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Is *Schistosoma mansoni* playing a part in liver carcinogenesis?

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Review Article

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Abstract

The relationship between *Schistosoma mansoni* (Sm) and hepatocellular carcinoma (HCC) has been evaluated by many studies that point towards a co-relation between schistosomal infection and HCC. While many such studies demonstrated that Sm infection in the presence of another carcinogenic factors leads to HCC, none of these studies could conclusively prove the cancer-inducing ability of Sm in humans, independent of other carcinogenic factors. The aim of this work is to present the current understanding on the association of Sm with HCC. Many epidemiological, pathological, and clinical studies have shown the role of multiple events like chronic inflammation and fibrosis as well as hepato-toxic agents like soluble egg antigens (SEAs), which help in creating a micro-environment which is suitable for HCC development. The role of Sm infection and deposited eggs in causing persistent inflammation, advanced fibrosis, and the role of SEAs, especially IPSE/alpha-1, is emphasised. This work concludes that Sm infection has the potential to induce cancer independently but the same has not been reported in humans to date. Extensive research is required to establish a causal relationship between Sm infection and HCC induction, or a complete lack thereof. However, Sm infection definitely acts along with other carcinogenic factors to induce HCC at a much faster pace and also leads to an aggressive form of liver cancer, which the other carcinogenic factor could not have achieved alone.

Introduction

Cancer induction is dependent upon drastic changes in cellular behaviour, making cells divide continuously, which interferes with normal physiology of the body (Cooper and Hausman 2007; Jain *et al.* 2019). Cancer induction is mostly dependent upon genetic mutations caused by the agents capable of cancer induction called carcinogens. At the genetic level, a 'loss-of-function' mutation in tumour suppressor genes like *BRCA1, p53*, and *Rb1* and/or a 'gain-of-function' mutation in proto-oncogenes like *Raf*, *Ras*, and *Her-2/Neu* leads to carcinogenesis (Lodish et al 2003; Jain and Kumar 2020).

Trematodes, which belong to phylum Platyhelminthes, are worm-like parasites which generally develop through the egg, larval, and adult stages (Roberts *et al.* 2012). Certain trematodes belonging to three genera – namely *Schistosoma*, *Clonorchis*, and *Opisthorchis* – have been classified as carcinogens by the International Agency for Research on Cancer (IARC) (Jain *et al.* 2023).

IARC classifies carcinogens into different groups on the basis of evidence supporting their carcinogenicity in humans. Agents in group 1 are carcinogenic to humans, whereas those in group 2 are plausible carcinogens lacking conclusive evidence of their cancer-inducing abilities in humans. Group 2 is divided into two sub-groups: 2A (probable carcinogens) and 2B (possible carcinogens). The terms 'probable' and 'possible'" have no quantifiable significance and only represent different levels of evidence of carcinogenicity, with group 2A agents having stronger indications for human carcinogenicity. Agents in group 3 are non-classifiable due to lack of a sufficient amount of data for their carcinogenic abilities (Jain and Rana 2024). The amended preamble of IARC (2019) defines clear categories and detailed combinations for evidence (evidence in humans, animals, and mechanistic evidences) to classify an agent in these groups. As per this amended preamble (IARC website) for agents in group 3, there exists a lack of any evidence for carcinogenicity in humans, but there is sufficient evidence of cancer in animal models, and there exists strong mechanistic evidence that does not operate in humans.

In 2020, liver cancer (LC) became the third leading cause of cancer deaths (830,000 deaths in 2020) globally and is the sixth most commonly diagnosed cancer. Mortality from LC among men is higher than women. LC is an umbrella term involving multiple cancers including hepatocellular carcinoma or HCC (75% to 85%) and intrahepatic cholangiocarcinoma or cancer of the bile duct (10% to 15%), along with rare LC types like liver angiosarcoma, fibrolamellar carcinoma, and hepatoblastoma (Sung *et al.* 2021). Recent studies have linked *Schistosoma mansoni* (Sm) infection with HCC induction. HCC induced by Sm has been a focus of research,

but the association is still understudied. Currently, IARC puts infection with Sm in group 3 of the classification of carcinogens.

HCC induction is linked with an array of risk factors that can work together to initiate liver fibrosis and cirrhosis, predisposing the liver to cancer induction (Pinter *et al.* 2016). Such risks include infection with Hepatitis B virus (HBV) and HCV (Ng and Wu 2012), chronic and heavy alcohol (above 80g ethanol/day) intake (Morgan *et al.* 2004), tobacco smoking (Jain *et al.* 2021), non-alcoholic steatohepatitis (Dhamija *et al.* 2019), exposure to hepatocarcinogen Aflatoxin B1 (Hamid *et al.* 2013), rare medical conditions like Wilson's disease (Xu and Hajdu 2008), Porphyria cutanea tarda (Baravelli *et al.* 2019), and untreated hereditary hemochromatosis (Elmberg *et al.* 2003). Interestingly, alcohol use can also lead to HCC induction without causing cirrhosis (Morgan *et al.* 2004).

Certain studies suggest Sm to be playing an active role in HCC induction. Hence, this review has two main aims. First, it presents multiple studies, including epidemiological, clinical, pathological, and case studies, which link Sm with HCC. Second, it highlights the probable induction mechanisms of HCC by Sm and comments upon the independent cancer induction potential of Sm.

Schistosoma mansoni: Life cycle

Schistosomes, or blood flukes, are largely parasitic to warm-blooded vertebrates, and they cause schistosomiasis (Roberts *et al.* 2012). Schistosomiasis is a unique disease as most of the pathogenesis occurs due to the deposited eggs and not the adult worms. The female worm deposits the eggs into smaller veins that traverse the walls of venule, some tissues, and depending upon the species of *Schistosoma*, the bladder or gut mucosa. Finally, they reach a position from where expulsion from the human host is possible (Colley *et al.* 2014).

Eggs hatch upon reaching freshwater, leading to the emergence of miracidia. After coming in contact with a suitable snail host, *Biomphalaria* spp. and *Tropicorbis* spp. in the case of Sm, miracidia develops into a mother sporocyst, which further produces daughter sporocysts. Daughter sporocysts lead to the emergence of cercaria, which infect humans by penetrating the skin and becoming schistosomulae by shedding their tails (Roberts *et al.* 2012; Colley *et al.* 2014).

These schistosomulae migrate through venous circulation to the lungs followed by the heart, and then develop in the liver. Upon maturity, Sm worms exit the liver through the portal vein system and migrate to veins draining the large intestine where they copulate and start producing eggs (CDC website). However, in some cases, few eggs travel back to the liver through the hepatic vessel instead of ending up into faeces and lead to granuloma formation (Deslyper *et al.* 2019).

Connection between Sm and HCC: Evidences from literature

Evidences from animal models

Initial studies on animal models suggested Sm infection to be acting in synergism with other factors and advancing induction of HCC where this other carcinogenic factor, independently, might have initiated carcinoma later and in milder form.

One such study involved a mouse model where female mice were divided in three groups where the first group was orally given a carcinogen (N-2-fluorenylacetamide), the second group was exposed to twenty cercariae of Sm, and the third group received both. At forty weeks post infection, 6.3% of mice in the first group (carcinogen alone) developed liver tumours, whereas no mice in second group (exposed to cercariae) developed tumours. Interestingly, about 47% of mice in third group developed liver tumours at forty weeks, signifying early and distinct production of liver tumours (Kakizoe 1985).

In a similar but relatively recent study, 500 parasite-free mice were divided into four groups where group 1 was exposed to a known carcinogen (diethylnitrosamine (DEN)), group 2 was exposed to a carcinogen as well as infected with Sm, group 3 was only exposed to Sm infection, and group 4 was the control. Tumour markers (i.e., alpha fetoprotein (AFP) and ferritin) were examined by ELISA, and the mice were later sacrificed for histo-pathological examination of livers. Results showed that Sm enhanced and aggravated the carcinogenic effects of DEN. When compared to controls, the serum level for AFP and ferritin showed earlier and statistically significant differences in group 2 than in group 1. This study also concluded that Sm accelerates hepatic dysplastic changes, which, along with other risk factors for carcinogenesis, makes an early and more aggressive cancer appearance (El-Tonsy *et al.* 2013).

Apart from the mouse model, a study reported a chimpanzee with HCC who had a chronic Sm infection and was negative for HBV and HCV infection (Abe *et al.* 1993).

Evidences from humans

Studies linking Sm infection with liver carcinoma in humans began in late 1900s. One such study dates back to 1978 when K. E. Mott published an observation suggesting a possible relationship between infection with *Schistosoma* spp. (Sm and *Schistosoma japonicum* (Sj)) and liver carcinoma (Mott 1978). However, a few years later, another study suggested that the association between Sm and HCC may be coincidental especially in regions where Sm is endemic (Pereira and Goncalves 1984).

A study that aimed at understanding the prevalence of hepatitis viruses and Sm infection among patients with chronic liver disease found that HCV infection along with Sm infection is a major risk factor for chronic liver disease (including liver cancer) in Egypt (Halim *et al.* 1999). In another study conducted in Brazil, an institutional database was screened from 2002 to 2015 to retrospectively identify patients with HCC who had Sm infection. A total of seven patients were identified in this analysis. All of these patients had negative HCV serology, and four were positive for HBV core antibodies but lacked any evidence of viral replication. The study concluded that Sm acts as an important co-factor for hepatic lesions and injury, but they could not conclude if Sm infection alone could induce HCC (Toda *et al.* 2015).

Another group from Egypt focused specifically on understanding the relationship between Sm infection and HCC induction. In this study, two groups were formed. The first group had 29 patients who were negative for schistosomiasis (tested by indirect hemagglutination assay (IHA)) with no history or evidence of current or previous Sm infection but were HCV positive. The second group had 46 patients who had positive IHA for schistosomiasis and were HCV positive. As all the patients in both the groups were positive for HCC, the study concluded that co-infection increased incidence of HCC in the second group. The aggression of HCC was also higher in the second group, which is in line with observations from previous studies (El-Tonsy *et al.* 2016).

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A clinical study carried out in Brazil analysed 6 HCC patients who were admitted for liver transplantation. Patients belonged to endemic regions of Sm infections and had Sm-associated fibrosis, but cirrhosis was not observed in the histo-pathological analysis of the resected livers. Further, all the patients had a negative serology for HBV and HCV, which suggested that Sm infection might have predisposed the patients towards HCC, but a causal relationship could not be established in this study as well (Filgueira *et al.* 2018).

A recent observational study with a much larger sample size, which ranged from years 2009 to 2019 (1,446 patients with HCC), divided the patients in two groups. Group 1 (688 patients) had patients with a history of Sm infection, whereas group 2 (758 patients) had no apparent history of Sm infection. It was concluded from all the studied parameters that Sm infection not only increases the risk of HCC but also interferes with HCC treatment response, as the response was found to be better in group 2 (Shousha *et al.* 2022).

Pathogenesis and carcinogenesis

The role of Sm in the induction and progression of HCC, or acting as a co-factor along with other carcinogens, remains controversial. Similar to this observation, its pathogenesis and probable mechanism in carcinogenesis (irrespective of inducer or promoter role) is also unclear; however, deregulation of many important signalling molecules and transcription factors indicate towards its role in carcinogenesis.

Pathogenesis

Sm pathogenesis develops with the initiation of a moderate Th1 response, which is marked by high levels of pro-inflammatory cytokines including interleukin-1 (IL-1), IL-6, tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ). After about 6 weeks of infection, Sm worms mature, and females start depositing eggs. These deposited eggs then release soluble egg antigens (SEAs), which interact with the immune system (Hiatt *et al.* 1979). SEAs lead to the release of pro-inflammatory cytokines through resident macrophages leading to recruitment of monocytes, lymphocytes, and neutrophils, which leads to initiation of granuloma formation and inflammation (Stadecker 1999; Shaker *et al.* 2014). With time, SEAs act as a key force behind the transition of a pro-inflammatory Th1 response to a relative anti-inflammatory Th2 response, which is characterised by increased levels of IL-4, IL-10, and IL-13 and recruitment of eosinophils (Pearce *et al.* 1991; Zheng *et al.* 2020).

The development of granulomas is supposed to be a beneficial response for the host as it sequesters the eggs, which, if left unchecked, can lead to a heightened and uncontrolled inflammatory response, leading to permanent tissue damage (Nono *et al.* 2017). However, granulomas become detrimental for the liver as it leads to liver fibrosis (Morais *et al.* 2008; Culver *et al.* 2016). Egg granulomas are majorly composed of a huge number of eosinophils, lymphocytes, monocytes, macrophages, and neutrophils (Liu *et al.* 2022) and are known to contain T lymphocytes of both Th1 and Th2 responses (Bogen *et al.* 1995). An SEA (i.e., IPSE/alpha-1 (interleukin-4-inducing factor from schistosome eggs)) is a major hepato-toxin (Abdulla *et al.* 2011) that is linked with the enlargement of these granulomas (Fahel *et al.* 2010).

Interestingly, the cores of granulomas have different immune cells depending upon the infecting schistosomal species (Jain and Rana 2024). Apart from Sm, Sj has also been implicated in HCC induction and has been classified as a possible carcinogen (group 2B of IARC classification) (IARC 1994). Both Sj and Sm are capable of granuloma formation, but the granulomas elicited by them show distinct cellular composition. The core of a granuloma elicited by Sj is mainly composed of neutrophils, whereas that of Sm is primarily composed of eosinophils. A chemokine binding protein that is secreted by Sm eggs is capable of binding to a specific chemokine and inhibiting its action. It binds to neutrophil chemo-attractant CXCL8 but does not bind to eosinophil chemo-attractant CCL11, which blocks the infiltration of neutrophils but not eosinophils (Chuah *et al.* 2014; Jain and Rana 2024).

Liver fibrosis, which initiates in response to the deposited Sm eggs and mainly occurs in the hepatic sinusoids and portal veins (Hoffmann *et al.* 2000; Wang *et al.* 2020), encompasses an excessive deposition of the extracellular matrix (ECM), including a down-regulation of ECM degradation and an up-regulation of ECM production. Hepatic stellate cells (HSCs) are a source of collagen and have the potential to abundantly secrete ECM proteins and tissue inhibitors of metalloproteinases, all of which are responsible for changing the liver architecture (Puche *et al.* 2013). These accumulated proteins initiate the distortion of the hepatic architecture (Bataller and Brenner 2005), which is followed by periportal hepatic fibrosis (PHF), the most serious manifestation of chronic schistosomal infection.

PHF impedes the blood flow and the nutrient reach to the liver, causing impairment of liver function. This can lead to an advanced stage of liver fibrosis leading to cirrhosis. Cirrhosis involves permanent replacement of healthy liver tissue with scar tissue. This interferes with the normal function of the liver, disposing it towards cancer induction (Pinter *et al.* 2016), and ultimately leads to portal hypertension, hepatomegaly, and splenomegaly. It also predisposes the patient to liver failure if not provided with appropriate treatment (Wiest *et al.* 1993; Coutinho *et al.* 2005; Kamdem *et al.* 2018; von Bülow *et al.* 2021; Jain and Rana 2024).

A number of studies have shown a very high proportion of people being infected with HBV and/or HCV viruses as well as Sm, especially in endemic regions (Michielsen *et al.* 2005; Gasim *et al.* 2015). In the case of HBV, 300 million people are globally co-infected with HBV and Sm (Khatami *et al.* 2021). Multiple studies show that the concomitant infection with hepatitis viruses and Sm causes advanced liver diseases and worsens the outcome especially if viral load is high, leading to an increased mortality rate. This increased mortality is a result of increased incidences of cirrhosis as well as advanced and more aggressive HCC progression (Omar 2019; Allam *et al.* 2023).

Carcinogenesis

All the pathologic factors from initiation of inflammation to fibrosis, cirrhosis, and co-infection with hepatitis viruses lead to a cascade of events at the molecular and genetic level that destabilises the genetic makeup. Mutations in proto-oncogenes and tumour suppressor genes lead to the induction of cancer. Chronic inflammation can lead to the production of reactive oxygen species (ROS), which exert an oxidative stress and induce oxidative damage to both nuclear and mitochondrial DNA as well as affect signal transduction pathways (Wang *et al.* 2016).

Similarly, an array of studies have linked liver fibrosis and cirrhosis with the shortening of telomere length in the liver cells (Donati and Valenti 2016; Barnard *et al.* 2018; Shin *et al.* 2021), and such telomere shortening in hepatocytes has been correlated with

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chromosomal instability, which has the potential to initiate hepatoma in humans (Plentz *et al.* 2004). A number of other signalling molecules, transcription factors, and cellular receptors have been linked with Sm and HCC and are described below.

A study involved the examination of the relationship between Sm infection and ROS production and inflammosome activation (Chen *et al.* 2019). It found that, along with a heightened release of ROS and other super-oxides, expression of an important transcription factor linked with expression of pro-inflammatory genes as well as cell survival (i.e., NF-κB) (Liu *et al.* 2017) is also increased along with activation of NLRP3 and AIM2 inflammasomes (Chen *et al.* 2019). This implied the role of Sm infection in prolonging cell survival as well as the creation of inflammatory conditions that predispose hepatic tissue to cancer. A recent study has shown that oxidative stress induced by deposited eggs triggers proliferation of human hepatoma cells, thus supporting cancer progression (von Bülow *et al.* 2024).

Another study (Roderfeld *et al.* 2020) analysed the activation of critical hepatic cancer regulators, c-Jun and STAT3, by Sm infection in the liver of hamsters, primary hepatocytes, Huh7 cells, and human liver biopsies. A permanent activation of these hepatic cancer-associated regulators (i.e., as c-Jun and linked transcription factor STAT3) was observed by SEAs released from tissue-trapped eggs, which seem to be significant contributors in the development of liver cancer in Sm-infected patient. Interestingly, IPSE/alpha-1 is one of the major SEAs behind the activation of these regulators (Roderfeld *et al.* 2020).

IPSE/alpha-1 is also linked with the development of B-regulatory cells (Bregs), which are known to accelerate HCC by inducing growth and promoting the migratory potential of cancer cells. Bregs also lead to the production of IL-10, which induces T-regulatory cells (Tregs) differentiation. Tregs induce a tolerogenic microenvironment encouraging cancer growth (Shao *et al.* 2014; Haeberlein *et al.* 2017; Lurje *et al.* 2020). This tolerogenic environment, which, along with Tregs, is also composed of Th2 milieu and tolerogenic dendritic cells, suppresses tumour-specific immune responses, and establishes an immunosuppressive tumour microenvironment linking Sm with HCC-inducing potential (Chaudhary and Elkord 2016).

SEAs from Sm eggs are also known to promote endothelial cell proliferation *in vitro* as well as up-regulate VEGF in human endothelial cells, hence inducing angiogenesis-related processes that can contribute to neo-vascularisation and help in development and progression of hepatic cancer (Freedman and Ottesen 1988; Loeffler *et al.* 2002).

Similarly, the expression level of a protein, high mobility group box 1 (HMGB1), has been reported to be heightened in serum levels of patients with schistosomiasis. It not only contributes to liver inflammation and tissue injury but also is responsible for enabling HSCs to change to a proliferative myofibroblast-like phenotype (Zhong *et al.* 2022). The initiation and progression of liver fibrosis involves activation and proliferation of HSCs. Quiescent HSCs (qHSCs) get activated in response to fibrotic stimuli, including persistent inflammatory responses induced by chronic infection, to become activated HSCs (aHSCs) (Wynn 2008; Li *et al.* 2015), which subsequently transform into myofibroblasts (Zhang *et al.* 2016). This predisposes heptic tissue to advanced fibrosis and probable cirrhosis, ultimately leading to a potential HCC.

Tumour aggressiveness in hepatic tissue cancer has been linked to the expression of programmed death ligand 1 (PD-L1). The expression of PD-L1 is increased in macrophages in patients with Sm infection. An increase in its expression promotes tumour progression and probably its induction as it helps cancer cells to escape the host's immune response, which is linked to T cell anergy (Smith *et al.* 2004; Calderaro *et al.* 2016).

Discussion

Epidemiological, clinical, observational, and surgical studies suggest a link between Sm infection and liver cancer; however, of all the above described studies, none claimed or conclusively proved that Sm is solely responsible for liver cancer induction.

There appears to be a spectrum of studies where on one end, very few studies claim Sm infection among HCC patients to be a co-incident (Pereira and Goncalves 1984). On the other end, many studies claim Sm being an important co-factor in liver carcinogenesis, where it definitely promotes the cancer in a more aggravated fashion once it has been induced by some other carcinogenic factor independently or along with Sm infection (Smith *et al.* 2004; El-Tonsy *et al.* 2013; Toda *et al.* 2015; El-Tonsy *et al.* 2016; Filgueira *et al.* 2018). This 'inconclusive conclusion' regarding the independent potential of Sm infection to induce HCC justifies its placement in group 3 of IARC carcinogen classification.

Immune response against the deposited Sm eggs is very much capable of granuloma formation (Morais *et al.* 2008; Culver *et al.* 2016), which leads to fibrosis, which can cause cirrhosis if left untreated (Pinter *et al.* 2016)). IPSE/alpha-1 further leads to the enlargement of granulomas, which can contribute to a strong fibrotic response (Fahel *et al.* 2010).

Conditions like chronic smoking, alcohol abuse, and non-alcoholic steatohepatitis, which are not linked with Sm infection, are known to induce HCC by causing heightened inflammation, fibrosis, and cirrhosis (Matsushita and Takaki, 2019; Jain *et al.* 2021; Dhamija *et al.* 2019; NIH 2022). A parallel can be drawn here. Sm infection can lead to fibrosis and cirrhosis, and fibrosis and cirrhosis have led to HCC in multiple cases not linked with Sm (cited above); hence, Sm infection has the potential to induce HCC here probably by employing similar mechanisms at the cellular and genetic level as in these Sm-independent HCC induction cases. Theoretically, it seems like a plausible hypothesis, but it has not been proven to date.

Studies on SEAs and their carcinogenic abilities, especially IPSE/alpha-1, further creates grounds for stringently evaluating Sm infection as a potential liver carcinogen. Not only does IPSE/alpha-1 lead to the enlargement of granulomas, but it leads to the activation of c-Jun and STAT3, is linked with Bregs development which causes HCC acceleration, and induces Tregs differentiation which dampens tumour specific immune responses. All these events create a tolerogenic microenvironment that favours HCC development and progression (Shao *et al.* 2014; Haeberlein *et al.* 2017; Lurje *et al.* 2020; Roderfeld *et al.* 2020).

Along with these factors, other responses like the activation of NLRP3 and AIM2 inflammasomes (Chen *et al.* 2019), HMGB1 induced inflammation and HSCs stimulation (Zhong *et al.* 2022), SEA induced up-regulation of VEGF and neo-vascularization (Freedman and Ottesen 1988; Loeffler *et al.* 2002), and up-regulation of PD-L1 in macrophages and linked T cell anergy (Smith *et al.* 2004; Calderaro *et al.* 2016) together are creating an inflammatory and angiogenic environment that is well suited for cancer induction.

All these changes can lead to many mutations at the genetic level in proto-oncogenes as well as tumour suppressor genes, which can lead to the induction of HCC. Sister chromatid exchanges, breakage of DNA strands, and disequilibrium of oncogenes and onco-suppressor genes are some of the contrivances through which

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mutations in these genes predispose hepatic cells towards malignant transformation (Herrera *et al.* 2005).

It can hence be concluded that Sm infection has the potential to predispose hepatic tissue towards carcinogenesis and induce cancer, but this independent induction of HCC by Sm infection has not been reported in humans. That being said, Sm infection definitely acts along with other carcinogenic factors to induce HCC at a much faster pace and also leads to a belligerent form of HCC, which the other carcinogenic factor could not have achieved alone.

Widespread epidemiological, clinical, pathological, and experimental studies are required to accurately examine and understand the relationship between Sm and HCC. Although multiple studies point in this direction, wide-ranging proofs will be required to test and conclusively state if Sm is a liver carcinogen. A beneficial step in this direction can be broad monitoring of Sm-infection positive patients suffering from HCC, especially in endemic regions, where HCC was not probably induced by other factors like hepatitis viruses, inherited genetic defects, liver injury, or substance abuse. This should help in clearly visualising a causal relationship between Sm infection alone and HCC induction, or an absence of it.

Abbreviations.

AFP:	Alpha fetoprotein
aHSCs:	Activated hepatic stellate cells
Bregs:	Regulatory B cells
DEN:	Diethylnitrosamine
ECM:	Extra-cellular matrix
HBV:	Hepatitis B virus
HCC:	Hepatocellular carcinoma
HCV:	Hepatitis C virus
HMGB1:	High mobility group box 1
HSC:	Hepatic stellate cells
IARC:	International Agency for Research on Cancer
IFN-γ:	Interferon gamma
IHA:	Indirect hemagglutination assay
IL:	Interleukin
IPSE/alpha-1:	Interleukin-4-inducing factor from schistosome eggs
LC:	Liver cancer
PD-L1:	Programmed death ligand 1
PHF:	Periportal hepatic fibrosis
qHSCs:	Quiescent hepatic stellate cells
ROS:	Reactive oxygen species
SEA:	Soluble egg antigens
Sj:	*Schistosoma japonicum*
Sm:	*Schistosoma mansoni*
TNF-α:	Tumour necrosis factor alpha
Tregs:	Regulatory T cells

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