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Reply to: "Finding fibroblast growth factor 19 during cholestasis: Does x mark the spot?

What is the cellular source of FGF19 during chronic liver disease?

To the Editor:

We thank Drs. de Haan and van Golen for discussing our recent study of bile acid metabolism and FGF19 in patients with alcohol use disorder and alcoholic hepatitis. Under physiological conditions, FGF19 is primarily expressed in intestinal epithelial cells of the terminal ileum and reaches the liver via the portal circulation to regulate bile acid synthesis in hepatocytes. Very high serum FGF19 level in patients with alcoholic hepatitis prompted us to test the hypothesis that hepatic expression contributes to elevated systemic levels. Plasma FGF19 and hepatic *FGF19* mRNA levels are elevated in patients with extrahepatic cholestasis, with a decrease in systemic and hepatic FGF19 following biliary drainage.[1] Indeed, we found a robust increase in hepatic FGF19 expression, while positive staining was confined to the cytoplasm of predominantly cholangiocytes and ductular cells from smaller ductules (likely progenitor cells) in patients with alcoholic hepatitis.[2] Gallbladder epithelial cells from a resected gall bladder served as appropriate positive staining control,[3] while non-neoplastic liver with portal tracts was negative for FGF19 protein,[3,4] although large caliber bile ducts showed weak positive staining for FGF19.[3] Our expression pattern is consistent with high FGF19 expression in non-parenchymal cells from human liver with biliary cirrhosis.[4] The latter study used flow cytometry sorting to separate hepatocytes from bile duct cells. A pure biliary ductal cell population expressed considerably higher amounts of FGF19 than hepatocytes.[4] Patients with primary biliary cholangitis (PBC) also have increased serum FGF19, hepatic FGF19 gene and protein expression.[5] In contrast to the expression pattern in alcoholic hepatitis and biliary cirrhosis, FGF19 co-localized with FGFR4 suggesting a predominant expression in hepatocytes.[5] Co-localization with other non-parenchymal liver cell markers was not performed.

Different disease etiologies might account for different cellular expression patterns. PBC is a cholangiocyte disease causing intrahepatic cholestasis, while alcoholic hepatitis is a hepatocellular disease associated with cholestasis and accumulation of bile acids in the liver. The severity of cholestasis is different between PBC (*e.g.* mean bilirubin 1.81 mg/dl[5]) and alcoholic hepatitis (*e.g.* mean bilirubin 15.5 mg/dl[2]), which might contribute to differences in FXR activity. Bile acid – FXR signaling induces FGF19 in cultured human hepatocytes.[6] Alcoholic hepatitis is often accompanied by a profound hepatic and systemic inflammatory response, which is not seen in PBC. Finally, alcoholic hepatitis is characterized by a strong ductular reaction. Hepatic progenitor cells fail to differentiate into hepatocytes contributing to impaired hepatocyte regeneration, but instead differentiate into biliary cells.[7] Failed differentiation might induce FGF19 in progenitor cells during alcoholic hepatitis.

As elaborated by Drs. de Haan and van Golen, although induction of hepatic *FGF19* likely increases serum FGF19 in patients with alcoholic hepatitis, other sites, such as the terminal ileum as the primary source for FGF19, might contribute to this systemic increase as well. Increased ileal *FGF19* mRNA expression was observed in actively drinking patients with cirrhosis when compared with patients with cirrhosis of non-alcoholic etiology.[8,9] Further analysis is required, although the severity of the disease often prohibits routine colonoscopies in patients with alcoholic hepatitis.

One of the questions that needs to be addressed is whether very high serum FGF19 may eventually lead to resistance in downstream signaling. This will be important to determine, in particular if FGF19 (analogs) are being considered as a therapeutic option in patients with alcoholic hepatitis.

Conflict of interest

B.S. reports a laboratory service agreement with NGM Bio. All other authors report no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

B.S. wrote, and K.B., P.H., L.J.J., and D.P.P. edited the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.09.017.

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