Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4

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Increased bacterial translocation is a hallmark of chronic liver disease and contributes hepatic inflammation and fibrosis. Here we tested the hypothesis that the gut microbiota and Toll-like receptors (TLRs) promote the development of hepatocellular carcinoma (HCC), a malignancy that predominantly arises in chronically inflamed and fibrotic livers. TLR4 inactivation decreased hepatocarcinogenesis in inflammatory and fibrotic HCC, but not in purely genotoxic HCC. Bone marrow transplantation experiments demonstrated that hepatocarcinogenesis was dependent on TLR4-expressing resident liver cells. Gut sterilization by antibiotics decreased, and lipopolysaccharide treatment increased HCC development. TLR4 inactivation and gut sterilization suppressed proliferation and expression of hepatomitogens epiregulin and HGF in early stages, and increased apoptosis in late stages of hepatocarcinogenesis. Gut sterilization restricted to late stages of hepatocarcinogenesis was highly efficient in preventing HCC. These results suggest that targeting the gut microbiota or TLR4 may represent novel therapeutic approaches for HCC prevention even in advanced liver disease.