Livers that are chronically infected with Hepatitis C virus (HCV) are at higher risk of developing hepatocellular carcinoma (HCC). Our studies have shown that aerobic bacteria are found in normal and cirrhotic liver tissues but the role of specific liver microbiome populations in the etiology of HCV-related cirrhosis and HCC are poorly understood. Microorganisms and their components are recognized by Toll like receptors (TLRs) that result in activation and subsequent production of pro-inflammatory cytokines and chemokines. Aberrant expression or activation of TLRs results in chronic inflammation promoting carcinogenesis. We hypothesize that changes in the liver microbiome can result in altered TLR expression that influences HCV-related cirrhosis and cancer development. In this study, we characterized bacterial flora and expression of TLR2 and TLR4 in normal liver, HCV-related cirrhotic (HCV) and HCV-related HCC (HCV/HCC) tissues. Gram-positive and Gram-negative organisms were present in all the liver tissues. There were no changes in the expression of TLR2 but TLR4 expression was reduced in HCV-cirrhotic and HCV/HCC compared to normal liver hepatocytes. In portal regions, HCV/HCC tissues showed the lowest expression of TLR4 followed by HCV-cirrhotic and normal tissues. Lower TLR4 expression in cirrhotic and HCC tissues could be due to altered microbial flora and a reflection of increased innate immune suppression during cirrhosis and cancer development. Our findings suggest that microbial communities may contribute towards immunosuppression of TLR4-mediated innate immunity in cirrhotic livers undergoing progression to HCC. Manipulating bacterial communities or TLR4 agonist treatment could prevent HCV-related liver cancer development.

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