researches show that Th cells play a crucial role in parasitic immune response. The balance of Th1/Th2 is associated with the normal function of human bodies. Besides, the disturbance of Th17/Treg cells may can autoimmune diseases and inflammation. Both increasing Th17 cells and decreasing Treg

cells can cause inflammatory disorders [22]. The imbalance of Th cells was also found in schistosomal immunity, which results in granulomas and hepatic fibrosis of the host.

Hepatic fibrosis caused by parasites are also the key and difficult points of prevention and treatment of parasitic diseases, our study about their molecular mechanism will provide us more thinking about parasitic effective prevention and treatment.

2. Hepatic Fibrosis Caused by Parasites

Currently, the parasites known to cause hepatic fibrosis are mainly *S. mansoni*, *S. japonicum*, *Clonorchis sinensi*s and toxoplasmosis, *Capillaria hepatica*, hydatid. This review mainly describes the hepatic fibrosis caused by schistosomes.

2.1. Hepatic Fibrosis Caused by Schistosome Infections

In hepatic fibrosis caused by schistosomes, cercariae drilled into the skin of the host, and then develop into schistosomulum, stay for about 24 hours before migrating to the lungs. Clinically, lung infiltration is related to the allergic reactions caused by metabolites and the heterologous proteins secreted by dead schistosomulum. When schistosomulum grow mature, they become adult. Adults mainly live in the veins, their metabolites, secretions, excreta and surface membrane proteins constantly updated, which are important factors in inducing host immunopathological changes. The eggs produced by the adult are deposited in the liver as blood flow, so the liver lesions are the earliest and heaviest. Some eggs successfully pass through intestinal mucosa to lumen, eventually to outside of the body by feces. While others are carried to liver by the portal vein blood flow, then these eggs stopped in the small pre-sinusoidal vessels. After eggs matured, soluble egg antigen (SEA) will be released into the surrounding tissue, inducing T cells releasing a variety of cytokines, such as IL-2, IL-4, IL-5, IL-10 [23]. Stimulated by these cytokines, a large number of macrophages, eosinophils, fibroblast, lymphocytes gathered around the eggs, then egg granuloma formed [24-26]. During the early schistosomiasis in mouse, due to the large diameter of schistosomal eggs, it is generally embolized at the end of the portal vein, so the liver is slightly swollen, and there are many off-white or gray-yellow nodes on the surface and in section of liver [27]. Continuous arrival of new eggs may destruct the peripheral portal vasculature and increase intra-hepatic portal pressure [28]. If there is a lesion in vasculature, then vessels spontaneously repute, and that may lead to host death by acute anaemia. In addition, intra-hepatic portal pressure may also made newly arrived eggs lodged into small veins, fibrosis may then involve large portal spaces, so typical lesions may appear, this is systemic schistosomal fibrosis [29]. But this may be temporary. When the functional equilibrium is deteriorated, ascites, muscular loss and hepatic failure may appear.

There are some differences in the fibrosis caused by schistosomiasis mansoni and schistosomiasis japonica. First, the fibrotic process of *S. japonica* is faster than *S. mansoni*. Sometimes, there is no interval between acute and chronic schistosomiasis japonica [30]; while for schistosomiasis mansoni, that maybe take 5-15 years [31, 32]. Second, female *S. japonicum* lay a large number of eggs, about 10 times as many as the *S. mansoni*. Because *S. japonicum* has a habbit of spawning in cluster, so the formed granuloma and lesion are larger than *S. mansoni* [33]. Third, the bleeding of the two types of schistosomiasis is various. Schistosomiasis mansoni tends to grow more severe as time pass by, while in *S. japonica*, bleeding is usually sudden and massive. Fourth, the mortality is different. Statistically, the mortality caused by *S. mansoni* is about 0.05%, with a case-fatality is 1.1% of oesophageal bleeding; while the available data for *S. japonica*, the case-fatality rate is about 1.8% in Philippines [34], though the data need to be corrected. Fifth, the cellular composition of granulomas are different. The granulomas caused by *S. japonicum* primarily consist of neutrophils, whereas *S. mansoni* are principally composed of mononuclear cells, eosinophils and a small number of neutrophils [35, 36].

2.2. Hepatic Fibrosis Caused by Other Parasites

Besides schistosomes, *Clonorchis sinensis* (*C. sinensis*), *Toxoplasma gondii* (*T. gondii*), *Capillaria hepatica* (*C. hepatica*), hydatid, which can also induce hepatic fibrosis.

C. sinensis, also known as liver fluke, causes clonorchiasis sinensisin human. People are often infected by eating freshwater fishes or prawns containing *C. sinensis* metacercariae. The metacercariae develop into juveniles in the duodenum, and then move to the intrahepatic bile duct where the juvenile worms become mature [37, 38]. Mild infection can be asymptomatic, severe infections that can appear cholangitis, adenomatous hyperplasia, cholelithiasis and complications such as liver cirrhosis [39]. However, molecular mechanism underlying fibrotic responses of hosts to these virulence factors is not fully elucidated [40]. The results of histopathological test showed that fibrosis occurring at 4 weeks post-infection was highly correlated with inflammatory infiltration, which suggested that massive infiltration of eosinophil and plasma cells caused by the infection might initiate cystic formation and fibrosis, which might play a role in the defense mechanism against the parasitism in the liver [41-43].

Toxoplasmosis is caused by the protozoan *Toxoplasma gondii* (*T. gondii*), which can infect humans and animals [44, 45]. Human become infected by ingesting raw meat containing cysts. In the small intestine, tachyzoite escape from cyst, and get into the blood circulation. As the blood flows, tachyzoite invade the mononuclear phagocyte system, and spread to the whole body by blood, which can invade any nucleated cells. When *T. gondii* invade liver, they firstly move to the surface of epithelial cell to Kupffer cells, and finally develop in the cytoplasm of hepatocytes [46], and causes pathological changes, progress from hepatomegaly, granuloma to hepatitis, and finally lead to liver necrosis [47].

Capillaria hepatica (*C. hepatica*) is a kind of parasites that can infect mouse and mammalian. Human can be infected by eating food or water contaminated by infected egg. The worms are matured in the liver, died and disintegrated soon after egg

laying. Dead worms and their eggs cause focal necrosis and inflammation in the liver. Focal necro-inflammatory lesions are encapsulated and resorbed [48, 49]. Although the dead-worm lesions tend to disappear, septal fibrosis seems progressive [49]. Septal fibrosis is a frequent morphological type of hepatic fibrosis. Soon its fine and long fibrous septa involve the whole liver parenchyma, connecting portal space to portal space, and eventually to central veins, creating a mosaic pattern of pseudo-lobules that resembles secondary biliary cirrhosis.

Echinococcosis or hydatid disease (HD) is a zoonosis caused by the larval stages of taeniid cestodes belonging to the genus *Echinococcus*. Hepatic echinococcosis is a life-threatening disease, mainly differentiated into alveolar and cystic forms, associated with *Echinoccus multilocularis* (*E. multilocularis*) and *Echinococcus granulosus* (*E. granulosus*) infection, respectively. HD caused by *E. multilocularis* is by oral uptake of eggs, an oncosphere larva is released from the egg and penetrates the intestinal lamina propria, reaching blood and lymph vessels which transport it to liver, lungs and other organs, where oncosphere larvae can develop into hydatid cysts. Humans can accidentally become "aberrant" intermediate hosts, after ingestion of echinococcus eggs excreted by infected carnivores. The parasite cysts gradually expand and cause a granulomatous host reaction, followed by the development of a fibrous tissue layer (pericyst). HD caused by *E. granulosus* can happen through direct contact with the definitive host or it can be indirect, through contamination of food or water with parasite eggs [50]. In the liver, parasitic lesions appear to be surrounded by large granulomas made up by macrophages, T-lymphocytes and myofibroblasts [51-53]. The research of Weiss et al showed that, lesions in dogs affected by echinococcosis were characterized by prominent proliferation of granulation tissue and fibrosis. Liu et al showed that the increased TGF-β1 and its association with liver fibrosis in the animal model of E. granulosus infection [54].

3. Immunopathogenesis for Hepatic Fibrosis

In the process of hepatic fibrosis, by secreting different cytokines, immune cells can mediate immune inflammatory response. $CD4^+$ T helper (Th) cells are necessary for granuloma formation [55, 56]. Naïve $CD4^+$ T cells could differentiate into Th1, Th2, Th17 and T regulatory (Treg) cells [57-60] (Figure 1).

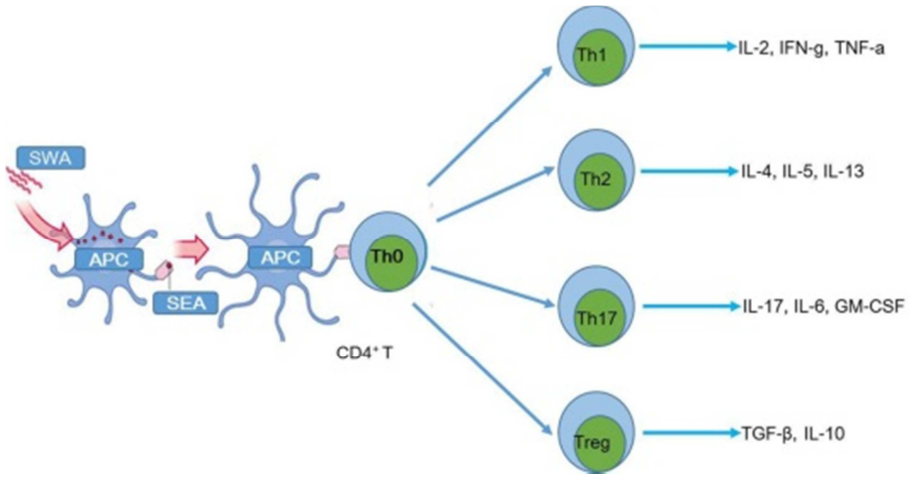

Figure 1. *Differentiation of $CD4^+$ T-cell subsets. Stimulated by antigen, naïve $CD4^+$ T cells can be differentiated into distinct Th cell subsets, namely Th1, Th2, Th17 and Treg cells. These cells participate in schistosomiasis immunity by secreting different cytokines. (SWA: soluble adult worm antigen; SEA: soluble eggs antigen; APC: antigen-presenting cell).*

As stated above, Th1, Th2, Th17 and Treg cells play a great role in immune response and inflammatory lesions caused by schistosomiasis.

3.1. Th1 & Th2

Th1 and Th2 subsets were first identified in the 1980s. If IL-12 and IFN-γ were added, $CD4^+$ T cells can be differentiated into Th1 cells [19, 61, 62]. Th1 cytokines, including IFN-γ, TNF-α, IL-2 and lymphotoxin, mainly participated in the phase of early schistosomiasis. If $CD4^+$ T cells were stimulated by IL-4, they will differentiate into Th2 cells. Th2 cytokines, including IL-4, IL-5, IL-10, IL-13 [63], are mainly linked to the immunity of egg-granuloma (Figure 1).

Studies showed that in *S. mansoni*-infected mice, imbalance of Th1/Th2 have an essential relationship with tissue fibrosis [64]. The Th1 immunoreaction plays a predominant role during the early phase by larval worms [65]. IFN-γ and TNF-α secreted by Th1 cells are higher than usual quantities with the formation of the egg granuloma. Eggs and SEA can directly induce Th2 immune reaction, promotes the expression of IL-4 and IL-13 [66, 67]. IL-4 and IL-13 play an important role in inducing Th2 immunoreaction [68]. Th2 immunoreaction gradually takes over the dominant position of the Th1 immunoreaction. The detection of the Th1 cytokines (such as IFN-γ, IL-2, TNF-α) and Th2 associated cytokines (such as IL-4, IL-5, IL-6, IL-9, IL-13) in granuloma formation showed the conversion of Th1 response to Th2 polarization [69-71]. While reduced Th2 response and enhanced production of Th1 cytokines was

correlated with decreased fibrosis [66, 72]. Therefore, the imbalance of Th1 and Th2 is believed to be crucial in the development of inflammatory and fibrosis [73, 74].

3.2. Th17 and Treg Cells

In 2003, Th17 as a third subset of $CD4^+$ T cell sub-group was found [75, 76]. Th17 cells are believed to participate in the immunopathogenesis of more wide ranges of diseases, such as autoimmune and allergy [77-80]. The differentiation of Th17 cells needs IL-6 and TGF-β [81]. First of all, IL-6 induces cells to synthesize IL-21 by STAT3 pathway then together with TGF-β to promote the differentiation of Th17 cells. Th17 mainly secrete IL-17A (IL-17), IL-17F, IL-21 to exert immune reactions for intercellular pathogens [60, 82-84]. Studies showed that IL-17 can enhance the inflammatory reaction of liver granulomas in mice infected by schistosome, which suggest that Th17 cells have the dual role of inducing inflammation and fibrosis. Researches show that in *S. japonicum* infected C57BL/6 mice, the proportion of Th17 cells and the secretion of IL-17 cytokines in spleen increase slowly within 5 weeks in post-infection, then increase rapidly after 5 weeks [85, 86] (Figure 2). Also, by secreting IL-17, Th17 cells participate in schistosome-host immune reaction. In schistosomiasis mansoni, IL-17 can reduce the chronic hepatic fibrosis caused by SEA. Cytokines secreted by Th17 can induce inflammatory chemokines, such as TGF-β，IL-6，raising neutrophile granulocytes to the tissue to anti-infection [87]. It shows that IL-17 is related to the occurrence and development of hepatic fibrosis in advanced schistosomiasis. In patients and animals infected by schistosome, the amount of IL-17 and collagen is higher compared with the normal [88, 89]. Therefore, Th17 or IL-17 can be regarded as one indicator of hepatic fibrosis.

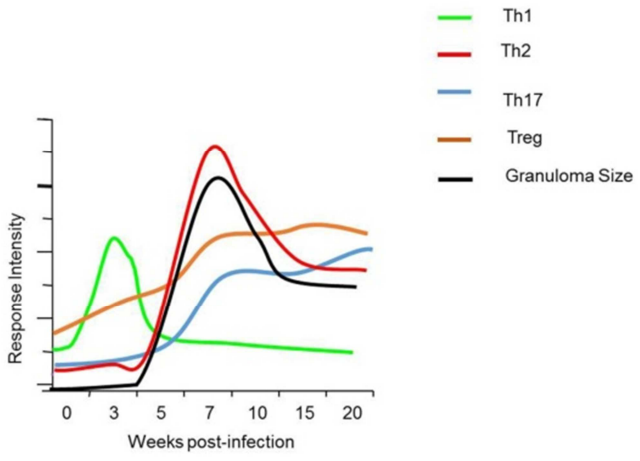

Figure 2. *The immunomodulation tendency of Th1, Th2, Th17, Treg during different phases of schistosomiasis. In the phase of early schistosomiasis, host immunity dramatically concentrates on Th1 response. Stimulated by cytokines IL-4, IL-5, IL-10 and IL-13, host immunity will shift from Th1 cell-mediated immune response to Th2 polarization. 7 weeks after infection, Th2 immunity peaked. The proportion of Th17 cells increase slowly within 5 weeks in post-infection, then increase rapidly after 5 weeks. The proportion of Treg cells continued to increase after infection in C57BL/6 mice infected with S. japonicum.*

Meanwhile, another newly identified T regulatory (Treg) cell was also found that can be differentiated from naïve $CD4^+$ T cell in vitro [90, 91], which mainly characterized by CD25 and forkhead family transcription factor 3 (Foxp3). When lacking of IL-6, TGF-β inducing the expression of Foxp3, then Foxp3 combined with RORγt, promoting naïve $CD4^+$ T cell differentiated to Treg cells. They mainly produce IL-10 and TGF-β immunosuppressive cytokines (Figure 1) [92]. Treg cells generally down-regulate immune response to diminish tissue damage [93, 94]. In chronic inflammation, Treg cells play a role in producing various anti-inflammatory factors. Studies have shown that in some parasitic infection, Treg cells are to regulate excessive immunity. Researches show that the proportion of Treg cells continued to increase after infection in the spleen of C57BL/6 mice infected with *S. japonicum* [95] (Figure 2).

The balance of Th17/Treg is conductive to the body's immune homeostasis. Normally, Th17/Treg cells are in homeostasis, multiple cytokines participate in regulating Th17/Treg balance. TGF-β together with IL-6 is not only participates in hepatic fibrosis, but also in regulating the balance between Th17 and Treg. Hepatic microcirculation changes and the amount of TGF-β and IL-6 changes, which strikes the balance of Th17/Treg by releasing a large number of inflammatory cytokines, activating hepatic stellate cells (HSC) into myofibroblast, release a large number of ECM, eventually lead to chronic fibrosis.

4. Conclusions

Th cell cytokines play an influential role in hepatic fibrosis process caused by schistosomes, especially the balance of Th immune response is closely related to the development of hepatic fibrosis. Reports have pointed out that Th2 and Th17 cells can raise granuloma formation by the secretion of IL-4 and IL-17 respectively; while Th1 and Treg cells can reduce granuloma formation [66, 96, 97]. Understanding the immune molecular mechanism of schistosomiasis will contribute more to effective prevention and control.

At present, anti-fibrosis treatment mainly focus on eliminating and inhibiting inflammation, there are no effective drugs that can significantly reduce or reverse fibrosis. Therefore, the pathogenesis and molecular mechanism of hepatic fibrosis caused by schistosomiasis is urgent. Besides, looking for potential drug targets, especially the cross targets to develop a highly specific anti-fibrosis drug is in urgent, so as to achieve the aim of reduce or even reverse fibrosis.

Conflict of Interest Statement

All the authors do not have any possible conflicts of interest.

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