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Commentary

Targeting the gut microbiota for treating colitis: Is FGF19 a magic bullet?

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In this issue of *EBioMedicine*, Gadaleta, et al. [1] used an engineered non-tumorigenic variant of the fibroblast growth factor 19 (FGF 19), M52, to study its effect on dextran sodium sulfate-induced colitis in wild type and farnesoid X receptor (FXR) deficient ($Fxr^{-/-}$) mice. Their results showed that M52 overexpression reduced intraluminal bile acid levels and bile acid toxicity, protected intestinal barrier function, and inhibited inflammatory immune response in the intestine. These beneficial effects were not observed in $Fxr^{-/-}$ mice, indicating a role for intestinal FXR in M52-mediated anti-inflammatory activity in colitis. M52 generated a beneficial shift in gut microbial diversity and increased the abundance of *Acetatifactor* and several other bacteria belonging to the phylum *Firmicutes*, which are decreased in inflammatory bowel disease (IBD) patients. These results also showed that FGF19 levels were reduced in Crohn's disease patients. The authors conclude that M52 treatment modulates the gut microbiota to preserve intestinal barrier function and inhibit inflammatory immune response in experimental IBD.

Bile acids are metabolic regulators and nutrient sensors that play a critical role in the regulation of lipid, glucose and energy metabolism. Bile acids control gut microbiota overgrowth, in turn, the gut bacteria modulates the bile acid pool through production of the secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA) from cholic acid (CA) and chenodeoxycholic acid (CDCA), respectively, thus determining the bile acid pool size and composition of circulating bile acids. Bile acids activate intestinal FXR to induce FGF19, which is a postprandial, insulin-like hormone that regulates hepatic bile acid synthesis and homeostasis by inhibiting cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme that directs bile acid synthesis (recently reviewed in [2]). However, FGF19 is a growth factor that increases tumorigenesis and hepatocellular carcinoma (HCC) [3]. Serum FGF19 levels are inversely correlated to CYP7A1 expression, and are increased in patients with extrahepatic cholestasis [4]. Bariatric surgery increases serum bile acids and FGF19, which are associated with improvement of glycemic control and diabetes in obese and diabetic patients [5]. Therefore, targeting FXR and FGF19 signaling to regulate bile acid synthesis and composition may have therapeutic potential for treating nonalcoholic steatohepatitis (NASH) and HCC [2], and this study provides a novel anti-inflammation mechanism for M52 in IBD.

It is interesting to point out that a previous study reported that an intestine-restricted FXR agonist, fexaramine, also increased the abundance of *Acetatifactor* in mice [6]. *Acetatifactor* has high bile salt hydrolase activity, which de-conjugates bile acids, and also has both 7α- and 7β-dehydroxylase activity that converts CDCA and its 7β epimer, ursodeoxycholic acid (UDCA), to LCA. Fexaramine also increased TβMCA, similar to the effect of M52 in this study. The secondary bile acids DCA and LCA are endogenous activators of Takeda G protein-coupled bile acid receptor 5 (TGR5), which improves insulin sensitivity through the release of glucagon-like peptide-1 (GLP-1) and promotes browning of adipose tissue and increased energy metabolism. It has been reported that dietary fats induced CA and expansion of *Bilophilia wardsworthia*, which is associated with increased proinflammatory immune response and colitis in $IL10^{-/-}$ mice [7]. Decreasing the ratio of TCA to TβMCA or 12-hydroxy-bile acids to non-12-hydroxy-bile acids reduces dietary fat, cholesterol absorption and pro-inflammatory cytokine production. Another study reported that FXR and TGR5 cross talk in L cells and that the FXR and TGR5 dual agonist INT-767 was more effective than the FXR-selective agonist obeticholic acid (OCA) in stimulating GLP-1 secretion and adipose tissue browning, and protected against diet-induced obesity and insulin sensitivity [8]. It is well documented that activation of TGR5 protects against inflammation (reviewed in [9]); therefore, the effect of M52 in reducing inflammation in colitis may involve TGR5 signaling.

Probiotics and prebiotic fibers have been used to target the gut microbiota and improve health and diseases [2]. This study demonstrated that the M52 may be a potential drug therapy for treating cholestasis, IBD and bile acid diarrhea (BAD). In IBD and BAD, chronic bile acid malabsorption due to ileal disruption or inflammation increases luminal bile acid levels to promote intestinal inflammation. Activation of FXR and TGR5 inhibits bile acid synthesis and inflammation and reshape the gut microbiome and protects the intestinal barrier. A non-tumorigenic FGF19 derivative, NGM282, is in clinical trials and a preliminary report indicated it reduced bile acid synthesis, bile acid pool size, and hepatic inflammation, and improved NASH fibrosis [10]. M52 is similar to NGM282 and may exhibit similar anti-inflammatory effects on IBD.

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Declaration of Competing Interest

Authors have no conflict of interest to declare.

Authors contribution

JC interpreted results, reviewed literatures, and wrote the commentary. JMF edited the manuscript.

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