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

To the Editor:

Reducing hepatocyte bile salt levels under cholestatic conditions is crucial to avoid the deterioration of liver function through bile salt toxicity. Hepatocyte bile salt production is largely controlled by fibroblast growth factor 19 (FGF19), normally produced by ileal enterocytes in response to activation of the intestinal bile salt receptor FXR.[1] Enterohepatic cycling of FGF19 prevents hepatic bile salt toxicity by downregulating hepatocyte bile salt production by CYP7A1. Although undetectable in native livers, the compensatory induction of hepatic FGF19 expression has been noted in patients with extrahepatic cholestasis.[2] Using alcoholic hepatitis (AH) as a template disease, the InTeam consortium[3] reveals several striking parallels between intrahepatic and extrahepatic cholestasis. In severe AH, hepatocyte bile salt synthesis by CYP7A1 was suppressed, while hepatic bile salt loading was reduced through the induction of bile salt export and suppression of bile salt uptake. More importantly, severe AH triggered hepatic FGF19 expression and an increase in plasma FGF19. As was previously reported for primary biliary cholangitis,[4] circulating FGF19 correlated with markers of AH disease severity. This supports the paradigm that the induction of hepatic FGF19 during cholestasis is a cytoprotective response that aims to limit bile salt toxicity when intestinal FGF19 production is compromised.

Little is known about how and where FGF19 is produced when hepatic bile salt load increases, owing to the fact that, with the exception of Gold Syrian hamsters,[5] no animal models are available to study this mechanism. Whereas some studies show that hepatocytes can produce FGF19 in an FXR-linked fashion[4,6,7] others have claimed that FGF19 actually derives from the non-parenchymal hepatic cell fraction.[8] Using immunohistochemistry, Brandl *et al.* propose that FGF19 expression in severe AH is confined to biliary epithelium and, possibly, some endothelial cells. As the expression of FGF19 was characterized as 'very low', it is questionable whether the observed FGF19-positive cells account for the noted steep rise in hepatic FGF19 mRNA expression. With respect to the immunohistochemistry, large intrahepatic bile ducts were also FGF19-positive in negative controls, which is in line with earlier findings.[9] The pattern of FGF19 staining in AH also differed considerably from patients with primary biliary cholangitis,[4] which is analogous to AH in terms of intrahepatic cholestasis. Beyond immunohistochemistry, no experiments were performed to characterize the FGF19-positive cells. As a control group with proven hepatic FGF19 induction was lacking (*i.e.*, patients with obstructive cholestasis), it is uncertain whether the presented data allow firm conclusions about the cell type(s) that express (or produce) FGF19 during AH. The latter is also supported by the fact that, inherent to the study population, no ileal biopsies were available to monitor the endogenous site of FGF19 production during AH and juxtapose this to systemic FGF19 dynamics. This is particularly interesting considering that intestinal bile salt delivery and, hence, ileal FGF19 production should not be fully compromised in AH, which differs from extrahepatic cholestasis. Direct effects of alcohol use on intestinal FGF19 production have also been noted. Lastly, these findings call into question how portal hypertension typically seen in severe AH and the consequent effects on intestinal barrier function affect ileal bile salt metabolism and FGF19 production.

Until hepatic FGF19 expression is mapped on a single-cell resolution, the cellular source of FGF19 during cholestasis remains uncertain. That notwithstanding, the data collected by the InTeam consortium show that adaptive changes in bile salt signaling are conserved between extrahepatic and intrahepatic cholestasis. Supported by early preclinical findings,[10] it reaffirms that therapeutic options beyond steroids may become available for AH.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.09.008.

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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

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