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Answer to reviewer's comments:

1. Q: In the first part "Gut microbiota in healthy and pathologic liver" , the discussion was not clear enough, and did not point out the characteristics and differences of GM between healthy and liver disease patients, and the content did not match the title.

   A: We thank the reviewer for this clarification. Unfortunately, in literature there is little information on the human microbiome of the healthy liver, so we preferred to change the title of the paragraph and treat only the correlations with liver diseases.

2. Q: Is there a difference between the intestinal flora of hepatitis B patients and hepatitis C patients? Can you discuss the reason for the difference?

   A: There is difference in the composition of the intestinal flora between the patients with HBV and HCV infection. HBV infection leads to progressive decline in butyrate-producing bacteria. However, LPS (lipopolysaccharides) - producing genera is enriched in HBV infection. In HBV infection, a beneficial bacterium, *Lachnospiraceae*, plays a role in the management of HBV infection via reduction in LPS section and bacterial translocation. Studies have shown that *Faecalibacterium*, *Neisseriaceae*, *Pseudobutyrivibrio*, *Lachnoclostridium*, *Ruminoclostridium*, *Prevotella*, *Alloprevotella*, and *Phascolarctobacterium* are increased in gut microbiota of HBV patients, and their role is in potential anti-inflammatory SCFA activity, which increases the abundance of butyrate compared to normal subjects (Chen et al., 2011; Ren et al., 2019; Liu et al., 2019). Chronic HBV patients have reduced *F. prausnitzii*, *E. faecalis*, *Enterobacteriaceae*, *Bifidobacteria*, and lactic acid bacteria (*Lactobacillus*, *Pediococcus*, *Leuconostoc*, and *Weissella*). During HBV infection, dysbiosis in the oral microbiota was observed, and yellow tongue coating is suggestive of a reduction in *Bacteroidetes* but an increase in *Proteobacteria*. In majority, copy numbers of Enterobacteriaceae and *Bacterioidetes* are increased in chronic HCV patients, opposite to HBV infection, but *Firmicutes* found to be decreased. HCV infection causes marked elevation in LPS, which is suggestive of microbial translocation and inflammation during disease progression (Dolganiuc et al., 2007; Inoue et al., 2018). It was observed that antiviral treatment of HCV with ribavirin (RBV) and immune modulator pegylated interferon (PEG-IFN) has no direct impact on gut dysbiosis.

In fact, it increases the production of bile acids, which is important for gut microbiota (Ponziani et al., 2018). Some pathogenic bacteria such as *Enterobacteriaceae*, *Staphylococcus*, and *Enterococcus* decreased the bile acid in HCV-infected cirrhotic patients, which normalized after a direct-acting antiviral treatment. Oral direct-acting antivirals (DAAs) were also found to be helpful in improving gut especially *Lachnospira* and *Dorea genera*, and restored TNFα levels (Pérez-Matute et al., 2019). It suggests conclusion that antiviral treatment plays an important role in the differences of composition of HBV and HCV patients gut microbiota. It was also suggested that endotoxemia in HCV patients seems to be multifactorial, more than in HBV patients, likely depending on impaired phagocytic functions and reduced T-cell-mediated antibacterial activity (Kefalakes and Rehermann, 2019). These differences in gut microbiota of HBV and HCV patients are presented in the Figures.

3. This review article only discuss the GM change in hepatitis, cirrhosis, liver cancer, I think it is better to review the mechanistic links between GM and liver disease
   A: as suggested, we inserted the mechanistic links between GM and liver disease form line 142 to line 229

4. Q: Are there other treatments for liver disease based on GM?
   A: Different therapeutic approaches have been proposed to improve the health of patients with chronic viral hepatitis through the manipulation of GM composition, the modulation of immune signaling, and the production of metabolites. Fecal microbiota transplantation (FMT) is considered to be a promising new treatment option for HBV and HCV infection, because of its ability to restore the gut microbiota dysbiosis. Detailed explanation about FMT and its potential in the treatment of liver hepatitis based on gut microbiota alteration is highlighted in the text of the manuscript. The use of probiotics in HBV positive patients showed benefit and suggested that probiotic plays an important role in the management of viral hepatitis (Dhiman 2014). Oral direct-acting antivirals (DAAs) were found to be helpful in improving gut microbiota especially Lachnospira and Dorea genera, and restored TNFα levels (Pérez-Matute et al., 2019). After DAA treatment, expression of calprotectin, ZO1, and LPS was found more in HCV patients with cirrhosis, compared to the HBV patents. It was also suggested that during HCV infection, L. acidophilus and Bifidobacterium spp. can act as a supportive

supplement with antiviral and antibacterial activities (Dore et al., 2014). Immune response in HCV patients can be stimulated by useful microbiota via activation of CD3+ cells and CD56+ NK cell counts, and it is further suggested that good flora increases the cytotoxic effects of NK cells against viral infected cells inhibiting the replication of HCV.