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Beyond FXR to target new therapies for NAFLD

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Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent liver disorder associated with insulin-resistance and obesity, although the pathogenesis is incompletely understood. Currently there are no approved medical treatments for NAFLD or its progressive form of non-alcoholic steatohepatitis (NASH). Farnesoid X receptor (FXR) and its downstream target small heterodimer partner (SHP) are liver nuclear receptors that mediate bile acid signaling. They regulate several metabolic functions including bile acid synthesis, glucose homeostasis and lipid metabolism. FXR activation may be beneficial in improving glucose metabolism and insulin sensitivity, thus FXR is a potential therapeutic target for metabolic liver diseases. The FXR agonist obeticholic acid has been approved to treat Primary Biliary Cholangitis, and is currently being used in clinical trials for the treatment of NASH and other liver diseases.

In this issue of *Hepatology*, Akinrotimi et al. (1) demonstrate that global FXR/SHP double knockout (DKO) mice fed a high fat diet have less weight gain and hepatic steatosis, and better glucose tolerance and insulin sensitivity, than high fat fed control mice. The authors also demonstrate the important finding that these beneficial effects are associated with increased energy expenditure, enhanced fat burning in muscle, decreased hepatic lipogenesis and increased fatty acid β -oxidation. To determine the respective role of hepatic FXR and its downstream target SHP, the authors used liver-specific FXR and liver-specific SHP single knockout (SKO) mice challenged with a high fat diet to demonstrate that SHP deletion in the liver similarly resulted in lower body weight, improved glucose metabolism and less hepatic steatosis. In contrast, these findings did not occur in liver-specific FXR SKO mice. These data suggest that the beneficial effects of the DKO mice are mediated, at least in part, by hepatic SHP signaling.

FXR activation can limit hepatic lipid accumulation and hepatic FXR stimulation increases liver SHP expression. However in the study by Akinrotimi et al. (1), liver-specific SHP deletion had a favorable effect on liver steatosis. Different mechanisms are most likely involved in these seemingly paradoxical findings. FXR regulates gene expression in both a SHP-dependent and SHP-independent manner. FXR SKO mice, SHP SKO mice and FXR/SHP DKO mice have distinct phenotypes (2, 3), therefore different cellular signaling pathways may be regulated by either FXR, SHP, or by both nuclear receptors. Furthermore, there are distinct liver-specific and intestine-specific functions of FXR. Intestinal FXR activation induces the expression of fibroblast growth factor 19 (FGF19, or the murine ortholog FGF15) which is an important regulator of hepatic bile acid synthesis and lipid metabolism.

Aged liver-specific FXR/SHP DKO mice fed chow fully phenocopy global FXR/SHP DKO mice, with lower hepatic triglycerides, improved glucose metabolism and accelerated fatty acid use (3). This phenocopy suggests that hepatic FXR/SHP is essential for the DKO phenotype. Future studies should determine if these mice are also phenocopies when fed a high fat diet. Global FXR SKO mice exhibit impaired insulin sensitivity on chow diets, but have improved glucose homeostasis and less weight gain in diet-induced and genetic models of obesity. The FXR agonist GW4064 also has opposite metabolic effects in diabetic mice and in high fat diet-fed mice (4, 5). In addition, both activation and deletion of intestinal FXR signaling have been shown to have multiple metabolic benefits (6, 7). The effects of global SHP knockout on insulin sensitivity also remain unclear (8, 9). The hepatic and systemic roles of FXR and SHP in metabolic diseases are complex and at times, seemingly contradictory. These differing data may be due to different mouse strain backgrounds, differing gut microbiome and potential off-target effects of pharmacologic agents.

In addition to FXR, bile acids are also endogenous ligands for G-protein coupled bile acid receptor 1 (Takeda G-protein receptor 5, TGR5, GPBAR1). TGR5 is expressed in many different types of cells, but not in hepatocytes. It regulates energy expenditure in skeletal muscles and brown adipose tissue, and improves insulin sensitivity via increasing glucagon-like peptide 1 (GLP-1) secretion from the intestine. TGR5 activation prevents high-fat diet induced obesity, hepatic steatosis and improves insulin sensitivity. Since FXR/SHP DKO mice have significantly elevated serum bile acids (2), the effects on energy expenditure in the FXR/SHP DKO mice may be due, at least in part, to peripheral effects of bile acids activating TGR5 in muscles and adipose tissue.

Bile acids regulate many metabolic processes in different tissues via a number of bile acid receptors including FXR, TGR5, pregnane X receptor (PXR), Vitamin D receptor (VDR) and constitutive androstane receptor (CAR). Distinct bile acid species have differing agonist affinities for these receptors. Therefore, it is essential to measure not only bile acid pool size and serum bile acid levels, but also bile acid species composition. Although the liver-specific SHP SKO mice had no change in bile acid pool size, determining the bile acid composition in these mice may provide additional mechanistic insights.

The FXR agonist obeticholic acid improves hepatic steatosis, inflammation and fibrosis in non-cirrhotic NASH patients, however, it has adverse effects on serum lipid profiles and possibly insulin-resistance. This raises long-term cardiovascular safety concerns in a patient population prone to cardiovascular disease. In addition to FXR, other bile-acid signaling pathways are being targeted for the treatment of NASH using FGF19 analogues and TGR5 agonists. A recent study in obese mice shows that a TGR5/FXR dual agonist improves glucose and insulin tolerance better than specific FXR or TGR5 agonists (10). Therefore, dual agonists may offer promise for the treatment of fatty liver disease.

The study by Akinrotimi et al. (1) demonstrates a central role of hepatic SHP in regulating glucose and fatty acid metabolism. These important findings suggest that this FXR downstream target may be an efficacious and potentially more specific target for drug development to treat fatty liver disorders. Additional basic investigations demonstrating how SHP, TGR5, FGF15/19 and other bile acid receptors attenuate hepatic steatosis,

steatohepatitis and disease progression are essential. Understanding these signaling pathways may further identify novel targets for the treatment of non-alcoholic fatty liver disorders.

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