Review

Role of resident liver cells in the pathogenesis of schistosomiasis

Barrie J. Anthony[1], Grant A. Ramm[2,3], and Donald P. McManus[1]

[1] Molecular Parasitology Laboratory, the Queensland Institute of Medical Research, Post Office Royal Brisbane Hospital, QLD 4029, Australia
[2] Hepatic Fibrosis Group, the Queensland Institute of Medical Research, Post Office Royal Brisbane Hospital, QLD 4029, Australia
[3] Faculty of Health Sciences, The University of Queensland, Brisbane, Australia

Pathology in schistosomiasis occurs as a result of eggs deposited in the liver by the schistosome parasite. A granulomatous reaction occurs, resulting in portal hypertension and hepatic fibrosis. Resident non-parenchymal cells within the liver take part in this process, including hepatic stellate cells, which are responsible for collagen production, and Kupffer cells, the liver macrophages involved in both host protection and in pathology. Other cells such as liver sinusoidal endothelial cells or portal fibroblasts may also be involved in this process. This review discusses the possible role of these resident liver cells in the pathology associated with schistosomiasis and provides information which may assist our understanding of the mechanisms associated with chronic liver disease in general.

Schistosomiasis-induced pathology and resident liver cells

Schistosomiasis is a human helminth infection that is estimated to afflict 200 million people worldwide [1,2]. Of these infections, 120 million are symptomatic [2], and 20 million have severe morbidity [1], resulting in the loss of at least 70 million disability-adjusted life years (DALYs) [3,4]. The majority of schistosomiasis-induced human liver disease is caused by *Schistosoma mansoni* and *Schistosoma japonicum*, of which *S. mansoni* infects approximately 83 million people in sub-Saharan Africa, South America, and the Caribbean [1], whereas up to 50 million people are at risk from infection by *S. japonicum* in China and the Philippines [5].

Adult schistosome worm pairs reside within the mesenteric veins of the intestine where they release large numbers of eggs, many of which pass through the gut wall into the gut lumen and are released into a fresh water environment in host faeces. However, more than 50% of the eggs become trapped in the liver sinusoids, being swept there via the portal circulation [6]. Over the course of a schistosome infection two main types of pathology arise: acute and chronic. The main pathology in acute disease is termed Katayama fever, a systemic hypersensitivity reaction occurring between one and four weeks after infection [7]. Acute symptoms in *S. mansoni* infection are more common in tourists and visitors to endemic foci, whereas *S. japonicum* infection can cause symptoms in both visitors and locals in an endemic area [7]. The main pathology in schistosomiasis is associated with chronic disease and reflects the host immune response to the eggs. During the early stage of infection there is a type 1 T helper cell (Th1) response induced by the migrating stages of the parasite and the adult worms. This response is then polarised into a Th2 response by the host reaction to the release of eggs occurring 4–6 weeks after initial infection. A granulomatous reaction occurs around trapped eggs in the liver, surrounding them with mononuclear cells, eosinophils, and neutrophils [8]. As the granuloma matures, collagen fibres and fibroblasts become the predominant feature, resulting in fibrosis. This fibrosis is mediated by IL-13, a major product of Th2 polarised cells. It is believed that IL-13 stimulates the transdifferentiation of hepatic

Glossary

α-Smooth muscle actin: protein found in myofibroblasts used in cellular contraction.
Fibrotic edge: scar margin between normal liver tissue and fibrosis (scar) where collagen is being produced.
Granuloma: the resulting lesion of a granulomatous reaction.
Granulomatous reaction: a localised immune reaction in which a foreign agent is surrounded by immune cells, fibroblasts, and collagen.
Gut lumen: interior of the gastrointestinal tract.
Hepatic fibrosis: build-up of increased extracellular matrix, scar tissue, and collagen in the liver.
Hepatic stellate cells: located in the space of Disse of the liver sinusoid where they are responsible for vitamin A storage and ECM maintenance. Can become activated by liver injury to a myofibroblast responsible for scar tissue build up and fibrosis.
Hepatopathology: pathology occurring within the liver.
Kupffer cells: resident tissue macrophages of the liver.
Liver non-parenchymal cells: cells of the liver, excluding hepatocytes. These include Kupffer cells, hepatic stellate cells, liver sinusoidal endothelial cells, and bile-duct cells.
Liver sinusoidal endothelial cells: specialised cells that make up endothelial lining of the smallest blood vessels of the liver, the sinusoids.
Liver sinusoids: sinusoidal blood vessels in the liver.
Mesenteric veins: veins that drain blood away from the intestine.
Myofibroblast: a fibroblast that expresses αSMA, which gives the cell a contractile phenotype.
Oil Red O staining: a histological stain used to show the presence of lipid droplets within cells. Lipid droplets stain red.
Partial hepatectomy: surgical removal of part of the liver.
Portal hypertension: high blood pressure in the portal vein.
Space of Disse: gap between the LSECs and hepatocytes in which there is a low-density extracellular matrix.
Th2 biasing: when the immune response is pushed to favour a Th2-type response, favouring the production of Th2-associated cytokines.
Transdifferentiation: transformation of a cell from one phenotype to another.

Corresponding author: Anthony, B.J. (barrie.anthony@qimr.edu.au)
Keywords: schistosomiasis; *Schistosoma mansoni*; *Schistosoma japonicum*; liver; macrophages; hepatic stellate cells; liver sinusoidal endothelial cells; Kupffer cells.

1471-4922/$ – see front matter http://dx.doi.org/10.1016/j.pt.2012.09.005 Trends in Parasitology, December 2012, Vol. 28, No. 12

stellate cells (HSCs) into activated myofibroblasts, which are responsible for production of collagen and fibrogenesis within the granuloma site. Alternatively activated macrophages (M2), derived from both local Kupffer cells (see Glossary) and circulating monocytes, also contribute to the process of fibrosis by promoting collagen production via FIZZ-1, which promotes the transdifferentiation of myofibroblasts from HSCs [9], and by the conversion of L-arginine into proline, a component of collagen, via arginase-1 [10,11]. As this builds up over time, and the number of granuloma sites increases, a more pronounced hepatic fibrosis occurs which obstructs the flow of blood through the liver, resulting in portal hypertension [6,12,13].

The liver is an organ with many specialised resident non-parenchymal cells, including HSCs, Kupffer cells, and liver sinusoidal endothelial cells (LSECs). HSCs play a major role in fibrogenesis in chronic disease by undergoing a process of transdifferentiation from normally quiescent cells into 'activated' fibrogenic myofibroblasts which are responsible for increased collagen and extracellular matrix deposition [14]. In recent years it has been demonstrated that activated HSCs play a contributory role in both murine and human disease caused by *S. japonicum* [15], and in human disease caused by *S. mansoni* [16]. Kupffer cells have a widely accepted role in fibrosis and are located around areas of tissue damage and fibrosis [17]. They are, in addition, a potential source of alternatively activated macrophages (M2) which have been shown to be involved in Th2 biasing, in the promotion of host protection, and also in the progressive pathology due to granuloma formation in schistosomiasis [18,19]. Little is known about the role of LSECs in schistosomiasis, but they are known to be involved in angiogenesis, a process that has been linked to granuloma formation and liver regeneration in schistosomiasis [20], as well as in antigen presentation and T cell activation [21].

Hepatic stellate cells

HSCs are located within the space of Disse of the liver sinusoid where they are responsible for maintenance of a low-density matrix and storage of vitamin A [22]. These cells have a well-defined central role in fibrogenesis within the liver [14]. In response to injury or insult to the liver, HSCs change from a quiescent form to an 'activated' myofibroblastic phenotype that loses its ability to store vitamin A and produces a scar-like matrix in the space of Disse, reducing the ability of the liver to function (Figure 1) [14]. The process of hepatic fibrogenesis involves three stages: initiation, perpetuation, and reversion. In the initiation step, HSCs undergo transdifferentiation as a result of hepatic insult, which can be due to infection, diet, or chemical induction. Perpetuation is then characterised by the proliferation of HSCs, which express the contractile microfilament α-smooth muscle actin (αSMA), produce extracellular matrix (ECM) components, and facilitate altered matrix remodelling. Inflammation is a key process associated with HSC activation and fibrogenesis, and HSCs are involved in enhanced inflammatory signalling and the recruitment of both new myofibroblasts and an inflammatory infiltrate [23,24]. All of these processes are tightly controlled by cytokine production from activated HSCs or neighbouring liver cells [22]. In the event that the injurious hepatic insult is removed, the normal wound-healing response is resolved and activated HSCs are lost [25], either by reversion back to a quiescent HSC phenotype or via apoptosis [26], and the fibrotic tissue is reabsorbed. However, in the process of chronic fibrosis this event fails to occur, and a continual process of HSC activation and perpetuation of matrix deposition results in significant scar-like tissue formation, leading ultimately to cirrhosis [14].

HSCs are believed to be a principal source of collagen deposition in the liver, with a major role in ECM remodelling in schistosomiasis [12] and a role in parasite-induced fibrosis [27]. Activated HSCs have been identified in the periphery of egg-induced granulomas in murine and human schistosomiasis [9,10,18]. This localisation towards the granuloma periphery is demonstrated in Figure 2. Administration of prostaglandin E1 in *S. japonicum* infection in rabbits was shown to reduce HSC-induced fibrosis [28]. In addition, the neuropeptide somatostatin has been linked to reduced fibrosis in *S. mansoni*-infected patients [29]. This peptide directly reduced primary rat HSC activation *in vitro*, reducing collagen production in these cells [30,31]. HSCs have been shown to express receptors for this peptide [31]. Interestingly, it has been observed that leptin deficiency in mice results in decreased fibrosis in *S. mansoni*-infected mice [32]. Leptin, expressed by activated HSCs, enhances the effect of the transforming growth factor-β (TGF-β) type 2 receptor, and therefore the ability to produce collagen [33]. Additionally, leptin expression has been demonstrated in granulomas of *S. mansoni*-infected mice [34]. The Chinese traditional medicines, heluoshugan and paeoniflorin, were observed to reduce collagen production by HSCs cultured *in vitro* [35,36], with the latter blocking IL-13-induced activation of HSCs in culture as well as reducing fibrosis in a murine model of *S. japonicum* infection [36].

IL-13 is considered to be the major inducing factor of fibrosis in schistosomiasis [37], and is produced at high levels as a result of the Th2 response induced by the eggs released by the mating adult worm pair in the chronic stage of the disease. IL-13 activates myofibroblasts and is an inducer of fibrosis in both schistosomiasis and asthma [38]. IL-13 induces rat primary HSCs to produce the profibrogenic cytokine connective tissue growth factor (CTGF) [39]. Elevated levels of CTGF are associated with fibrosis in schistosomiasis. In addition, CTGF has been demonstrated to increase collagen production in a human HSC cell line [40]. In the case of schistosomiasis, IL-13 produced in the granulomatulous reaction is likely to induce HSC transdifferentiation and cause the fibrogenesis occurring within the lesion. This likely occurs by IL-13 inducing CTGF in these cells which, in turn, directly leads to collagen production. Defining the role of IL-13 in driving fibrosis in this manner in schistosomiasis may assist in understanding the mechanisms of fibrosis in other chronic liver diseases because IL-13 expression is correlated positively with fibrosis in hepatitis C virus, hepatitis B virus, alcoholic steatohepatitis (ASH), and non-alcoholic steatohepatitis (NASH) [41].

A direct functional interaction between schistosome eggs and an immortalised HSC cell line has been demonstrated