Osteopontin is a novel player and potential biomarker in hepatosplenic schistosomiasis mansoni

Schistosomiasis or bilharzia is a tropical disease caused by worms of the genus *Schistosoma.* Over 440 million people from 76 countries and territories are infected (Fig. 1). This water-based disease is considered the second most important parasitic infection after malaria. *Schistosoma mansoni* is the only species in the Americas and Brazil is the most affected country in that continent.

People from or visiting endemic areas can get infected by entering in contact with water containing infected fresh water snails that release the larval form of the parasite. These larval forms penetrate the skin of humans and develop to adult worms, which live in intestine blood vessels. The worm couple mates constantly and the female lays about 300 eggs per day and part of the eggs are passed out of the body in faeces. About 100 eggs per day are directed to the liver which causes inflammation and can lead to severe fibrosis and associated portal hypertension, a very life-treating form of the disease know as hepatosplenic schistosomiasis (Fig. 1.).

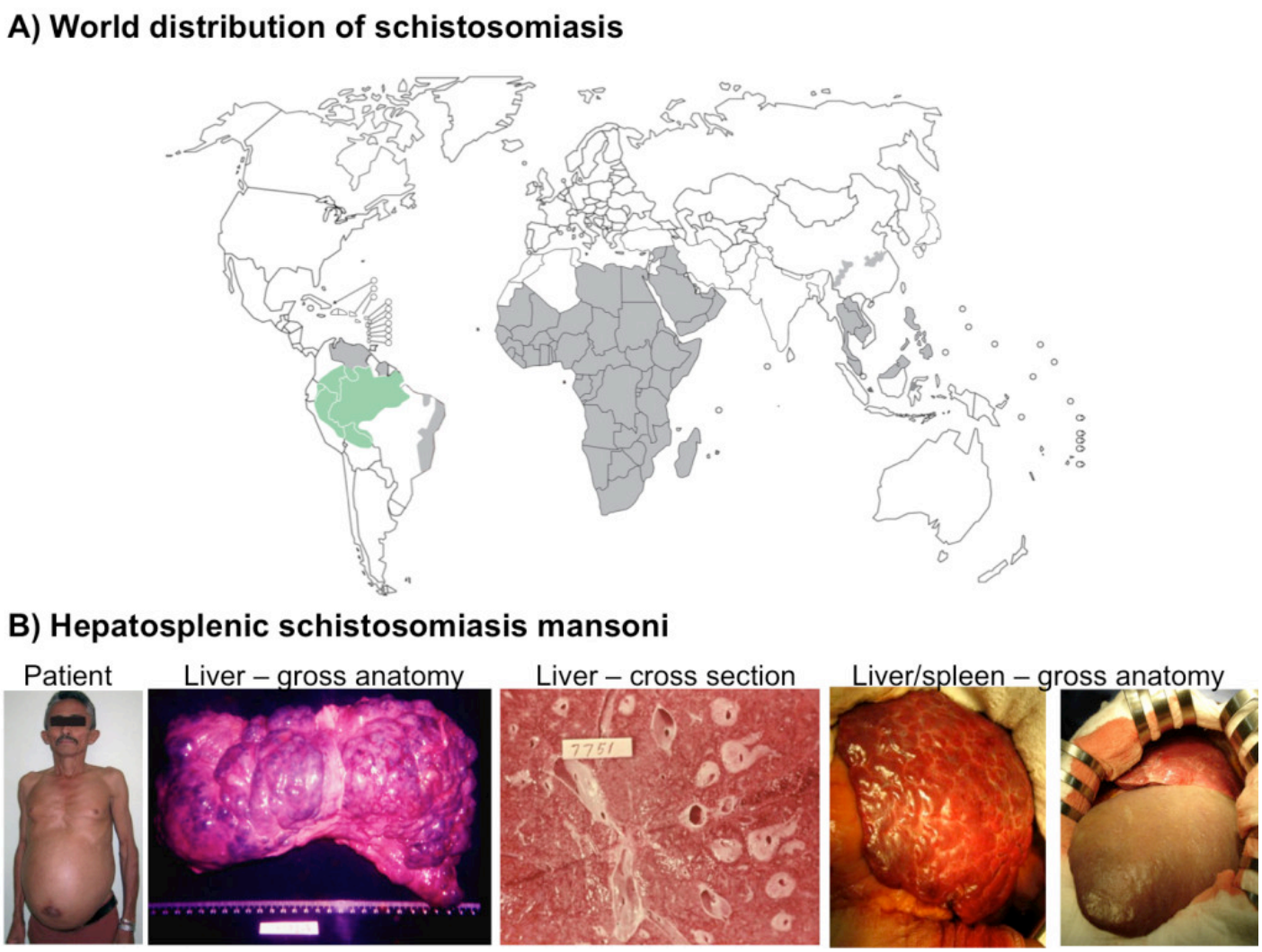

Fig. 1. Schistosomiasis world distribution and clinical aspects. A) Global distribution of schistosomiais. Endemic countries/regions are shown in grey. Amazon region is shown in green. B) Clinical aspects of the severe form of schistosomiasis known as hepatosplenic schistosomiasis mansoni. Young patient with severe liver fibrosis and portal hypertension. Gross anatomy of the liver of a patient with hepatosplenic schistosomiasis; observe the nodular surface. Cross section of the liver of a patient with hepatosplenic schistosomiasis; the white plaques are fibrotic tissue. Liver and spleen of a patient undergoing splenectomy (removal of spleen to reduce portal hypertension); surgery is the only avaiable therapy against portal hypertension and is not curative. Notice the enormous size of the spleen that occupies almost all abdominal cavity. Image credit: Fausto Pereira M.D., PhD; José R. Lambertucci M.D., PhD.; Vivian Resende M.D., PhD.; Izabela Voieta M.D., PhD.

The reason why infected people develop hepatosplenic schistosomiasis is still an open question.

This gap in knowledge has limited the development of both effective treatments to inhibit fibrosis and non-invasive biomarkers. Treatment with the drug praziquantel kills the adult worms but is not sufficient to reverse liver fibrosis and associated portal hypertension, which can kill the patients.

Recently the molecule osteopontin has been implicated in several types of liver disease and could be a potential biomarker and therapeutic target to treat liver fibrosis. Many authors demonstrated that this molecule correlate with the degree of fibrosis and could be a non-invasive fibrosis marker. Some studies suggested that inhibition of this molecule could ameliorate fibrosis. However no study investigated its role in portal hypertension. In order to investigate if osteopontin could also regulate schistosomiasis fibrosis and portal hypertension we conducted a study using human samples, an animal model of the disease and cell culture studies.

We demonstrated for the first time that schistosomal egg antigens directly induce host liver bile ductular cells to proliferate and produce the pro-fibrogenic molecule osteopontin. Serum/plasma and hepatic osteopontin levels not only correlate with the degree of liver fibrosis but strictly match the level of portal hypertension.

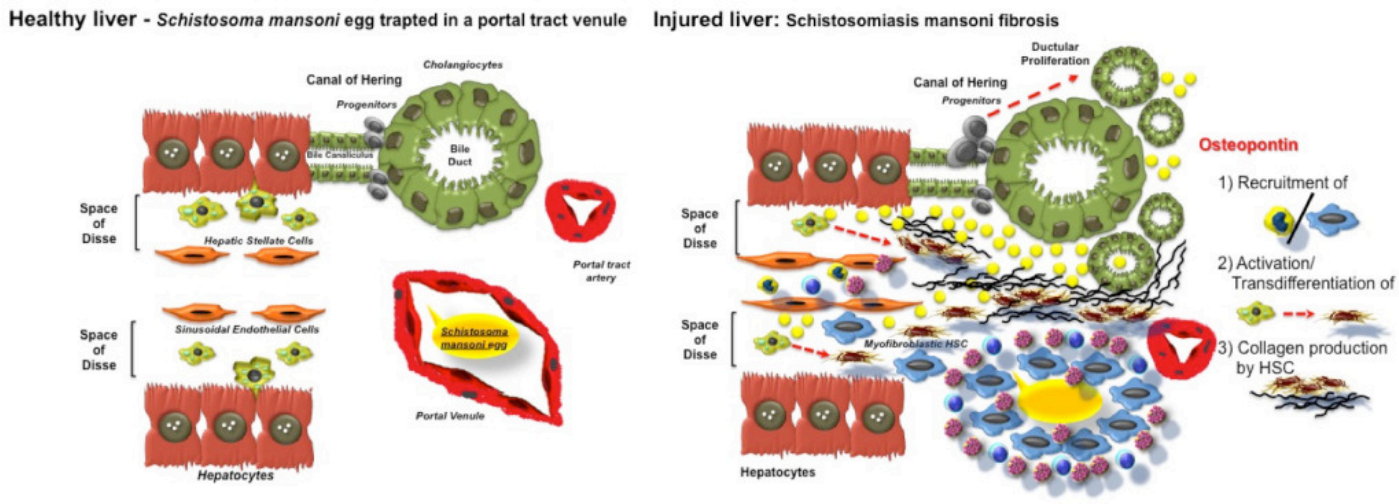

Fig. 2. Working hypothesis. When Schistosoma mansoni eggs are trapted in small vessels in the liver an inflammatory response is installed (left panel). The bile ducts (also know as cholangiocytes) proliferate and produce Osteopontin that plays a role in 1) the recruitment of inflammatory cells (Monocytes/Macrophages), 2) activation of hepatic stellate cells (that install the fibrosis) and 3) induction of collagen synthesis (main constitution of the fibrous scar tissue) contributing to schistosomiasis fibrosis and associated portal hypertension. Figure credit: Steve S. Choi M.D; Thiago A. Pereira PhD; Alessia Omenetti M.D., PhD.

Figure 2 resume our working hypothesis. When *Schistosoma mansoni* eggs are trapped in small vessels in the liver an inflammatory response is installed. The bile ducts proliferate and produce

Osteopontin that plays a role in the recruitment of inflammatory cells, activation of hepatic stellate cells (that install the fibrosis) and induction of collagen synthesis (main constitution of the fibrous scar tissue) contributing to schistosomiasis fibrosis and associated portal hypertension.

This new findings indicate that Osteopontin could be a novel therapy target candidate to treat schistosomiasis fibrosis and portal hypertension and a possible non-invasive biomarker in schistosomiasis mansoni.

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