Molecular mechanism of enhanced liver fibrosis during HCV/HIV coinfection

BACKGROUND AND SIGNIFICANCE: HCC is the third leading cause of cancer-related deaths worldwide (1). Chronic HCV infection is one of the major causes of HCC. It accounts for the majority of cases worldwide as 200 million people have been shown to be infected with HCV. Approximately 20% of HCV infected patients develop HCC (1, 2) and HCC is a third leading causes of cancer related deaths in world wide (3). Furthermore, the contribution of HCV to HCC in industrialized countries has significantly increased in recent years, as in Japan (90%) and the US (52%) of HCV patients develop HCC (2). HCV is a positive-strand RNA virus of the *Flaviviridae* family and is a major causative agent of liver disease. Pathogenesis of HCV is characterized by acute necrosis of hepatocytes, inflammation, steatosis, fibrosis and cirrhosis (3). In chronically infected HCV patients, cirrhosis is an important contributor in the development of HCC. Cirrhosis is the terminal stage of fibrosis. Fibrosis results from excessive accumulation of extracellular matrix (ECM). The accumulation of ECM proteins distorts the hepatic architecture by forming a fibrous scar and the subsequent development of nodules of regenerating hepatocytes defines cirrhosis. Activated production of proinflammatory and profibrogenic cytokines associated with steatosis could play a role in the liver fibrosis.

Apart from the, Hepatocellular carcinoma (HCC) one of third leading cause of cancer-related deaths worldwide, Over 40 million people are infected with HIV worldwide despite the available HAART therapy, which has been shown to reduce mortality due to HIV, HCC has emerged as a major source of mortality and morbidity in HIV infected patients [4-14]. It has been reported that ~30-40% of HIV infected patients are co-infected with hepatitis C virus (HCV). Chronic HCV infection is a main risk factor for development of HCC. Furthermore, incidence of HCC has been reported to be 5 times higher in HIV-HCV co-infected people than in those with HCV alone [15-16]. HIV has been shown to accelerate progression to HCC in HCV patients. It has been shown that co-infected patients have a higher incidence of liver fibrosis and increased death from liver disease. Once chronic infection is established, HIV/HCV-coinfected patients exhibit higher necro-inflammatory activity on liver biopsies, faster rates of fibrosis progression, and earlier development of end-stage liver disease. Despite the significant adverse clinical consequences of HIV/HCV coinfection, the underlying molecular mechanisms by which HIV infection impacts HCV disease progression and development of HCC are not known. Recently some studies has been shown that HIV and HCV envelope proteins induce hepatocytes dysfunction via a novel “innocent bystander” mechanism due to cell surface binding of viral envelope proteins independent of viral infection [17-20]. Several studies has been studies that mir122 a microRNA important for the HCV infection. Till to date there is no data shows the microRNA changes during HCV/HIV co-infection. Our hypothesis is that that HIV can either infect or activate the hepatocytes, HSCs and induces the microRNAs changes which are important for inflammatory, profibrogenic cytokines molecules, leading to enhanced progression of HCC.
Since fibrosis/cirrhosis plays an important role in the development of HCC, it has been shown that Epithelial Mesenchymal Transition (EMT) may regulate the development of myofibroblasts from hepatocytes which are ultimately important for fibrosis. Furthermore, not much is known about induction of EMT and its role in HCV/HIV induced liver fibrosis/HCC. Recent studies have been shown that profibrogenic cytokines like TGF-B are important for the development of myofibroblasts from hepatocytes by EMT. We are hypothesizing that HCV/HIV co-infection will enhance the myofibroblast populations in the liver and leads to excessive accumulation of ECM which leads to liver fibrosis.

**SPECIFIC AIMS:** The overall focus of this project is to characterize the microRNA changes during the HCV/HIV co-infection. The second objective of my study is the analysis of molecular mechanism of EMT during the generation of myofibroblasts by HCV/HIV co-infection.

**Specific Aim 1: Analyze the expression of microRNAs during the HCV/HIV co-infection:** Our hypothesis is that HCV/HIV co-infection induces small microRNAs expression, which are different from HCV mono infection, might plays important role in cellular gene expression, which are ultimately leads to the enhanced liver fibrosis compared to HCV mono-infection.

A. Analyze the expression of microRNAs during HCV/HIV co-infection using HCV expressing cell lines and HIV virus.

B. Characterization of differentially expressed microRNAs in enhanced liver fibrosis during co-infection compared to HCV mono infection. Analyze the differentially expressed micro RNAs in liver fibrosis.

**Specific Aim 2: Further characterize the role of HCV/HIV co-infection in Epithelial Mesenchymal Transition of hepatocytes to Myofibroblasts:** Analyze the role of HCV/HIV co-infection in the transformation of hepatocytes into myofibroblasts (EMT) by using HCV expressing cell lines and HIV virus.

**References:**


