Journal of Helminthology

www.cambridge.org/jhl

Can *Schistosoma japonicum* infection cause liver cancer?

S. Jain

Independent Researcher, Institute for Globally Distributed Open Research and Education (IGDORE), Rewari, Haryana, India

Review Article

Cite this article: Jain S (2025). Can *Schistosoma japonicum* infection cause liver cancer?. *Journal of Helminthology*, **99**, e11, 1–11
https://doi.org/10.1017/S0022149X24000762.

Received: 05 September 2024
Revised: 20 October 2024
Accepted: 24 October 2024

Keywords:
Schistosoma japonicum; liver cancer; inflammation; cirrhosis; granuloma

Corresponding author:
S. Jain;
Email: jain.sidhant482@gmail.com

Abstract

A co-relation between *Schistosoma japonicum* (Sj) and liver cancer (LC) in humans has been reported in the literature; however, this association is circumstantial. Due to the inconclusive nature of this association, the International Agency for Research on Cancer has placed Sj in Group 2B for LC, signifying it to be a 'possible carcinogen'. Many epidemiological, pathological and clinical studies have identified multiple factors, linked with Sj infection, which can lead to liver carcinogenesis. These factors include chronic inflammation in response to deposited eggs (which leads to fibrosis, cirrhosis and chromosomal instability at cellular level), hepatotoxic effects of egg-antigens, co-infection with hepatitis viruses, and up-regulation of glycolysis linked genes among others which predisposes hepatic tissue towards malignant transformation. The objective of this work is to present the current understanding on the association of Sj infection with LC. Mechanisms and factors linked with Sj infection that can lead to LC are emphasized, along with measures to diagnose and treat it. A comparison of liver carcinogenesis is also provided for cases linked with and independent of Sj infection. It appears that Sj, alone or with another carcinogen, is an important factor in liver carcinogenesis, but further studies are warranted to conclusively label 'infection with Sj alone' as a liver carcinogen.

Introduction

Cancer involves significant changes in the normal behaviour of cells, making them divide continuously, which interferes with normal physiology of the body (Cooper & Hausman 2007; Jain et al., 2019; Jain, 2024). Carcinogens are agents capable of cancer induction that takes place mostly by genetic mutations. At the genetic level, a 'gain-of-function' mutation in proto-oncogenes like *Her-2/Neu*, *Raf*, *Ras* or a 'loss-of-function' mutation in tumour suppressor genes like *p53*, *Rb1*, and *BRCA1* lead to cancer induction (Lodish et al 2003; Jain & Kumar, 2020).

Helminths are worm-like parasites with flat, elongated or round bodies and they generally develop through egg, larval and adult stages (Roberts et al., 2012). Helminths belonging to three genera, namely *Schistosoma*, *Clonorchis* and *Opisthorchis*, have been classified as human carcinogens by International Agency for Research on Cancer (IARC) (Jain et al., 2023). IARC classifies carcinogens into three different groups on the basis of evidence of their cancer-causing ability towards humans. Group 1 agents are carcinogenic to humans whereas those in group 2 are plausible carcinogens which lack a confirmatory evidence of their carcinogenicity towards humans. Group 2 is bifurcated into two sub-groups: 2A (probable carcinogens) and 2B (possible carcinogens). Importantly, the terms 'probable' and 'possible' have no quantitative significance and only depict different levels of evidence of carcinogenicity, with group 2A agents having a relatively higher level of evidence for human carcinogenicity. Agents in group 3 are non-classifiable due to lack of sufficient amount of data for their carcinogenic abilities in humans (Jain & Rana, 2024; Jain, 2024).

In 2020, liver cancer (LC) has been identified as third leading cause of cancer deaths worldwide and is the sixth most commonly diagnosed cancer. Approximately 830,000 deaths were reported in 2020, with mortality among men being higher than women. LC primarily includes hepatocellular carcinoma (HCC; 75%–85%) and intrahepatic cholangiocarcinoma (10%–15%) and other rare LC types like fibrolamellar carcinoma, hepatoblastoma and liver angiosarcoma (Sung et al., 2021).

Recent studies have linked *Schistosoma japonicum* (Sj) infection with LC. LC linked with Sj (SJLC) has been a focus of research but the association is still understudied. The IARC has placed Sj in group 2B (i.e., possible carcinogen) (IARC, 1994). Hence, the aim of this review is multi-directional. First, it presents multiple studies, including epidemiological, pathological and clinical studies which link Sj with LC. It is followed by a detailed explanation of probable induction mechanism along with discussion of third-party risk factors (hepatitis viruses) and contrasts it with induction of LCs not associated with Sj. Finally, the work further looks into diagnosis and treatment modalities for SJLC and comments upon the current understanding of the probable causal role of Sj in liver carcinogenesis.

1. *Schistosoma japonicum*: Life cycle and Schistosomiasis

Schistosomes are ordinarily known as blood flukes and are largely parasitic to warm-blooded vertebrates and cause Schistosomiasis (Roberts et al., 2012). Schistosomiasis is a unique disease as almost the entire pathogenesis occurs due to eggs and not adult worms. The female deposits the eggs into smaller veins which then traverse the walls of venule, some tissues, and bladder or gut mucosa (depending upon the species of *Schistosoma*) and reaches a position from where they can be expelled from the human host (Colley et al., 2014).

Upon reaching fresh water, the hatching of eggs takes place; this is facilitated by the lower osmolarity of water, leading to emergence of miracidia. After coming in contact with suitable snail host, *Oncomelania* spp. in the case of Sj, miracidia develops into mother sporocyst which produces daughter sporocysts. This is followed by emergence of cercaria from the daughter sporocysts about 4 weeks after the snail host has been initially infected (Roberts et al., 2012; Colley et al., 2014). These cercaria then infect humans by penetrating the skin and shed their tail, becoming schistosomulae. The schistosomulae migrate through venous circulation to lungs, then to the heart, and then develop in the liver. Upon attaining maturation, worms exit the liver through the portal vein system (CDC 2024).

Sj first interacts with the liver when immature worms pass through it, but once the infection by cercaria and maturation of worms is completed in the liver, worms inhabit the mesenteric venules, where they copulate and produce eggs. In the case of Sj, which is mostly confined to Asia, the adult worms are more frequently found in superior mesenteric veins of the small intestine (Rudge et al., 2008; McManus et al., 2018). However, in some cases, a few eggs travel back to the liver through hepatic vessel instead of ending up in faeces. These eggs then induce granuloma formation (Deslyper et al., 2019).

2. Liver Cancer

LC induction is linked with an array of risk factors. These factors can act alone, but LC induction independently by these factors is extremely unfavourable and LC is generally induced when these factors occur together. Most of them lead to liver fibrosis and cirrhosis, which increases chances of LC induction. Cirrhosis involves replacement of healthy liver tissue with scar tissue which in turns blocks the blood flow to the liver. This interferes with the normal working of the liver, disposing it towards cancer induction (Pinter et al., 2016).

Risk factors leading to cirrhosis include infection with hepatitis B and C viruses (HBV and HCV) and chronic alcohol intake. Chronic HBV and HCV infection leads to chronic inflammation of healthy liver tissue which ultimately leads to cirrhosis (Ng & Wu, 2012). Heavy (>80 g ethanol/day) and chronic alcohol intake is also known to be an important risk factor in LC induction which leads to liver cirrhosis in many cases. However, alcohol use can also lead to LC induction without causing cirrhosis (Morgan et al., 2004). Similarly, tobacco smoking is another important risk factor in LC induction (Jain et al., 2021).

Non-alcoholic steatohepatitis, commonly known as NASH, is a severe form of non-alcoholic fatty liver disease (NAFLD) and is another important risk factor in LC (Dhamija et al., 2019). Aflatoxin B1, a chemical produced by fungus and a dangerous food contaminant, is a genotoxic hepatocarcinogen which leads to cancer induction by causing detrimental genetic changes in liver cells (Hamid et al., 2013). Rare genetic and medical conditions including Wilson's disease (Xu & Hajdu, 2008), Porphyria cutanea tarda (Baravelli et al., 2019), untreated hereditary hemochromatosis (Elmberg et al., 2003) among other issues are important risk factors in LC induction.

3. SJLC: Are they really connected?

The initial epidemiological studies, mostly carried out in Japan, to find a probable association between Sj infection and LC generated varied results. Several studies conducted in the Yamanashi Prefecture found possible connections between Sj and LC (Inaba, 1987). Three major studies were carried out in this project, specifically from the view point of epidemiology. First, a descriptive study, which found that relative to the country of Japan as a whole, an endemic area of schistosomiasis showed a higher mortality rate for LC (Inaba, 1987). Second, a case-controlled study found higher odds ratio for cases having a history of schistosomiasis but these values were similar to cases which had hepatitis B antigen (Inaba et al., 1984). Finally, a retrospective cohort study showed significant higher rates of mortality among male LC patients who were residing in the endemic areas (Inaba, 1984). All these studies pointed towards a strong yet circumstantial link between Sj and LC (Inaba, 1984; Inaba et al., 1984; Inaba, 1987).

A similar study in the Yamanashi Prefecture involving subjects who resided in the region between 1973 through 1992 (Takemura et al., 1998) also found possible connections between Sj and LC. It was concluded that chronic effects of Sj could contribute to high mortality rates of LC patients in endemic areas but cautioned about the other etiological factors like alcohol intake and infection with HBV and HCV.

In contradiction to these observations, another study from the Yamanashi Prefecture reported HCC incidences among patients enduring chronic schistosomiasis, but they did not find significant correlation between the same and blamed HCV for the development of HCC in schistosomiasis patients (Iida et al. 1999). A follow-up study in liver cirrhosis patients showed no difference in death rate among patients positive or negative for schistosomal infection, although the sample size in this study was small (from Inaba, 1987).

To avoid the interference by HBV and HCV, a case-controlled study was carried out on hepatitis-negative patients in China. This study concluded that Sj infection probably contributes to both colon cancer and LC (Qiu et al. 2005).

A pathological study involving 24 Sj-positive specimens found that Sj on its own, might not be responsible for HCC but probably has a synergistic role in HCC induction along with HBV (Nakashima et al., 1975). An autopsy study on 59 cases also could not generate conclusive evidence to label Sj as a direct factor in HCC induction but also found HBV to play a synergistic role (Kojiro et al., 1986).

In specific case studies, fine-needle aspiration and smear preparations have confirmed the co-existence of Sj and HCC (Chen et al., 2007; Saharti et al., 2018). A study which aimed to analyse the role of a specific heat shock protein in hepatic fibrosis using a mouse model showed Sj infection to be linked with hepatic fibrosis (Huang et al., 2014). Another study associated enhanced Wnt signalling pathway caused by Sj infection with liver fibrosis (Wang et al., 2017). Recently, a similar study which aimed at identifying gut micro-biota signatures in Sj-infected patients highlighted the induction of liver cirrhosis by Sj infection (Gui et al., 2021). Both liver fibrosis and cirrhosis are important events in

https://doi.org/10.1017/S0022149X24000762 Published online by Cambridge University Press

induction of LC, as discussed later. Yet another study found Sj responsible for significant prevalence of LC tumours in infected patients, among other digestive system tumours (Liu et al., 2023).

4. How is Sj likely inducing LC?

SJLC seem to be induced by an array of factors involving chronic inflammation in response to deposited eggs and secreted egg antigens (SEAs), granuloma formation followed by liver fibrosis and cirrhosis, ultimately inducing changes in genetic makeup and creating significant microenvironment conditions suitable for LC induction. Co-infection with HBV and HCV further facilitates LC induction.

4.1 Chronic inflammation

Liver pathology begins with lodging of schistosomal eggs in the liver sinusoids. These eggs, along with SEAs, trigger a significant T-helper 1 (Th1) type immune response. This involves an increased expression of Th1 type cytokines involving interleukin-1 (IL-1), IL-2, IL-6, interferon gamma, tumour necrosis factor alpha (Stadecker et al., 2004; Butrous et al., 2019; Zheng et al., 2020; Wang et al., 2023). Though Th-1 type immune response has a killing effect over schistosomes, it appears that humans lack the capacity to eliminate schistosomes, which might also be linked to escape mechanism used by these parasites (Trottein et al., 1999). Continuous stimulation by eggs and SEAs lead to an excessive Th1 inflammatory response.

After about four weeks of infection and egg production, the Th1 response shifts towards a Th2 response which exerts anti-inflammatory effects and regulates the immunopathology of Th1 response (Zheng et al., 2020). This response is marked by heightened secretion of Th2 cytokines involving IL-4, IL-5, and IL-13. These promote polarization of macrophages to M2 type macrophages, creating a microenvironment having a high level of type 2 immune responses which further promotes the formation of granulomas (Oliphant et al., 2011; Yunna et al., 2020).

4.2 Granuloma formation

Granuloma formation is supposedly beneficial for the host because it blocks the toxic effects of egg antigens released from the eggs (Morais et al. 2008; Jain & Rana 2024). Once the type 2 immune responses set in, granuloma formation begins. Egg granulomas are generally composed of massive number of lymphocytes, monocytes, macrophages, eosinophils and neutrophils (Liu et al., 2022). Granulomas contain T-lymphocytes of both Th-1 and Th-2 response types (Bogen et al., 1995).

The core of granuloma might have different immune cells depending upon the species of schistosome that has infected the host (Jain & Rana 2024). Apart from Sj, *Schistosoma mansoni* (Sm) has also been implicated in LC induction but currently has been assigned to Group 3 of IARC classification (von Bülow et al., 2021). Regardless of LC induction, both parasites are capable of granuloma formation. Granulomas elicited by Sj and Sm show distinct cellular composition. Chemokine binding protein 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. This blocks the infiltration of neutrophils but does not block the infiltration of eosinophils as shown in Figure 1, hence leading to a distinct granulomatous pathology where granulomas elicited by Sj will have core mainly of neutrophils, whereas that elicited by Sm will have a core mainly of eosinophils (Figure 1) (Chuah et al. 2014; Jain & Rana 2024). While granulomas rarely cause structural liver damage (Culver et al., 2016), they lead to fibrosis in the periportal space.

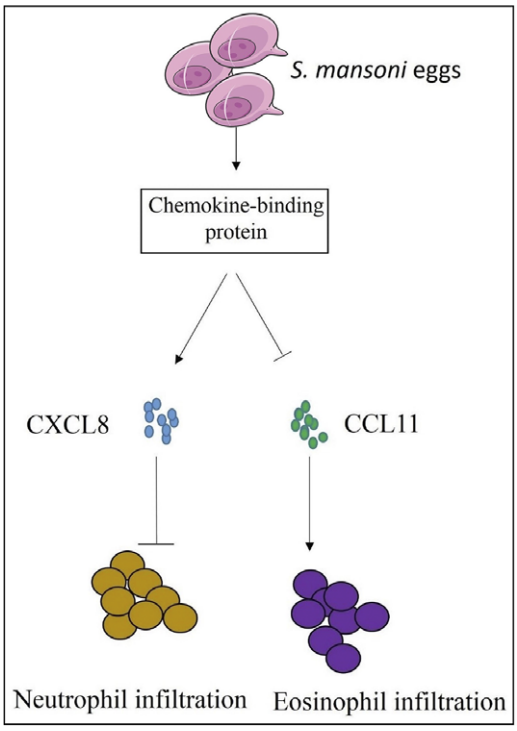

Figure 1. Granuloma's core composition in case of infection with *Schistosoma japonicum* and *Schistosoma mansoni*. Binding of a specific chemo-attractant to chemokine-binding protein secreted by *Schistosoma mansoni* leads to recruitment of eosinophils in the core of granuloma elicited by it. This is distinct to the core of granuloma elicited by *Schistosoma japonicum* which is mainly composed of neutrophils.

A study conducted in mice showed that neutrophils can cause major hepatic necrosis and are progenitors of hepatic fibrosis in acute stage of schistosomal infection (Hirata et al., 2002). The neutrophil core further produces pro-inflammatory cytokines, including IL-1α, IL-1β, IL-6, TNF, CCL3 and CXCL1, which contributes to overall local tissue damage (Chuah et al., 2013; Llanwarne & Helmby, 2021). These granulomas ultimately promote severe liver fibrosis, another step in LC induction (Wynn & Cheever, 1995).

4.3 Liver Fibrosis

Liver fibrosis involves excessive deposition of extracellular matrix (ECM) in the liver which also involves an up-regulation of ECM production and down-regulation of ECM degradation. These accumulated ECM proteins start distorting the hepatic architecture (Bataller & Brenner, 2005). Liver fibrosis occurs in the hepatic sinusoids and portal veins (Hoffmann et al., 2000; Wang et al., 2020).

These changes in hepatic architecture are followed by periportal fibrosis, which is also known as periportal hepatic fibrosis (PHF), the most serious manifestation of chronic schistosomal infection. PHF impedes the blood flow and hence impedes the nutrient reach to the liver, causing liver function impairment which can lead to an

https://doi.org/10.1017/S0022149X24000762 Published online by Cambridge University Press

advanced stage of liver fibrosis leading to cirrhosis. It ultimately leads to portal hypertension and hepatomegaly, splenomegaly and predisposes the infected person to a potential failure of liver if not provided with appropriate treatment (Wiest et al., 1993; Coutinho et al. 2005; Kamdem et al. 2018).

The initiation and progression of liver fibrosis to an advanced stage involves activation and proliferation of hepatic stellate cells (HSCs). Quiescent HSCs (qHSCs) are activated in response to fibrotic stimuli, including chronic inflammatory reactions, to become activated HSCs (aHSCs) (Wynn, 2008; Li et al., 2015). qHSCs are situated in the space of Disse, between hepatocytes and sinusoidal endothelial cells and constitute about 15% of the total liver resident cells. qHSCs play important roles in liver regeneration, vitamin A storage, immuno-regulation among others (Li et al., 2015; Zhang et al., 2016). aHSCs are 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).

A recent study found that schistosomal egg ribonuclease SjCP1412 promotes granuloma formation and accelerates liver fibrosis (Li et al., 2023). Another study which used a mouse model, concluded that aHSCs play an important role in liver fibrosis in Sj-infected host (Huang et al., 2022a). All these changes lead to an advanced stage of liver fibrosis and cirrhosis, which are major risk factors for HCC (Dhar et al., 2020). Interestingly, an egg antigen Sjp40 supresses HSC activation; however, it appears that it does so to prevent egg death as collagen deposits near the eggs are detrimental for their survival. This observation is supported by the fact that HSCs tend to be located on the margins of granulomas (Zhu et al., 2018; Li et al., 2022). Figure 2 shows a proposed mechanism on how Sj infection alone is inducing LC through chronic inflammation and SEAs, leading to fibrosis and cirrhosis and ultimately paving way for carcinogenesis.

4.4 Co-infection with HBV and HCV

Concurrent infections of Sj with HBV or/and HCV can lead to heightened liver deterioration and severe illness and is a risk factor for LC induction (Jain & Rana, 2024). Chronic schistosomiasis coupled with HBV or/and HCV infection not only affects the architecture of hepatocyte arrangement but is detrimental for the viability of hepatocytes (Omar, 2019).

A study reported that HBV/*Schistosoma* spp. concurrent infection from the years 1980–2014 ranged from as low as 9.6% to as high as 64% in Egypt among all reported schistosomiasis patients. For HCV, the figures for same period ranged between 1% in Ethiopia to 50% in Egypt. Same study also collated interesting data on the prevalence of co-infection HCV/HBV and hepatosplenic schistosomiasis (HSS). For HCV, of total patients with schistosomiasis, those with HCV and HSS ranged from as low as 0.06% in China to 40.2% in Egypt, whereas with all the same parameters, the cases for HBV and HSS ranged from 15.8% in Brazil to 58.4% in Egypt (Gasim et al., 2015). Concurrent infection of Sj and hepatitis

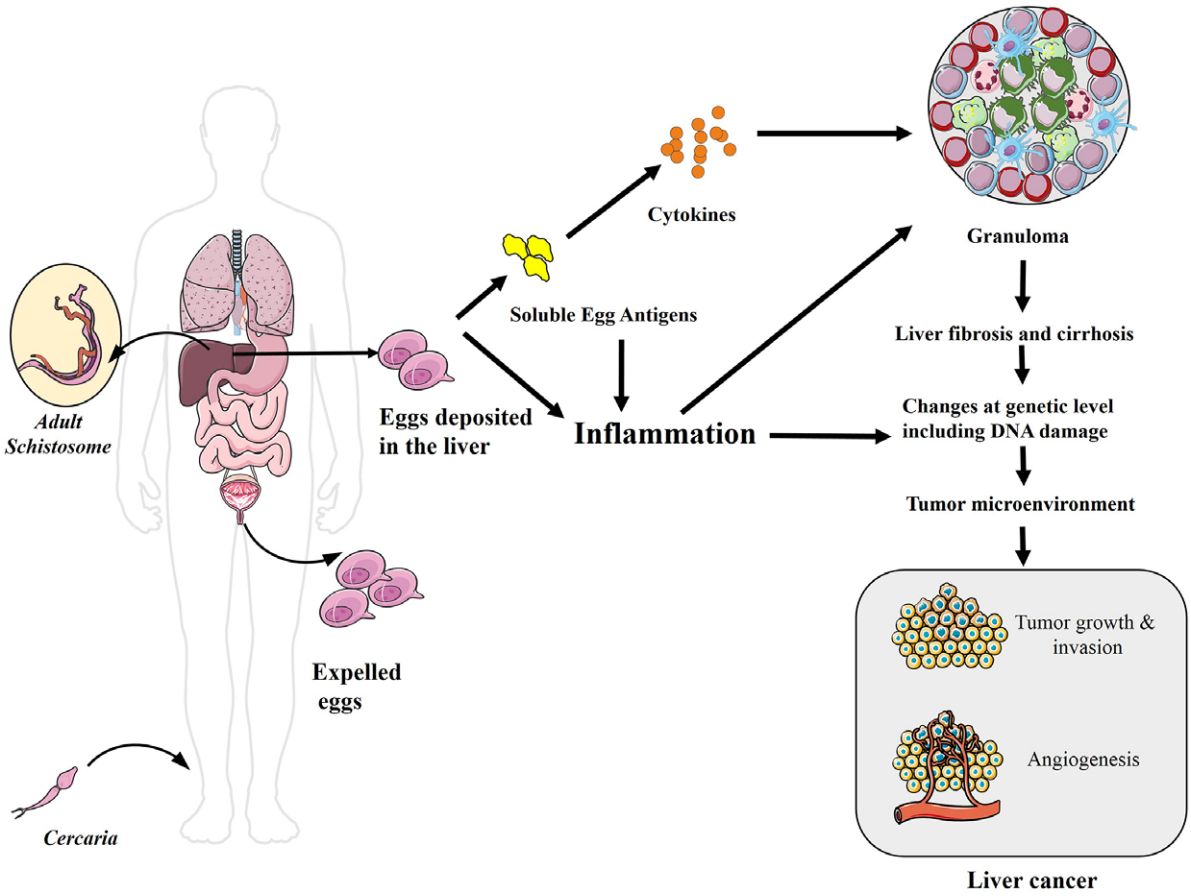

Figure 2. Proposed mechanism of liver cancer induction by *Schistosoma japonicum.* Deposited eggs lead to inflammation and release SEAs, which causes granuloma formation. Chronic infection and inflammation lead to liver fibrosis and cirrhosis and lead to DNA damage, creating a suitable microenvironment for induction of liver cancer.

https://doi.org/10.1017/S0022149X24000762 Published online by Cambridge University Press

viruses can lead to liver cirrhosis and a synergistic effect can be expected leading to exacerbated liver pathology (Gasim et al., 2015).

Studies have reported an increased susceptibility for HBV in patients with chronic schistosomiasis (Zhang et al., 2020). While few studies point out that this might be due to frequent blood transfusions which are necessary for chronic schistosomiasis patients (Gasim et al., 2015), other studies have rejected the hypothesis altogether for different schistosomal species (Larouzé et al., 1987; Ye at al., 1998). Nonetheless, chronic schistosomiasis and HBV co-infection is expected to end in liver cirrhosis and HCC in advanced cases (Omar, 2019).

Moreover, the co-infection prolongs the carriage stage which facilitates chronic hepatitis with significant cirrhosis (Abruzzi et al., 2016). Similar observations were made in patients with chronic schistosomiasis and HCV infection, where a decreased capability of resolving HCV infection was observed in schistosomiasis patients (Kamal et al., 2001) and higher liver fibrosis, cirrhosis and HCC were reported (Abruzzi et al., 2016; Omar, 2019).

Conversely, an observational study has reported no increase in liver damage in schistosomiasis infected patients who were co-infected with HBV in non-endemic area (Marchese et al., 2020).

4.5 Changes at genetic level

As discussed previously, chronic inflammation, granuloma formation, fibrosis, cirrhosis and co-infection with hepatitis viruses are probable factors leading to initiation of SJLC; however, it is important to note that all these factors work simultaneously to induce changes at genetic and molecular level, which ultimately leads to cancer induction.

An important aspect of chronic inflammation is the generation of reactive oxygen species (ROS) (Wang et al., 2016). During early infection, the activated macrophages contribute to heightened generation of ROS. SEAs induce ROS generation by NADPH oxidase 2 and mitochondria in macrophages, which is essential for M2 macrophage differentiation, which further promotes granuloma formation and fibrosis (Yu et al., 2021). Oxidative stress, exerted by ROS, disrupts normal cell function, interferes with genetic elements and affects signal transduction pathways (Wang et al., 2016). At genetic level, it induces oxidative damage to both nuclear and mitochondrial DNA, whereas it plays key roles in Wnt/β-catenin and Notch pathways (Li et al., 2023). All these changes predispose liver towards HCC.

Many studies have linked liver fibrosis and cirrhosis with shortening of telomere length in the hepatocytes (Donati & Valenti, 2016; Barnard et al., 2018; Shin et al., 2021). This shortening of telomere in hepatocytes has been previously correlated with chromosomal instability which is known to cause hepatoma in humans (Plentz et al., 2004). Further, telomere length and its shortening has also been linked to HCC diversity (Ningarhari et al., 2021). Development of hypoxic environment which is possibly related to cirrhosis has also been reported. The study has labelled this hypoxic liver parenchyma as highly angiogenic (Yu et al., 2010), another factor probably linked with SJLC induction and progression.

A recent study confirmed the role of B-lymphoma Mo-MLV insertion region 1, a known proto-oncogene, which encodes a crucial histone modifying protein Polycomb group protein in SJLC. The group conducted bioinformatics study where multiple proteins were identified and role of B-lymphoma Mo-MLV insertion region 1 in SJLC was confirmed through molecular studies and studies in mouse models (Sheng et al., 2024).

Further, recent studies have identified siRNA and miRNA, which are derived from Sj, and are capable of inhibiting hepatoma cell growth. In one study, miRNA-7-5p, which was detected in host hepatocytes during Sj infection, inhibited the growth and migration of hepatoma cells. Inhibition was achieved by cross-species down-regulation of the S-phase kinase-associated protein 2 gene in the human hepatoma cell lines *in vitro* (Hu et al., 2019). In another study, the inhibition was achieved by miRNA-71a, which targeted the *FZD4* host gene (Jiang et al., 2022). Detection of these RNAs in human host cells probably hint towards the cancer inducing capabilities of Sj.

One interesting study found up-regulation of glycolysis linked genes during Sj infection. *Ldha*, *Glut4*, *Pkm2*, *Pfkfb3*, *Aldoc* and *HK2* genes were found to be up-regulated (Xu et al., 2019). Interestingly, up-regulation of all these genes, except *Aldoc*, has been directly linked to liver fibrosis and LC as shown in Table 1. While *Aldoc* gene has not been directly linked with LC, it is known to promote non-small cell lung cancer by regulating Wnt signalling pathway (Shang et al., 2023). It needs to be determined if Wnt signalling among hepatocytes is also altered by up-regulation of *Aldoc* gene.

4.6 SJLC and LC not linked with Sj

Different mechanisms of cancer induction, both at cellular and genetic level, are observed in SJLC and LC not linked with Sj. As noted previously, LC can be induced by an array of factors not linked with Sj. HBV and/or HCV are independently capable of inducing LC. Hepatitis viruses are capable of insertional mutagenesis of both oncogenes as well as tumour suppressor genes. Hepatocyte transformation is further aided by the accumulation of preS1 large envelope proteins and preS2/S mutant proteins through unfolded protein response (Levrero & Zucman-Rossi, 2016).

Similarly, multiple factors are responsible for initiating LC in case of tobacco smoking. Tobacco constituents like tar and nicotine not only supress T-cell–related responses but *p53* gene reduction is also reported. Chronic smoking further promotes pro-inflammatory

Table 1. Up-regulated glycolysis genes due to Sj infection and their links with liver fibrosis and liver cancer

Up-regulated gene	Link with liver fibrosis and/or liver cancer
Ldha	• Deletion of *Ldha* impaired HCC development in mouse (Serra et al., 2022) • Heightened expression of *Ldha* in LC generates energy through glycolysis which supports cancer growth (Feng et al., 2018).
Glut4	• *Glut4* is highly expressed in HCC tissues which helps in glucose uptake (Huang et al., 2022b). • *Glut4* induces chronic system diseases, hence increasing the cancer risk (Chang et al., 2023)
Pkm2	• *Pkm2* induces immunosuppressive microenvironment and aids HCC (Li et al., 2020). • Overexpression of *Pkm2* in HCC patients is linked with poor prognosis (Zhao et al., 2020).
Pfkfb3	• *Pfkfb3* activates mouse and human HSCs leading to liver fibrosis (Mejias et al., 2020). • Inhibition of *Pfkfb3* prevents HCC proliferation (Dou et al., 2023)
HK2	• *HK2* promotes histone lactylation leading to HSC activation and liver fibrosis (Rho et al., 2023).

https://doi.org/10.1017/S0022149X24000762 Published online by Cambridge University Press

cytokines and other toxins which are responsible for necro-inflammation and hepatic lesions and may also cause iron deposition leading to liver fibrogenesis (Jain et al., 2021). Excessive alcohol intake produces similar results, where the pathology begins with a fatty liver proceeding to hepatitis which leads to cirrhosis and ultimately causes HCC (Matsushita & Takaki, 2019).

NAFLD ranges from simple steatosis (fat build-up not linked with alcohol intake) to NASH (excessive amount of fat accumulation in hepatic tissue) (Dhamija et al., 2019; Peng et al., 2020). While the exact cause of NASH is unknown, in case of certain obese people with NASH, fat deposition leads to inflammation, fibrosis and further to cirrhosis which transforms into HCC in significant number of patients (Dhamija et al., 2019; NIH, 2022).

From the previous discussion, although different factors might utilise overlapping mechanisms of inflammation, fibrosis and cirrhosis with a synergistic effect of HBC/HCV infection in HCC induction, the inducing factors are totally different. For example, deposited Sj eggs and SEAs seem to be playing a major carcinogenic through granuloma formation which is seldom reported in other cases discussed previously.

5. SJLC Management

SJLC can be managed at multiple levels, first by stopping the schistosomal infection; second by preventing it from causing severe pathology after infection; third by treating the patients if the infection has led to fibrosis; and fourth by treatment for cancerous stage. The first two levels involve control of schistosomal infections by use of multiple prophylactic techniques (Campbell et al., 2018) or by treating infection through techniques involving therapeutic vaccines (Molehin, 2020; Molehin et al., 2022) and other new methodologies like use of adjuvants or histone modifying enzymes (Pierce et al., 2011; Pierce et al., 2012). These methodologies have been recently covered by us in a related work involving Sj and colorectal cancer (Jain et al., 2023). The treatment modalities are discussed ahead.

SJLC comes with an extremely complex clinical scenario owing to the result of chronic infection and egg deposition that comes along with granuloma formation, fibrosis and cirrhosis. Along with the Sj infection–linked symptoms, other LC symptoms include abdominal pain, weight loss, malaise and fatigue with an enlarged, irregular and nodular liver that can be detected by physical examination (Szklaruk et al., 2003). The clinical management of SJLC begins with diagnosis, which can involve an array of imaging studies like ultrasound, computed tomography scans and magnetic resonance imaging (MRI). Serum alpha-fetoprotein is sometimes tested as a biomarker for HCC in combination with imaging studies. It can also be used alone, if levels are markedly elevated, which happens in less than 50% cases of HCC at the time of diagnosis (Bialecki & Di Bisceglie, 2005).

The diagnosis is generally followed by staging and is mostly done by TNM method in most medical organisations. Staging allows to understand the extent of tumour spread inside the liver, vascular invasion and any possible extra-hepatic spread which will further guide the treatment modalities (Szklaruk et al., 2003). For HCC not linked with Sj, the diagnosis and staging measures remain the same however in case of SJLC, MRI is the gold standard for detection of schistosomiasis (Bilgin et al., 2016).

As schistosomal infection leads to fibrosis, liver functions are usually impaired which impacts both the treatment options and prognosis. However, if the pathology has not advanced, liver fibrosis can be managed and events leading to cirrhosis and HCC can be prevented. Interestingly, by this time the normal liver structure is still preserved and lobular architecture is retained with an absence of nodular regenerative hyperplasia, implying that fibrosis could be reversible till some extent (Elbaz & Esmat, 2013). As pathology advances, eggs inside the granulomas lead to formation of marked portal fibrosis which along with angiogenesis leads to schistosomal lesions (Andrade & Santana, 2010).

Recent studies have highlighted the effectiveness of JQ-1, a bromodomain inhibitor, as a reliable anti-tumour molecule in mouse model. It relieves fibrosis caused by Sj by inhibiting JAK2/STAT3 signalling and can act as a novel therapeutic in controlling liver fibrosis caused by Sj (Ding et al., 2021), thus preventing SJLC induction. Until few years ago, the advanced stages of liver fibrosis, regardless of the reason of fibrosis, could have only been treated by a liver transplant. However, therapies targeting various steps in activation of HSCs, are now being worked upon, which can prevent advanced stages of liver fibrosis and hence preventing cancer induction (Koyama et al., 2016). Propranolol, a non-selective beta blocker, is used in the clinical management of hepatic schistosomiasis to treat portal hypertension occurring as a result of PHF (Tamarozzi et al., 2021).

If the infection has led to a cirrhotic liver and induced HCC, then the choice of surgical or non-surgical methodologies for targeting SJLC depends upon multiple factors including extent of liver involvement, stage of cancer, extent of fibrosis and cirrhosis, vascular invasion and overall patient health. As the arena of non-surgical methodologies for HCC treatment is extremely vast, the same has not been covered here as it would be outside the scope of this work. In short, non-surgical methodologies can be loco-regional or systemic chemotherapy. Loco-regional therapies involve intra-arterial or trans-catheter approaches, local ablative approaches (including chemical ablation and thermal or non-thermal energy-based ablation), radiation-based approaches or a combination of them (Voizard et al., 2019).

However, if regional lymph nodes are involved or if there is an extra-hepatic presence, loco-regional treatment is seldom the choice. Similarly, when main blood vessels of portal system are involved, intra-arterial approaches are not preferred and systemic therapies, including chemotherapy, immunotherapy and targeted therapy, are favoured (Johnson, 2005; Chami et al., 2023). Efficacy of systemic therapies is limited however due to pathologies associated with schistosomal infection relative to cases with no Sj infection.

If the HCC has reached the advanced stages, surgical treatment and liver transplantation are the preferred options. A number of factors govern this decision including tumour size and number, absence of extra-hepatic metastasis, extent of cirrhosis, and overall patient health (Ahmed et al., 2007; Raza & Sood, 2014). However, in cases where liver transplant is not viable as a result of patient health status and possible metastasis in extra-hepatic regions, palliative care is the only support which can be provided including managing symptoms, reducing pain (Voizard et al., 2019) and decreasing parasitic load.

Discussion

IARC classifies Sj as a possible carcinogen for LC; however, epidemiological and clinical studies suggest a co-relation between LC and Sj infection (Inaba, 1984; Inaba et al., 1984; Inaba, 1987; Takemura et al. 1998; Qiu et al., 2005). Further many studies proved

https://doi.org/10.1017/S0022149X24000762 Published online by Cambridge University Press

that schistosomal infection is playing a central role in hepatic fibrosis and cirrhosis, both of which are important determinants in LC induction (Huang et al., 2014; Gui et al., 2021; Liu et al., 2023). While these studies offer an idea on an association but they themselves face certain limitations. The studies done by Inaba and Takemura only involves population from Japan, specifically the Yamanashi Prefecture and hence does not paint a global picture. Further, two studies (Inaba et al., 1984; Takemura et al., 1998) also cautioned about other etiological factors for their results, especially HBV and alcohol intake. Another study (Iida et al. 1999) advocated for absence of any such association altogether.

Chronic inflammation and immune responses which are generated as a result of deposited eggs and SEAs seem to be the initial factors in SJLC pathology, which paves the way for granuloma formation followed by liver fibrosis and cirrhosis. All these changes trigger a series of reactions at genetic and cellular level, transforming the normal hepatocytes into cancerous cells. These events are further aided by concurrent infections with HBV and/or HCV. Peculiar genetic changes involve ROS-induced DNA damage which leads to issues such as mutations, sister chromatid exchanges, breakage of DNA strand and disequilibrium of oncogenes and onco-suppressor genes (Herrera et al., 2005), all of which contribute to the initiation of LC (Figure 2).

Disruption of metabolic genes specifically linked with glycolysis as a result of Sj infection is one of the most recently developing field which sheds light on the potential of Sj to induce LC by up-regulating these genes (Xu et al., 2019). As depicted in Table 1, up-regulation of these genes is essential for heightened glycolysis to provide energy for cancer growth and many studies have targeted these genes to slow down HCC.

In contrast to SJLC, other factors which induce LC, might utilise similar pathway for liver carcinogenesis (i.e., liver fibrosis and cirrhosis), leading to genetic changes which is contributing to LC, however, both the inducer (alcohol/ tobacco smoking/ HBV/HCV/ NASH) and the genetic changes (e.g., *p53* gene reduction due to tobacco smoking), are different. As pointed out previously, *p53* gene reduction is observed in the cases of LC induced due to tobacco smoking, while it is possible that *p53* gene expression is affected in case of SJLC, however, a specific reduction as in case of tobacco smoking is not reported in literature to date.

Similarly liver inflammation initiates as a result of excess fat deposition in NASH or the liver attains a fatty pathology due to access alcohol, both of which contribute to initiation of LC. However, in case of SJLC, inflammation takes place in response to deposited eggs and SEAs and leads to initiation of LC. While the mechanism of inflammation which is probably inducing LC remains the same however, inflammation itself is triggered by different factors here.

The diagnosis of SJLC is based on imaging studies where MRI is still the gold standard to detect schistosomiasis and LC. Depending upon the diagnosis, a number of techniques can be deployed to manage SJLC ranging from reversing liver fibrosis to certain extent (if infection has not led to LC), to non-surgical and surgical approaches depending upon stage of infection and cancer and overall health of the patient and to a liver transplant if advances stage is reached. However, if there is an extra-hepatic presence or of lymph nodes or blood vessels are also involved, systemic therapies may be the best choice.

With the presented arguments in this work it can be concluded that Sj definitely acts in synergism with other factors, most importantly HBV and HCV, to induce LC. Owing to this synergism its control should decrease cancer cases, at least in endemic regions. It is also likely that Sj can alone induce liver carcinogenesis as observed in a Chinese study (Qiu et al., 2005), but these results need to be reproduced at a global scale with a check on other LC inducing factors, so that Sj alone can be labelled as a causative factor for LC. Extensive epidemiological, clinical, pathological and experimental studies are required to precisely examine and understand the probably causative relationship between Sj and LC, or its absence.

Screening of liver tissue from patients who resided in Sj-endemic region and died of LC (and lacked other co-factors), population and case specific studies, are some methods which can provide important data. At genetic level, chemicals generated in response to Sj infection can be tested for their oncogenic potential in a large-scale population which can provide important results. For example, nitrosamines and increased cyclooxygenase-2 in response to infection of urinary bladder with *S. haematobium* are known to induce oncogenic mutations in oncogenes such as *p53*, *RB*, *ERBB2* and *EGFR* (Santos et al., 2021; Jain & Rana, 2024) which leads to urinary bladder cancer. Such analyses among others can help in establishing causality of LC from Sj infection alone beyond any doubt.

Acknowledgements. I would like to acknowledge "smart.servier.com", an online platform, which was used to make the figures. I would also like to thank Dr. Meenakshi Rana for providing help with Figure 2.

Data availability. Not applicable.

Author contribution. S.J. is solely responsible for all the aspects linked with this manuscript.

Funding source. No funding source.

Competing interest. None declared.

Ethics approval. Not applicable

Consent to participate. Not applicable.

Consent to publish. Not applicable

Clinical trial registration. Not applicable.

References

Abruzzi A, Fried B and Alikhan SB (2016) Coinfection of *Schistosoma* species with hepatitis B or hepatitis C viruses. *Advances in Parasitology* **91**, 111–231. https://doi.org/10.1016/bs.apar.2015.12.003

Ahmed K, Safdar K, Kemmer N, Atiq M, Wang J and Neff GW (2007) Intestinal schistosomiasis following orthotopic liver transplantation: a case report. *Transplantation Proceedings* **39(10)**, 3502–3504. https://doi.org/10.1016/j.transproceed.2007.07.093

Andrade ZA and Santana TS (2010) Angiogenesis and schistosomiasis. *Memorias do Instituto Oswaldo Cruz* **105(4)**, 436–439. https://doi.org/10.1590/s0074-02762010000400013

Baravelli CM, Sandberg S, Aarsand AK and Tollånes MC (2019) Porphyria cutanea tarda increases risk of hepatocellular carcinoma and premature death: a nationwide cohort study. *Orphanet Journal of Rare Diseases* **14(1)**, 77. https://doi.org/10.1186/s13023-019-1051-3

Barnard A, Moch A and Saab S (2018) Relationship between telomere maintenance and liver disease. *Gut and Liver* **13(1)**, 11–15. https://doi.org/10.5009/gnl18081

Bataller R and Brenne, DA (2005) Liver fibrosis. *The Journal of Clinical Investigation* **115(2)**, 209–218. https://doi.org/10.1172/JCI24282

Bialecki ES and Di Bisceglie AM (2005) Diagnosis of hepatocellular carcinoma. *HPB* **7(1)**, 26–34. https://doi.org/10.1080/13651820410024049

Bogen SA, Flores Villanueva PO, McCusker ME, Fogelman I, Garifallou M, el-Attar ES, Kwan P and Stadecker MJ (1995) In situ analysis of cytokine

responses in experimental murine schistosomiasis. *Laboratory Investigation* **73**(**2**), 252–258.

Butrous G (2019) Schistosome infection and its effect on pulmonary circulation. *Glob Cardiol Sci Pract* **2019**(**1**), 5. doi: 10.21542/gcsp.2019.5.

Campbell SJ, **Biritwum NK**, **Woods G**, **Velleman Y**, **Fleming F and Stothard JR** (2018) Tailoring water, sanitation, and hygiene (WASH) targets for soil-transmitted helminthiasis and schistosomiasis control. *Trends in Parasitology* **34**(**1**), 53–63. https://doi.org/10.1016/j.pt.2017.09.004

CDC (2024) Schistosomiasis. https://www.cdc.gov/dpdx/schistosomiasis/index.html. Accessed November 21, 2024.

Chami P, **Jarnagin W**, **Abou-Alfa GK**, **Harding J**, **Kim N**, **Lin H**, **El Homsi M**, **Crane C and Hajj C** (2023) Non-surgical locoregional therapies alone or in combination with systemic therapy in patients with hepatocellular carcinoma. *Cancers* **15**(**6**), 1748. https://doi.org/10.3390/cancers15061748

Chang YC, **Chan MH**, **Yang YF**, **Li CH and Hsiao M** (2023) Glucose transporter 4: insulin response mastermind, glycolysis catalyst and treatment direction for cancer progression. *Cancer Letters* **563**, 216179. https://doi.org/10.1016/j.canlet.2023.216179

Chen HZ, **Chuang SC**, **Hsieh FC**, **Lin LJ**, **Hung RM and Lee KT** (2007) Diagnosis of Schistosomiasis japonica infection coincident with hepatocellular carcinoma by fine-needle aspiration. *Diagnostic Cytopathology* **35**(**11**), 722–724. https://doi.org/10.1002/dc.20725

Chuah C, **Jones MK**, **Burke ML**, **McManus DP and Gobert GN** (2014) Cellular and chemokine-mediated regulation in schistosome-induced hepatic pathology. *Trends in Parasitology* **30**(**3**):141–150. doi: 10.1016/j.pt.2013.12.009

Chuah C, **Jones MK**, **Burke ML**, **Owen HC**, **Anthony BJ**, **McManus DP**, **Ramm GA and Gobert GN** (2013) Spatial and temporal transcriptomics of Schistosoma japonicum-induced hepatic granuloma formation reveals novel roles for neutrophils. *Journal of Leukocyte Biology* **94**(**2**), 353–365. https://doi.org/10.1189/jlb.1212653

Colley DG, **Bustinduy AL**, **Secor WE and King CH** (2014) Human schistosomiasis. *Lancet* **383**(**9936**), 2253–2264. https://doi.org/10.1016/S0140-6736(13)61949-2

Cooper GM and Hausman RE (2007) *The cell-a molecular approach*. Sinauer Associates, USA: Sunderland

Coutinho HM, **McGarvey ST**, **Acosta LP**, **Manalo DL**, **Langdon GC**, **Leenstra T**, **Kanzaria HK**, **Solomon J**, **Wu H**, **Olveda RM**, **Kurtis JD and Friedman JF** (2005) Nutritional status and serum cytokine profiles in children, adolescents, and young adults with Schistosoma japonicum-associated hepatic fibrosis, in Leyte, Philippines. *The Journal of Infectious Diseases* **192**(**3**), 528–536. https://doi.org/10.1086/430929

Culver EL, **Watkins J and Westbrook RH** (2016) Granulomas of the liver. *Clinical Liver Disease* **7**(**4**), 92–96. https://doi.org/10.1002/cld.544

Deslyper G, **Doherty DG**, **Carolan JC and Holland CV** (2019) The role of the liver in the migration of parasites of global significance. *Parasites & Vectors* **12**(**1**), 531. https://doi.org/10.1186/s13071-019-3791-2

Dhamija E, **Paul SB and Kedia S** (2019) Non-alcoholic fatty liver disease associated with hepatocellular carcinoma: an increasing concern. *The Indian Journal of Medical Research* **149**(**1**), 9–17. https://doi.org/10.4103/ijmr.IJMR_1456_17

Dhar D, **Baglieri J**, **Kisseleva T and Brenner DA** (2020) Mechanisms of liver fibrosis and its role in liver cancer. *Experimental Biology and Medicine (Maywood, N.J.)* **245**(**2**), 96–108. https://doi.org/10.1177/1535370219898141

Donati B and Valenti L (2016) Telomeres, NAFLD and chronic liver disease. *International Journal of Molecular Sciences* **17**(**3**), 383. https://doi.org/10.3390/ijms17030383

Dou Q, **Grant AK**, **Callahan C**, **Coutinho de Souza P**, **Mwin D**, **Booth AL**, **Nasser I**, **Moussa M**, **Ahmed M and Tsai LL** (2023) PFKFB3-mediated proglycolytic shift in hepatocellular carcinoma proliferation. *Cellular and Molecular Gastroenterology and Hepatology* **15**(**1**), 61–75. https://doi.org/10.1016/j.jcmgh.2022.09.009

Elbaz T and Esmat G (2013) Hepatic and intestinal schistosomiasis: review. *Journal of Advanced Research* **4**(**5**), 445–452. https://doi.org/10.1016/j.jare.2012.12.001

Elmberg M, **Hultcrantz R**, **Ekbom A**, **Brandt L**, **Olsson S**, **Olsson R**, **Lindgren S**, **Lööf L**, **Stål P**, **Wallerstedt S**, **Almer S**, **Sandberg-Gertzén H and Askling J** (2003) Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. *Gastroenterology* **125**(**6**), 1733–1741. https://doi.org/10.1053/j.gastro.2003.09.035

Feng Y, **Xiong Y**, **Qiao T**, **Li X**, **Jia L and Han Y** (2018) Lactate dehydrogenase A: a key player in carcinogenesis and potential target in cancer therapy. *Cancer Medicine*, **7**(**12**), 6124–6136. https://doi.org/10.1002/cam4.1820

Gasim GI, **Bella A and Adam, I.** (2015). Schistosomiasis, hepatitis B and hepatitis C co-infection. *Virology Journal* **12**, 19. https://doi.org/10.1186/s12985-015-0251-2

Gui QF, **Jin HL**, **Zhu F**, **Lu HF**, **Zhang Q**, **Xu J**, **Yang YM and Xiao C** (2021) Gut microbiota signatures in *Schistosoma japonicum* infection-induced liver cirrhosis patients: a case-control study. *Infectious Diseases of Poverty*, **10**(**1**), 43. https://doi.org/10.1186/s40249-021-00821-8

Hamid AS, **Tesfamariam IG**, **Zhang Y and Zhang ZG** (2013) Aflatoxin B1-induced hepatocellular carcinoma in developing countries: geographical distribution, mechanism of action and prevention. *Oncology Letters* **5**(**4**), 1087–1092. https://doi.org/10.3892/ol.2013.1169

Herrera LA, **Benítez-Bribiesca L**, **Mohar A and Ostrosky-Wegman P** (2005) Role of infectious diseases in human carcinogenesis. *Environmental and Molecular Mutagenesis* **45**(**2-3**), 284–303. https://doi.org/10.1002/em.20122

Hirata M, **Hara T**, **Kage M**, **Fukuma T and Sendo F** (2002). Neutropenia augments experimentally induced Schistosoma japonicum egg granuloma formation in CBA mice, but not in C57BL/6 mice. *Parasite Immunology* **24**(**9-10**), 479–488. https://doi.org/10.1046/j.1365-3024.2002.00491.x

Hoffmann KF, **Cheever AW and Wynn TA** (2000) IL-10 and the dangers of immune polarization: excessive type 1 and type 2 cytokine responses induce distinct forms of lethal immunopathology in murine schistosomiasis. *Journal of Immunology (Baltimore, Md. : 1950)* **164**(**12**), 6406–6416. https://doi.org/10.4049/jimmunol.164.12.6406

Hu C, **Zhu S**, **Wang J**, **Lin Y**, **Ma L**, **Zhu L**, **Jiang P**, **Li Z and Pan W** (2019) *Schistosoma japonicum* MiRNA-7-5p inhibits the growth and migration of hepatoma cells via cross-species regulation of S-phase kinase-associated protein 2. *Frontiers in Oncology* **9**, 175. https://doi.org/10.3389/fonc.2019.00175

Huang JQ, **Tao R**, **Li L**, **Ma K**, **Xu L**, **Ai G**, **Fan XX**, **Jiao YT and Ning Q** (2014) Involvement of heat shock protein 47 in *Schistosoma japonicum*-induced hepatic fibrosis in mice. *International Journal for Parasitology* **44**(**1**), 23–35. https://doi.org/10.1016/j.ijpara.2013.08.009

Huang P, **Ma H**, **Cao Y**, **Zhan T**, **Zhang T**, **Wang X**, **Zhang Y**, **Xu J and Xia C** (2022a) Activation of primary hepatic stellate cells and liver fibrosis induced by targeting TGF-β1/Smad signaling in schistosomiasis in mice. *Parasites & Vectors* **15**(**1**), 456. https://doi.org/10.1186/s13071-022-05584-1

Huang Y, **Xian L**, **Liu Z**, **We, L**, **Qin L**, **Xiong Y**, **H, L**, **Zho, S**, **Fu Q**, **Li B and Qin Y** (2022b) AMPKα2/HNF4A/BORIS/GLUT4 pathway promotes hepatocellular carcinoma cell invasion and metastasis in low glucose microenvironment. *Biochemical Pharmacology*, **203**, 115198. https://doi.org/10.1016/j.bcp.2022.115198

IARC (1994) Infection with schistosomes (*Schistosoma haematobium, Schistosoma mansoni* and *Schistosoma japonicum*). *IARC Monogr Eval Carcinog Risks Hum* **61**, 45–119.

Iida F, **Iida R**, **Kamijo H**, **Takaso K**, **Miyazaki Y**, **Funabashi W**, **Tsuchiya K and Matsumoto Y** (1999) Chronic Japanese schistosomiasis and hepatocellular carcinoma: ten years of follow-up in Yamanashi Prefecture, Japan. *Bulletin of the World Health Organization* **77**(**7**), 573–581.

Inaba Y (1984) A cohort study on the causes of death in an endemic area of schistosomiasis japonica in Japan. *Annals of the Academy of Medicine, Singapore* **13**(**2**), 142–148.

Inaba Y (1987) Liver cancer in an endemic area of schistosomiasis japonica in Yamanashi Prefecture, Japan. *Princess Takamatsu Symposia* **18**, 211–218.

Inaba Y, **Maruchi N**, **Matsuda M**, **Yoshihara N and Yamamoto S** (1984) A case-control study on liver cancer with special emphasis on the possible aetiological role of schistosomiasis. *International Journal of Epidemiology* **13**(**4**), 408–412. https://doi.org/10.1093/ije/13.4.408

Jain D, **Chaudhary P**, **Varshney N**, **Bin Razzak KS**, **Verma D**, **Khan Zahra TR**, **Janmeda P**, **Sharifi-Rad J**, **Daştan SD**, **Mahmud S**, **Docea AO and Calina D** (2021) Tobacco smoking and liver cancer risk: potential avenues for carcinogenesis. *Journal of Oncology*, 2021, 5905357. https://doi.org/10.1155/2021/5905357

https://doi.org/10.1017/S0022149X24000762 Published online by Cambridge University Press

Jain S (2024) Is *Schistosoma mansoni* playing a part in liver carcinogenesis? *Journal of Helminthology* **98**, e61. https://doi.org/10.1017/S0022149X24000506

Jain S and Kumar S (2020) Cancer immunotherapy: dawn of the death of cancer?. *International Reviews of Immunology* 1–18. Advance online publication. https://doi.org/10.1080/08830185.2020.1775827

Jain S and Rana M (2024) From the discovery of helminths to the discovery of their carcinogenic potential. *Parasitology Research* **123**(**1**), 47. https://doi.org/10.1007/s00436-023-08022-y

Jain S, **Rana M**, **Choubey P and Kumar S** (2023). *Schistosoma japonicum* associated colorectal cancer and its management. *Acta Parasitologica* **68**(**4**), 723–734. https://doi.org/10.1007/s11686-023-00707-9

Jain S, **Sengupta M and Jain P** (2019) Non-viral parasites associated with carcinogenesis. *Cancer Investigation* **37**(**9**), 453–462. https://doi.org/10.1080/07357907.2019.1662918

Jiang P, **Wang J**, **Zhu S**, **Hu C**, **Lin Y and Pan W** (2022) Identification of a *Schistosoma japonicum* microRNA that suppresses hepatoma cell growth and migration by targeting host *FZD4* gene. *Frontiers in Cellular and Infection Microbiology* **12**, 786543. https://doi.org/10.3389/fcimb.2022.786543

Johnson PJ (2005) Non-surgical treatment of hepatocellular carcinoma. *HPB* **7**(**1**), 50–55. https://doi.org/10.1080/13651820410024076

Kamal, SM, **Rasenack JW**, **Bianchi L**, **Al Tawil A**, **El Sayed Khalifa K**, **Peter T**, **Mansour H**, **Ezzat W and Koziel M** (2001) Acute hepatitis C without and with schistosomiasis: correlation with hepatitis C-specific CD4(+) T-cell and cytokine response. *Gastroenterology* **121**(**3**), 646–656. https://doi.org/10.1053/gast.2001.27024

Kamdem SD, **Moyou-Somo R**, **Brombacher F and Nono JK** (2018) Host regulators of liver fibrosis during human schistosomiasis. *Frontiers in Immunology* **9**, 2781. https://doi.org/10.3389/fimmu.2018.02781

Kojiro M, **Kakizoe S**, **Yano H**, **Tsumagari J**, **Kenmochi K and Nakashima T** (1986) Hepatocellular carcinoma and schistosomiasis japonica. A clinicopathologic study of 59 autopsy cases of hepatocellular carcinoma associated with chronic schistosomiasis japonica. *Acta Pathologica Japonica* **36**(**4**), 525–532. https://doi.org/10.1111/j.1440-1827.1986.tb01041.x

Koyama Y, **Xu J**, **Liu X and Brenner DA** (2016) New developments on the treatment of liver fibrosis. *Digestive Diseases (Basel, Switzerland)* **34**(**5**), 589–596. https://doi.org/10.1159/000445269

Larouzé B, **Dazza MC**, **Gaudebout C**, **Habib M**, **Elamy M and Cline B** (1987) Absence of relationship between Schistosoma mansoni and hepatitis B virus infection in the Qalyub Governate, *Egypt*. Annals of Tropical Medicine and Parasitology **81**(**4**), 373–375. https://doi.org/10.1080/00034983.1987.11812134

Levrero M and Zucman-Rossi J (2016). Mechanisms of HBV-induced hepatocellular carcinoma. *Journal of hepatology* **64**(**1** Suppl), S84–S101. https://doi.org/10.1016/j.jhep.2016.02.021

Li D, **He L**, **Guo H**, **Chen H and Shan H** (2015) Targeting activated hepatic stellate cells (aHSCs) for liver fibrosis imaging. *EJNMMI Research* **5**(**1**), 71. https://doi.org/10.1186/s13550-015-0151-x

Li QF, **Li YX**, **Yang YY**, **Dong PP**, **Mei CJ**, **Lu JL**, … **Yang K** (2023) The egg ribonuclease SjCP1412 accelerates liver fibrosis caused by Schistosoma japonicum infection involving damage associated molecular patterns (DAMPs). *Parasitology* 1–36. doi:10.1017/S0031182023001361

Li TE, **Wang S**, **Shen XT**, **Zhang Z**, **Chen M**, **Wang H**, **Zhu Y**, **Xu D**, **Hu BY**, **Wei R**, **Zheng Y**, **Dong QZ and Qin LX** (2020) PKM2 drives hepatocellular carcinoma progression by inducing immunosuppressive microenvironment. *Frontiers in Immunology* **11**, 589997. https://doi.org/10.3389/fimmu.2020.589997

Li Y, **Yu Y**, **Yang L and Wang R** (2023) Insights into the role of oxidative stress in hepatocellular carcinoma development. *Frontiers in Bioscience (Landmark edition)* **28**(**11**), 286. https://doi.org/10.31083/j.fbl2811286

Liu XF, **Ju S**, **Wang KY**, **Li Y and Qiang JW** (2023). The prevalence rate, mortality, and 5-year overall survival of *Schistosoma japonicum* patients with human malignancy. *Frontiers in Oncology* **13**, 1288197. https://doi.org/10.3389/fonc.2023.1288197

Liu Z, **Zhang L**, **Liang Y and Lu L** (2022) Pathology and molecular mechanisms of Schistosoma japonicum-associated liver fibrosis. *Frontiers in Cellular and Infection Microbiology* **12**, 1035765. https://doi.org/10.3389/fcimb.2022.1035765

Llanwarne F and Helmby H (2021). Granuloma formation and tissue pathology in Schistosoma japonicum versus Schistosoma mansoni infections. *Parasite Immunology* **43**(**2**), e12778. https://doi.org/10.1111/pim.12778

Lodish H, **Berk A**, **Zipursky SL**, **Matsudira P**, **Baltimore D and Darnell JE** (2003) *Molecular cell biology*, 5th edn. W. H. Freeman, New York.

Marchese V, **Beltrame A**, **Angheben A**, **Marocco S**, **Gaeta GB and Bisoffi Z** (2020) The impact of schistosomiasis co-infection in the presentation of viral hepatitis B in migrants: an observational study in non-endemic area. *Travel Medicine and Infectious Disease* **35**, 101467. https://doi.org/10.1016/j.tmaid.2019.101467

Matsushita H and Takaki A (2019) Alcohol and hepatocellular carcinoma. *BMJ Open Gastroenterology* **6**(**1**), e000260. https://doi.org/10.1136/bmjgast-2018-000260

McManus DP, **Dunne DW**, **Sacko M**, **Utzinger J**, **Vennervald BJ and Zhou XN** (2018) Schistosomiasis. *Nature Reviews* **4**(**1**), 13. https://doi.org/10.1038/s41572-018-0013-8

Mejias M, **Gallego J**, **Naranjo-Suarez S**, **Ramirez M**, **Pell N**, **Manzano A**, **Suñer C**, **Bartrons R**, **Mendez R and Fernandez M** (2020) CPEB4 increases expression of PFKFB3 to induce glycolysis and activate mouse and human hepatic stellate cells, promoting liver fibrosis. *Gastroenterology* **159**(**1**), 273–288. https://doi.org/10.1053/j.gastro.2020.03.008

Molehin AJ (2020) Schistosomiasis vaccine development: update on human clinical trials. *Journal of Biomedical Science* **27**(**1**), 28. https://doi.org/10.1186/s12929-020-0621-y

Molehin AJ, **McManus DP and You H** (2022) Vaccines for human schistosomiasis: recent progress, new developments and future prospects. *International Journal of Molecular Sciences* **23**(**4**), 2255. https://doi.org/10.3390/ijms23042255

Morais CN, **Souza JR**, **Melo WG**, **Aroucha ML**, **Miranda P**, **Domingues AL**, **Abath FG and Montenegro SM** (2008). Cytokine profile associated with chronic and acute human schistosomiasis mansoni. *Memorias do Instituto Oswaldo Cruz* **103**(**6**), 561–568. https://doi.org/10.1590/s0074-02762008000600009

Morgan TR, **Mandayam S and Jamal MM** (2004) Alcohol and hepatocellular carcinoma. *Gastroenterology* **127**(**5** Suppl 1), S87–S96. https://doi.org/10.1053/j.gastro.2004.09.020

Nakashima T, **Okuda K**, **Kojiro M**, **Sakamoto K and Kubo Y** (1975) Primary liver cancer coincident with Schistosomiasis japonica. A study of 24 necropsies. *Cancer* **36**(**4**), 1483–1489. https://doi.org/10.1002/1097-0142(197510)36:4%3C1483::AID-CNCR2820360441%3E3.0.CO;2-9

Ng J and Wu J (2012) Hepatitis B- and hepatitis C-related hepatocellular carcinomas in the United States: similarities and differences. *Hepatitis Monthly* **12**(**10** HCC), e7635. https://doi.org/10.5812/hepatmon.7635

NIH (2022) National Cancer Institute- study identifies potential drug target to prevent some liver cancers. (https://www.cancer.gov/news-events/cancer-currents-blog/2022/spectrin-fatty-liver-disease-liver-cancer#:~:text=In%20people%20with%20NASH%2C%20a,with%20NASH%20often%20develop%20HCC.)

Ningarhari M, **Caruso S**, **Hirsch TZ**, **Bayard Q**, **Franconi A**, **Védie AL**, **Noblet B**, **Blanc JF**, **Amaddeo G**, **Ganne N**, **Ziol M**, **Paradis V**, **Guettier C**, **Calderaro J**, **Morcrette G**, **Kim Y**, **MacLeod AR**, **Nault JC**, **Rebouissou S and Zucman-Rossi J** (2021) Telomere length is key to hepatocellular carcinoma diversity and telomerase addiction is an actionable therapeutic target. *Journal of Hepatology* **74**(**5**), 1155–1166. https://doi.org/10.1016/j.jhep.2020.11.052

Oliphant CJ, **Barlow JL and McKenzie AN** (2011) Insights into the initiation of type 2 immune responses. *Immunology* **134**(**4**), 378–385. https://doi.org/10.1111/j.1365-2567.2011.03499.x

Omar HH (2019) Impact of chronic schistosomiasis and HBV/HCV co-infection on the liver: current perspectives. *Hepat Med* **11**, 131–136. https://doi.org/10.2147/HMER.S155962

Peng C, **Stewart AG**, **Woodman OL**, **Ritchie RH and Qin CX** (2020) Non-alcoholic steatohepatitis: a review of its mechanism, models and medical treatments. *Frontiers in Pharmacology* **11**, 603926. https://doi.org/10.3389/fphar.2020.603926

Pierce RJ, **Dubois-Abdesselem F**, **Caby S**, **Trolet J**, **Lancelot J**, **Oger F**, **Bertheaume N and Roger E** (2011) Chromatin regulation in schistosomes and histone modifying enzymes as drug targets. *Memorias do Instituto*

Oswaldo Cruz **106**(7), 794–801. https://doi.org/10.1590/s0074-02762011000700003

Pierce RJ, Dubois-Abdesselem F, Lancelot J, Andrade L and Oliveira G (2012) Targeting schistosome histone modifying enzymes for drug development. *Current Pharmaceutical Design* **18**(**24**), 3567–3578.

Pinter M, Trauner M, Peck-Radosavljevic M and Sieghart W (2016) Cancer and liver cirrhosis: implications on prognosis and management. *ESMO Open* **1**(**2**), e000042. https://doi.org/10.1136/esmoopen-2016-000042

Plentz RR, Caselitz M, Bleck JS, Gebel M, Flemming P, Kubicka S, Manns MP and Rudolph KL (2004) Hepatocellular telomere shortening correlates with chromosomal instability and the development of human hepatoma. *Hepatology (Baltimore, Md.)* **40**(**1**), 80–86. https://doi.org/10.1002/hep.20271

Puche JE, Saiman Y and Friedman SL (2013) Hepatic stellate cells and liver fibrosis. *Comprehensive Physiology* **3**(**4**), 1473–1492. https://doi.org/10.1002/cphy.c120035

Qiu DC, Hubbard AE, Zhong B, Zhang Y and Spear RC (2005) A matched, case-control study of the association between Schistosoma japonicum and liver and colon cancers, in rural China. *Annals of Tropical Medicine and Parasitology* **99**(**1**), 47–52. https://doi.org/10.1179/136485905X19883

Raza A and Sood GK (2014) Hepatocellular carcinoma review: current treatment, and evidence-based medicine. *World Journal of Gastroenterology* **20**(**15**), 4115–4127. https://doi.org/10.3748/wjg.v20.i15.4115

Rho H, Terry AR, Chronis C and Hay N (2023) Hexokinase 2-mediated gene expression via histone lactylation is required for hepatic stellate cell activation and liver fibrosis. *Cell Metabolism* **35**(**8**), 1406–1423. e8. https://doi.org/10.1016/j.cmet.2023.06.013

Roberts L, Janovy J and Nadler S (2012) *Foundations of parasitology*. McGraw-Hill Education, USA

Rudge JW, Carabin H, Balolong E, Tallo V, Shrivastava J, Lu DB, Basáñez MG, Olveda R, McGarvey ST and Webster JP (2008) Population genetics of Schistosoma japonicum within the Philippines suggest high levels of transmission between humans and dogs. *PLoS Neglected Tropical Diseases* **2**(**11**), e340. https://doi.org/10.1371/journal.pntd.0000340

Saharti S, Ding X, Massarani-Wafai R and Pambuccian SE (2018) Fine-needle aspirate of the liver showing coexistence of *Schistosoma japonicum* ova and hepatocellular carcinoma. *Diagnostic Cytopathology* **46**(**8**), 716–720. https://doi.org/10.1002/dc.23969

Santos LL, Santos J, Gouveia MJ, Bernardo C, Lopes C, Rinaldi G, Brindley PJ and Costa JMCD (2021) Urogenital schistosomiasis-history, pathogenesis, and bladder cancer. *Journal of Clinical Medicine* **10**(**2**), 205. https://doi.org/10.3390/jcm10020205

Serra M, Di Matteo M, Serneels J, Pal R, Cafarello ST, Lanza M, Sanchez-Martin C, Evert M, Castegna A, Calvisi DF, Mazzone M and Columbano A (2022) Deletion of lactate dehydrogenase-a impairs oncogene-induced mouse hepatocellular carcinoma development. *Cellular and Molecular Gastroenterology and Hepatology* **14**(**3**), 609–624. https://doi.org/10.1016/j.jcmgh.2022.06.003

Shang B, Lu F, Jiang S, Xing M, Mao X, Yang G and Zhang H (2023) ALDOC promotes non-small cell lung cancer through affecting MYC-mediated UBE2N transcription and regulating Wnt/β-catenin pathway. *Aging* **15**(**18**), 9614–9632. https://doi.org/10.18632/aging.205038

Sheng S, Chen B, Xu R, Han Y, Mao D, Chen Y, Li C, Su W, Hu X, Zhao Q, Lowe S, Huang Y, Shao W and Yao Y (2024) A prognostic model for *Schistosoma japonicum* infection-associated liver hepatocellular carcinoma: strengthening the connection through initial biological experiments. *Infectious Agents and Cancer* **19**(**1**), 10. https://doi.org/10.1186/s13027-024-00569-4

Shin HK, Park JH, Yu JH, Jin YJ, Suh YJ, Lee JW, Kim W and **Korean Nonalcoholic Fatty Liver Study Group (KNSG)** (2021) Association between telomere length and hepatic fibrosis in non-alcoholic fatty liver disease. *Scientific Reports* **11**(**1**), 18004. https://doi.org/10.1038/s41598-021-97385-2

Stadecker MJ, Asahi H, Finger E, Hernandez HJ, Rutitzky LI and Sun J (2004) The immunobiology of Th1 polarization in high-pathology schistosomiasis. *Immunological Reviews* **201**, 168–179. https://doi.org/10.1111/j.0105-2896.2004.00197.x

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F (2021) Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* **71**(**3**), 209–249. https://doi.org/10.3322/caac.21660

Szklaruk J, Silverman PM and Charnsangavej C (2003) Imaging in the diagnosis, staging, treatment, and surveillance of hepatocellular carcinoma. *AJR American Journal of Roentgenology* **180**(**2**), 441–454. https://doi.org/10.2214/ajr.180.2.1800441

Takemura Y, Kikuchi S and Inaba Y (1998) Epidemiologic study of the relationship between schistosomiasis due to Schistosoma japonicum and liver cancer/cirrhosis. *The American journal of tropical medicine and hygiene* **59**(**4**), 551–556. https://doi.org/10.4269/ajtmh.1998.59.551

Tamarozzi F, Fittipaldo VA, Orth HM, Richter J, Buonfrate D, Riccardi N and Gobbi FG (2021) Diagnosis and clinical management of hepatosplenic schistosomiasis: a scoping review of the literature. *PLoS Neglected Tropical Diseases* **15**(**3**), e0009191. https://doi.org/10.1371/journal.pntd.0009191

Trottein F, Nutten S, Angeli V, Delerive P, Teissier E, Capron A, Staels B and Capron M (1999) *Schistosoma mansoni* schistosomula reduce E-selectin and VCAM-1 expression in TNF-alpha-stimulated lung microvascular endothelial cells by interfering with the NF-kappaB pathway. *European Journal of Immunology* **29**(**11**), 3691–3701. https://doi.org/10.1002/(SICI)1521-4141(199911)29:11<3691::AID-IMMU3691>3.0.CO;2-L

Voizard N, Cerny M, Assad A., Billiard JS, Olivié D, Perreault P, Kielar A, Do RKG, Yokoo T, Sirlin CB and Tang A (2019) Assessment of hepatocellular carcinoma treatment response with LI-RADS: a pictorial review. *Insights Into Imaging* **10**(**1**), 121. https://doi.org/10.1186/s13244-019-0801-z

von Bülow V, Lichtenberger J, Grevelding CG, Falcone FH, Roeb E and Roderfeld M (2021) Does *Schistosoma mansoni* facilitate carcinogenesis? *Cells* **10**(**8**):1982. doi: 10.3390/cells10081982.

Wang Q, Chou X, Guan F, Fang Z, Lu S, Lei J, Li Y and Liu W (2017) Enhanced Wnt signalling in hepatocytes is associated with *Schistosoma japonicum* infection and contributes to liver fibrosis. *Scientific Reports* **7**(**1**), 230. https://doi.org/10.1038/s41598-017-00377-4

Wang X, Tang Q, Bergquist R, Zhou X and Qin Z (2023) The cytokine profile in different stages of Schistosomiasis Japonica. *Pathogens (Basel, Switzerland)* **12**(**10**), 1201. https://doi.org/10.3390/pathogens12101201

Wang Y, Fan X, Lei N, He X, Wang X, Luo X, Zhang D and Pan W (2020) A microRNA derived from Schistosoma japonicum promotes schistosomiasis hepatic fibrosis by targeting host secreted frizzled-related protein 1. *Frontiers in Cellular and Infection Microbiology* **10**, 101. https://doi.org/10.3389/fcimb.2020.00101

Wang Z, Li Z, Ye Y, Xie L and Li W (2016) Oxidative stress and liver cancer: etiology and therapeutic targets. *Oxidative Medicine and Cellular Longevity* **2016**, 7891574. https://doi.org/10.1155/2016/7891574

Wiest PM, Wu G, Zhong S, McGarvey ST, Tan E, Yuan J, Peters P, Olveda RM and Olds G R (1993) Schistosomiasis japonica on Jishan Island, Jiangxi Province, People's Republic of China: persistence of hepatic fibrosis after reduction of the prevalence of infection with age. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **87**(**3**), 290–294. https://doi.org/10.1016/0035-9203(93)90133-b

Wynn TA (2008) Cellular and molecular mechanisms of fibrosis. *The Journal of Pathology* **214**(**2**), 199–210. https://doi.org/10.1002/path.2277

Wynn TA and Cheever AW (1995) Cytokine regulation of granuloma formation in schistosomiasis. *Current Opinions in Immunology* **7**, 505.

Xu R and Hajdu CH (2008) Wilson disease and hepatocellular carcinoma. *Gastroenterology & Hepatology* **4**(**6**), 438–439.

Xu ZP, Chang H, Ni YY, Li C, Chen L, Hou M and Ji MJ (2019) Schistosoma japonicum infection causes a reprogramming of glycolipid metabolism in the liver. *Parasites & Vectors* **12**(**1**), 388. https://doi.org/10.1186/s13071-019-3621-6

Ye XP, Fu YL, Anderson RM and Nokes DJ (1998) Absence of relationship between Schistosoma japonicum and hepatitis B virus infection in the Dongting lake region, China. *Epidemiology and Infection* **121**(**1**), 193–195. https://doi.org/10.1017/s0950268898008917

Yu DC, Chen J and Ding YT (2010).Hypoxic and highly angiogenic non-tumor tissues surrounding hepatocellular carcinoma: the 'niche' of endothelial progenitor cells. *International Journal of Molecular Sciences* **11**(**8**), 2901–2909. https://doi.org/10.3390/ijms11082901

Yu Y, Wang J, Wang X, Gu P, Lei Z, Tang R, Wei C, Xu L, Wang C, Chen Y, Pu Y, Qi X, Yu B, Chen X, Zhu J, Li Y, Zhang Z, Zhou S and Su C (2021) Schistosome eggs stimulate reactive oxygen species production to enhance M2 macrophage differentiation and promote hepatic pathology in

schistosomiasis. *PLoS Neglected Tropical Diseases* **15**(**8**), e0009696. https://doi.org/10.1371/journal.pntd.0009696

Yunna C, **Mengru H**, **Lei W and Weidong C** (2020) Macrophage M1/M2 polarization. *European Journal of Pharmacology* **877**, 173090. https://doi.org/10.1016/j.ejphar.2020.173090

Zhang CY, **Yuan WG**, **He P**, **Lei JH and Wang CX** (2016) Liver fibrosis and hepatic stellate cells: etiology, pathological hallmarks and therapeutic targets. *World Journal of Gastroenterology* **22**(**48**), 10512–10522. https://doi.org/10.3748/wjg.v22.i48.10512

Zhang Y, **Xie Y**, **Chen Q**, **Chen X**, **Dong Z and Tan X** (2020) Prevalence and co-infection of schistosomiasis/hepatitis B among rural populations in endemic areas in Hubei, China. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **114**(**3**), 155–161. https://doi.org/10.1093/trstmh/trz086

Zhao R, **Li L**, **Yang J**, **Niu Q**, **Wang H**, **Qin X**, **Zhu N and Shi A** (2020) Overexpression of pyruvate kinase M2 in tumor tissues is associated with poor prognosis in patients with hepatocellular carcinoma. *Pathology Oncology Research* **26**(**2**), 853–860. https://doi.org/10.1007/s12253-019-00630-3

Zheng B, **Zhang J**, **Chen H**, **Nie H**, **Miller H**, **Gong Q and Liu C** (2020) T Lymphocyte-mediated liver immunopathology of schistosomiasis. *Frontiers in Immunology* **11**, 61. https://doi.org/10.3389/fimmu.2020.00061

Zhu D, **Yang C**, **Shen P**, **Chen L**, **Chen J**, **Sun X**, **Duan L**, **Zhang L**, **Zhu J and Duan Y** (2018) rSjP40 suppresses hepatic stellate cell activation by promoting microRNA-155 expression and inhibiting STAT5 and FOXO3a expression. *Journal of Cellular and Molecular Medicine* **22**(**11**), 5486–5493. https://doi.org/10.1111/jcmm.13819

https://doi.org/10.1017/S0022149X24000762 Published online by Cambridge University Press