Induction of the proto-oncogene c-Jun and downstream metabolic functions in cell culture models of *Schistosoma mansoni*/Hepatitis-B-Virus co-infection

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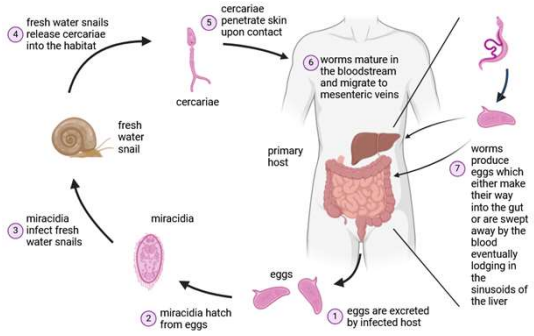
Introduction

Schistosoma Mansoni

Schistosomiasis, a parasitic helminth infection, affects over 250 million people worldwide[1]. Adult worms of *S. mansoni* move to their hosts mesenteric veins where they produce eggs, which make passage into the gut or get swept away by the bloodstream, eventually lodging in the sinusoids of the liver. The carcinogenicity of *S. mansoni* is so far undetermined[2], however, we previously showed that the proto-oncogene c-Jun is activated by *S. mansoni* egg antigens in hepatocytes[3-6].

Figure 1: Life cycle of *S. mansoni*



Hepatitis B Virus

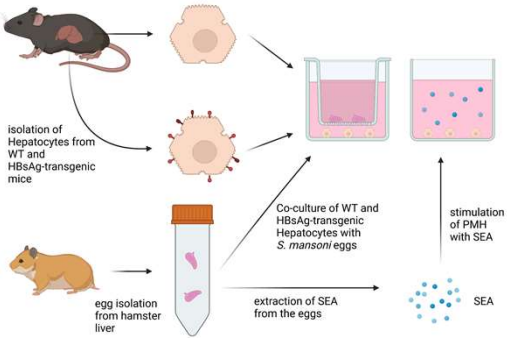
HBV is a partially double-stranded DNA virus, which causes hepatic inflammation and necrosis. These processes facilitate mutations in infected liver cells, which eventually lead to hepatocellular carcinoma (HCC). Worldwide, HBV is responsible for 75% of all HCC cases[7]. HBV entry into hepatocytes is facilitated through three viral surface proteins collectively labeled HBV surface antigen (HBsAg)[8]. The expression of these surface antigens in a murine model alone leads to chronic liver injury, regenerative hyperplasia, adenomas and HCC[9].

Co-Infection

Coinfections of *S. mansoni* and HBV occur disproportionately often in endemic areas[10] and lead to a more rapid progression of liver pathology, increasing the incidence and mortality of HCC[11,12].
It has been shown that immune responses to *S. mansoni* and HBV infections subtly interact. A Schistosome-induced immune response might be auxiliary in controlling HBV[13].
However, the influence of a concomitant infection with *S. mansoni* and HBV on the liver parenchyma remains unclear. This cooperative study address the elucidation of molecular mechanisms of parenchymal damage through hepatocellular stress, fibrosis, and carcinogenesis.

Methods

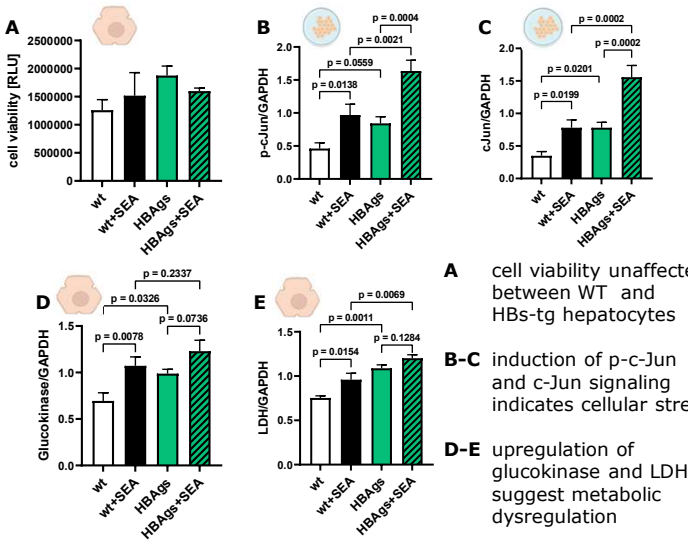
Figure 2: Experimental setup



Primary mouse hepatocytes (PMH) from HBsAg-transgenic (HBs-tg) mice as well as transiently transfected HepG2 cells served as model systems for HBV infection. HepG2 cells and PMH from wild type (WT) mice were kept in cell culture to be stimulated with soluble egg antigens (SEA) or directly in co-culture experiments with *S. mansoni* eggs.

Results

Figure 3: Co-Infection models induce c-Jun activation and cause metabolic dysregulation



A cell viability unaffected between WT and HBs-tg hepatocytes

B-C induction of p-c-Jun and c-Jun signaling indicates cellular stress

D-E upregulation of glucokinase and LDH suggest metabolic dysregulation

Conclusiuon & Outlook

The induction of the proto-oncogene c-Jun might cause a considerable induction of hepatocellular proliferation. Furthermore, the upregulation of key enzymes of carbohydrate metabolism indicate an influence of both pathogens on hepatic metabolism. Further experiments will confirm preliminary results and append insight into underlying mechanisms. In addition, the influence of both pathogens on hepatocyte proliferation, DNA-repair and ER-stress will be focus points for further investigation.

Literature & Funding

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