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REVIEW

Recent insights into farnesoid X receptor in non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome and is one of the most prevalent liver disorders worldwide. NAFLD can gradually progress to liver inflammation, fibrosis, cirrhosis and even hepatocellular carcinoma. However, the pathogenesis of NAFLD is complex, and no efficient pharmaceutic treatments have yet been established for NAFLD. Accumulating data have shown that the farnesoid X receptor (FXR) plays important roles not only in bile acid metabolism, but also in lipid and carbohydrate homeostasis, inflammatory responses, among others. In this review, we aim to highlight the role of FXR in the pathogenesis and treatment of NAFLD.

Key words: Farnesoid X receptor; Non-alcoholic fatty liver disease; Mechanism; Therapy; Lipid metabolism

Core tip: Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent liver disorders worldwide and has great risk potentials. While the mechanisms under NAFLD are still in the mist, farnesoid X receptor (FXR) provides a new aspect in this field. In addition to regulate bile acid metabolism, FXR can also be actively involved in lipid (cholesterol, triglyceride, fatty acid) and glucose metabolism, furthermore, FXR participates in regulating inflammation and NAFLD progression. Several FXR agonists are identified and both experimentally and clinically proved to be optimistic in preventing and treating NAFLD, indicating FXR quite a therapeutic target for NAFLD.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by the presence of lipid droplets in hepatocytes in the absence of alcohol consumption. The spectrum of NAFLD is from simple steatosis to non-alcoholic steatohepatitis (NASH) and eventually cirrhosis and hepatocellular carcinoma (HCC). NAFLD is affecting 15%-40% of the general population[1], and among them at least 10%-20% would develop to NASH[2], which is a potentially serious condition with poor prognosis. NASH is currently the most rapidly growing indication for liver transplantation (LT) in patients with HCC in the United States, and is predicted to become the leading indication for LT in the near future[3]. A recent large cohort study indicated that the prevalence of colorectal malignant neoplasm is also closely associated with NAFLD[4].

Frequently, NAFLD clusters with metabolic abnormalities, including type 2 diabetes, obesity, hypertension, hyperlipidemia, *etc*. Growing evidence has suggested that NAFLD is associated not only with liver-related mortality and morbidity but also with an increased incidence of chronic kidney disease[5,6], cardiovascular disease[5,7] and aortic valve sclerosis[8]. NAFLD is thus becoming a major health issue. To date, no optimal treatment has been found, underscoring the need for further efforts in elucidating the pathogenesis of NAFLD and distinguishing effective pharmacological therapies.

Farnesoid X receptor (FXR) is a ligand-activated transcription factor belonging to the nuclear hormone receptor superfamily, it is abundantly expressed in the liver, intestine, kidney, and adrenal cortex, while low levels of FXR have been detected in a variety of tissues including the heart, lung, adipose tissue, *etc*[9,10]. It was initially thought to be the receptor of intermediate metabolites, farnesol, from which the name "Farnesoid X receptor" was derived. In 1999, bile acids (BAs) were found as the natural ligands of FXR, which has since been known as bile acid receptor[11]. As a transcription factor, it binds to DNA either as a monomer or as a heterodimer with a common partner-retinoid X receptor (RXR) to regulate the expression of various genes involved in BA, lipid and glucose metabolism[12,13].

It has been observed that hepatic expression of FXR is decreased in NAFLD patients, which is associated with hepatic triglyceride (TG) accumulation and hepatic steatosis[14], FXR deficiency animal models display hepatic steatosis, hyperlipidaemia, hyperglycemia, BA overload, inflammation and fibrosis[15-18]. However, these can be improved by FXR activation[19,20], indicating FXR could be a key regulator of metabolic homeostasis. Thus FXR appears to be a promising target for the treatment of NAFLD.

POTENTIAL PATHOGENESIS OF NAFLD

The pathogenesis and progression of NAFLD are multifactorial and not quite so clear, while generally explained by the "two-hit" theory[21]. The "first hit" is hepatic fat accumulation owing to increased hepatic *de novo* lipogenesis (DNL) and fatty acid uptake, inhibition of fatty acid β oxidation (FAO), impaired TG clearance and decreased very-low-density lipoprotein (VLDL) export[22]. Oxidative stress and subsequent inflammation are key factors of the "second hit", which ultimately cause further liver damage. Studies have shown that multiple parallel hits, including genetic differences, intestinal microbiota, adipose-derived cytokines and so on account for the progression of NAFLD[23].

Loss of the body's ability to retain excess lipids in "classical" adipose tissue stores can lead to the overdevelopment of ectopic fat deposition, often creating severe perturbations of both glucose and lipid homeostasis[24]. Excessive fat accumulation in the liver is recognized as a pathological state. Hepatic ectopic fat deposition, especially TG, cholesterol and fatty acid eventually lead to disordered hepatic lipid metabolism.

TG derives from the esterification of free fatty acid (FFA) that may come from dietary fats, adipose tissue and DNL, and can be used for energy through FAO in mitochondria. Hepatic TG lipolysis is mediated by lipases, which release FFA for oxidation. After synthesis, hepatic TG may be stored as lipid droplets or packaged with ApoB into VLDL and then secreted into circulation[25].

MECHANISMS OF FXR IN NAFLD

Although inappropriate lipid metabolism, insulin resistance, and inflammation represent important risk factors for the development of NAFLD, the precise mechanisms controlling disease pathogenesis remain largely undefined. Recent studies on FXR have provided new opportunities to elucidate the pathogenesis of NAFLD, and the beneficial role of FXR on NAFLD is through multiple mechanisms.

FXR in regulating bile acid metabolism

BAs are the end products of cholesterol catabolism, produced in the liver, then secreted into the bile canaliculi and subsequently stored in the gall bladder. After ingestion of food, bile flows into the duodenum, where it contributes to the absorption of dietary lipid and fat-soluble vitamins. Most of these BAs (95%) are then reabsorbed from the terminal ileum and transported back to the liver *via* the portal vein, which is known as enterohepatic circulation. Only about 5% of them escapes from reabsorption per cycle and expels from the body in the feces[9,10,26]. BA synthesis *via* two different pathways: the classical pathway and alternative pathway. Two primary BAs cholic acid (CA), chenodeoxycholic acid (CDCA) are the end products of these two pathways. Secondary BAs deoxycholic acid (DCA) and lithocholic acid (LCA) are derived from primary BAs in the intestine by bacterial enzymes.

Three enzymes play major regulatory roles in these two pathways. Cholesterol 7α-hydroxylase (CYP7A1) is the rate-limiting enzyme in the classical pathway, whereas sterol-27 hydroxylase (CYP27A1) is the first enzyme in the alternative pathway, followed by sterol 12 α-hydroxylase (CYP8B1)[10,26]. Several members participate in bile acid transport and enterohepatic circulation. The bile salt export pump (BSEP) is mainly responsible for bile acid transport at the canalicular membrane. Na^+-dependent taurocholate transporter (NTCP) is responsible for basolateral bile acid transport into the hepatocytes. BAs are reabsorbed mostly in the terminal ileum, and are mainly mediated by the apical sodium-dependent bile salt transporter (ASBT). Once absorbed into the enterocytes, BAs then bind the intestinal bile acid binding protein (I-BABP) and are transported to the basolateral membrane for secretion[27].

Although BAs have many physiological roles, abnormal high levels of BAs would increase the risk of hepatotoxicity, because they can cause oxidative stress,

inflammation, necrosis, and eventually fibrosis and cirrhosis[28,29], which are key roles of the pathogenesis of NAFLD. On the other hand, they also function as signaling molecules and metabolic regulators that activate dedicated BA receptors such as FXR to protect against toxic accumulation of BAs, and regulate hepatic lipid, glucose, and energy homeostasis and maintain metabolic homeostasis[10,30].

FXR plays a central role in bile acid homeostasis by regulating genes involved in bile acid synthesis, secretion and reabsorption. FXR inhibits *de novo* BA biosynthesis through up-regulation of the small heterodimer partner (SHP), which interacts with and represses the transcriptional activator, liver related homolog 1 (LRH-1) and hepatocyte nuclear factor-4α (HNF-4α), thus bind to the *CYP7A1* gene promoter, and inhibiting *CYP7A1* gene transcription[31,32]. Additionally, FXR can induce intestinal fibroblast growth factor 19 (FGF19) in humans, as well as FGF15, the mouse ortholog of human FGF19, which then activate the cell-surface receptor, FGF receptor 4 (FGFR4), to eventually inhibit *CYP7A1* gene transcription and bile acid synthesis intracellular *via* intracellular Jun N-terminal kinase (JNK) pathway[33-36]. FXR encompasses the regulation of the enterohepatic circulation. Through up-regulation of BSEP and multidrug resistance protein 2 (MRP2, human canalicular bilirubin conjugate export pump) and inhibition of NTCP, FXR reduces hepatocellular BA levels by stimulating bile acid secretion at the canalicular membrane and limit bile acid uptake from the portal circulation[37-39]. FXR is also able to induce alternative basolateral BA transport through organic solute transporter α/β (OSTα/β), to efflux BAs to systemic circulation and, subsequently, are eliminated by renal excretion[38,40]. Given the above, FXR regulates the synthesis and export of BAs, hence activation of FXR can protect against the liver from toxic accumulation of BAs.

FXR on cholesterol metabolism

In recent years, the role of FXR in cholesterol metabolism has been widely explored. Emerging experimental and clinical evidence has linked altered hepatic cholesterol homeostasis and free cholesterol (FC) accumulation to the risk and severity of NAFLD and the pathogenesis of NASH[41]. It is considered that hepatic accumulation of cholesterol rather than TG may play a critical role in the NAFLD progression[42].

In hepatocytes, cholesterol homeostasis pathways include cholesterol *de novo* synthesis, uptake in the form of low density lipoprotein (LDL) and chylomicron remnants, excretion into the blood in the form of VLDL, excretion and uptake through bile, and synthesis of BAs and their excretion[42]. Since FXR is a key regulator of bile acid metabolism, it is also critical in maintaining cholesterol homeostasis. FXR deficiency mice display increased levels of hepatic and serum cholesterol[43,44], and FXR negatively regulates cholesterol levels *via* various mechanisms.

LDL receptor (LDLR), the scavenger receptor class B type I (SR-BI) and cluster differentiation protein-36 (CD-36) are involved in hepatic cholesterol uptake. Increased LDLR and CD-36 expression, and decreased SR-BI expression are detected in NAFLD, which correlates with the severity of steatosis[45]. Activation of FXR represses the expression of proprotein convertase subtilisin/kexin type 9 (PCSK9), an inhibitor of LDLR, thus increases LDLR activity, and potentiates the hypolipidemic effect of statins[46]. SR-BI is critical for reverse cholesterol transport by transporting high-density lipoprotein (HDL) cholesterol into liver where a part of the cholesterol is metabolized to BAs[47,48]. FXR null mice exhibit reduced SR-BI expression[44]. A recent study showed that FXR positively regulates SR-BI expression, and three binding sites in the first intron of the *SR-BI* gene were identified[47]. Meanwhile, FXR induced reduction of CD36 also effectively prevents liver from steatosis[49]. In the liver, FXR enhances ATP-binding cassette G member 5 and member 8 (ABCG5/G8) expression, a heterodimeric cholesterol efflux transporter, which accounts for increased cholesterol excretion[50]. Collectively, FXR inhibits cholesterol uptake and synthesis and promotes cholesterol excretion, eventually improves cholesterol overload.

FXR in mediating fatty acid and triglyceride metabolism

Hepatic steatosis is the hallmark of NAFLD due to an imbalance between TG synthesis and clearance. From a liver centric point of view, this imbalance results from abnormalities in one or more of the following four processes: (1) hepatic uptake of fatty acid, lipoprotein and glucose; (2) *de novo* TG synthesis; (3) TG degradation and FAO; and (4) lipoprotein secretion in the form of VLDL[51].

FXR has shown considerable impact on lipogenesis. Hepatic lipogenesis is mainly regulated by sterol regulatory element binding protein 1c (SREBP-1c), which is known as the master regulator of lipid biosynthesis and regulates the expression of several genes involved in lipogenesis[52]. FXR activation can inhibit the expression of SREBP-1c and its target enzymes, such as fatty acid synthase (FAS), stearoyl-coenzyme A desaturase 1 (SCD-1) and acetyl-CoA carboxylase (ACC), and prevent excessive fatty acid synthesis and overproduction of TG[19,53,54]. FXR null mice develop hepatic steatosis and hypertriglyceridemia[55]. In NAFLD patients, decreased expression of hepatic FXR also displays elevated TG synthesis, due to increased expression of SREBP-1c[14]. FXR activation effectively prevents hepatic TG accumulation; the underlying mechanisms may be due to FXR-mediated SHP activation, thus suppressing the expression of SREBP-1c and its lipogenic target genes[18]. Other mechanisms independent of the FXR-SHP-SREBP-1c pathway may also contribute to FXR-mediated TG homeostasis[25].

FXR also demonstrates an ability to enhance TG clearance. FXR is known to induce apolipoprotein C-II (Apo C-II) and apolipoprotein AIV (Apo AIV) and inhibit apolipoprotein C-III (Apo C-III) and angiopoietin-like 3 expression, thus activating lipoprotein lipase (LPL)-

mediated lipolysis of TG rich lipoproteins[56]. Peroxisome proliferator-activated receptor alpha (PPARα) is a key regulator of FAO and activation of FXR induces the expression of PPARα and its target gene, carnitine palmitoyltransferase 1 (CPT1), the rate-limiting enzyme in FAO[57]. Furthermore, FXR activation by natural and synthetic BAs increases the expression and secretion of fibroblast growth factor 21 (FGF21), which has been reported to profoundly reduce hepatic TG levels *via* inhibition of SREBP-1c[58,59]. Furthermore, FGF21 induces gluconeogenesis, FAO, and ketogenesis in the liver[60].

In addition, FXR-induced hepatic expression of aldo-keto reductase B7 (Akr1b7) has revealed a striking effect on ameliorating hepatic lipid accumulation in *db/db* mice[61]. A recent study showed that hepatic carboxylesterase 1 (CES1) plays a key role in regulating both normal and FXR-controlled lipid homeostasis. Overexpression of hepatic CES1 lowered hepatic TG, while knockdown of hepatic CES1 increased hepatic TG and plasma cholesterol levels. These effects likely resulted from the TG hydrolase activity of CES1. Activation of FXR induced hepatic CES1, and reduced the levels of hepatic and plasma TG as well as plasma cholesterol in a CES1-dependent manner[62]. Lu *et al*[63] have identified YY1 as a novel transcription factor involved in hepatic TG metabolism in obesity. YY1 expression is markedly up-regulated in HFD-induced obese mice and NAFLD patients. YY1 suppresses FXR expression *via* interaction with the YY1 binding site at the first intron of the *FXR* gene. Liver-specific ablation of YY1 ameliorates liver TG accumulation in obese mice.

FXR and inflammation

Inflammation and fibrosis are main pathological manifestations of NASH. Recently, it has become clear that FXR can down-regulate genes involved in inflammation. FXR deficiency is considered as a significant risk factor in the development of NASH. $LDLR^{-/-}/FXR^{-/-}$ mice fed a high-fat diet (HFD) display higher levels of pro-inflammatory and pro-fibrogenic cytokines, such as tumor necrosis factor α (TNFα), intercellular adhesion molecule-1 (ICAM-1), α-smooth muscle actin (α-SMA), tissue inhibitor of metalloproteinase (TIMP)-1, transforming growth factor (TGFβ), procollagen 1α1 and type 1 collagen compared to $LDLR^{-/-}/FXR^{+/+}$ mice[16]. These studies indicated that activation of FXR may be a therapeutic target in curing NASH.

Indeed, FXR activation appears to protect mice against methionine and choline-deficient (MCD) diet-induced NASH. The reduction in inflammatory cell infiltration and hepatic fibrosis correlated with decreased levels of hepatic inflammation markers such as keratinocyte derived chemokine (mKC), MCP-1, VCAM-1, *etc*, and fibrosis markers such as TIMP-1, α1(I) collagen, α-SMA, TGF-β1, matrix metalloproteinase 2 (MMP-2) and α2(I) collagen[20]. Furthermore, the observation that FXR null mice are more susceptible to LPS-induced liver injury, indicating a direct anti-inflammatory role of FXR, which has been explained *via* negatively mediating the nuclear factor kappa-B (NF-κB) pathway[64]. Additionally, in the intestine, FXR is required to improve biliary obstruction, inhibit bacterial overgrowth, mucosal injury and bacterial translocation[65]. Another anti-inflammatory effect of FXR involves induction of suppressor of cytokine signaling 3 (SOCS3) that inhibits signal transducer and activator of transcription (STAT3) signaling[66]. Recently, Peng *et al*[67] identified *REC*K, a membrane-anchored inhibitor of *MMP-9*, as a novel target gene of FXR in mouse liver. Whether the FXR agonist attenuates hepatic inflammation and fibrosis in a mouse NASH model through the FXR-RECK-MMP-9 cascade still needs further investigation. On the other hand, cholesterol over-intake and BAs accumulation are correlated with the onset and severity in NASH, while the role of FXR in the process need to be further clarified[68].

Some microRNAs have been found to be target genes of FXR, and regulate the process of liver fibrogenesis. FXR-mediated miR-29a up-regulation in hepatic stellate cells (HSCs) leads to decreased amounts of extracellular matrix, and thus protects against liver fibrosis[69]. In another study, liver tissues from patients with severe fibrosis are found to have lower levels of FXR and liver kinase B1 (LKB1) with up-regulated miR-199a-3p. FXR is further confirmed to protect hepatocytes from injury by repressing miR-199a-3p and thereby increasing levels of LKB1[70]. Taken together, the anti-inflammatory actions of FXR are obtained from intra-hepatic and extra-hepatic mechanisms, more experiments are needed to elucidate the molecular mechanisms under the actions.

Other possible mechanisms

Type 2 diabetes is an established risk factor for development of hepatic steatosis and NAFLD. Indeed, the prevalence of NAFLD is higher in patients with type 2 diabetes[71]. Several animal studies have shown that FXR activation can improve insulin sensitivity and down-regulate phosphoenoylpyruvate kinase (PEPCK) and glucose-6-phosphatase (G-6-Pase), two key enzymes in gluconeogenesis[17,49]. Activation of FXR is also reported to induce the phosphorylation of glycogen synthase kinase 3β (GSK3β) to enhance glycogen storage in *db/db* mice[72]. FXR also has a novel role in promoting liver regeneration/repair after liver damage, including physical resection or toxic injury[73]. Apart from this, research has addressed the role of FXR on oxidative stress. FXR-null mice generated enhanced oxidative stress, which may be attributable to a continuously high level of hepatic BAs. On the other hand, FXR activation appeared to repress CYP2E1 expression and attenuate oxidative stress, thus ameliorating liver injury in a murine model of alcoholic liver disease (ALD)[74,75]. FXR is proved to have anti-atherosclerotic effects as well[76]. Recently, down-regulation of hepatic FXR expression by endoplasmic reticulum (ER) stress has been proposed to be in close association with aging-induced fatty liver in mice, mainly through inhibition of hepatocyte nuclear factor 1 alpha (HNF1α)

transcriptional activity[53]. In general, these findings suggest extra mechanisms of FXR in treating NAFLD.

FXR AGONISTS IN TREATING NAFLD

Up to date, no efficient treatments are available for management of NAFLD. As FXR plays critical roles in mediating metabolic homeostasis and inhibiting inflammatory response, it is emerging as an ideal target for treatment of NAFLD. Numerous natural, semisynthetic, and synthetic FXR agonists have shown protective role in animal models and patients with NAFLD.

GW4064 is a non-steroidal synthetic FXR agonist. Activation of FXR by GW4064 suppressed weight gain and attenuated hepatic inflammation in C57BL/6 mice fed with either HFD or high-fat and high-cholesterol diet. GW4064 treatment also repressed diet-induced hepatic steatosis as evidenced by lower TG and FFA level in the liver, possibly due to markedly reduced lipid transporter CD36 expression. In this model, GW4064 improved hyperinsulinemia and hyperglycemia *via* decreasing PEPCK and G6pase[49]. Adiponectin and its receptors are two important factors in treatment of NAFLD. A recent study showed that treatment of GW4064 can up-regulate the expression of PPARγ2, adiponectin, adiponectin receptor 2 (adipoR2) in 3T3-L1 preadipocytes and adipoR2 in HepG2 cells, indicating that FXR agonist has a therapeutic potential in NAFLD[77]. GW4064 strongly induced FGF19 and inhibit CYP7A1, in which the hepatic FGF19/FGFR4/Erk1/2 pathway played a key role, which is independent of SHP. In addition to inducing FGF19 in the intestine, BAs in hepatocytes may activate the liver FGF19/FGFR4 signaling pathway to inhibit BA synthesis and prevent accumulation of toxic bile acid in human livers[35].

Obeticholic acid (OCA or INT-747, 6α-ethyl-chenodeoxycholic acid) is a semisynthetic derivative of the primary human bile acid chenodeoxycholic acid, and the natural agonist of FXR. Administration of OCA reversed hepatic steatosis and insulin resistance in Zucker (*fa*/*fa*) obese rats, protecting against body weight gain and fat deposition in liver and muscle, due to FXR-induced lipogenesis and gluconeogenesis decrease[19]. OCA can inhibit NF-κB-mediated hepatic inflammation, however, the anti-inflammatory effect of OCA are not liver-specific, OCA treatment can also reduce intestinal inflammation and permeability in experimental models of colitis[78]. Also, in primary rat HSCs, 6E-CDCA reduced thrombin-induced up-regulation of α1 (I) collagen, α-SMA and TIMP-1/2 mRNA expression and protected against fibrosis[79]. In a phase 2 clinical trial in patients with type 2 diabetes mellitus and NAFLD (ClinicalTrials.gov, No. NCT00501592), administration of 25 or 50 mg OCA for 6 wk was well tolerated. OCA was found to increase insulin sensitivity and significantly decrease levels of γ-glutamyltransferase and alanine aminotransferase (ALT). Markers of liver inflammation and fibrosis were also decreased in these patients[80].

WAY-362450, a synthetic potent FXR agonist, could attenuate hepatic inflammation and fibrosis in MCD diet induced NASH mice[20]. WAY-362450 treatment was also found to attenuate oxidative stress in a murine model of ALD[75]. Furthermore, treatment of obese *db*/*db* mice with INT-767, a dual FXR/TGR5 (a G-protein-coupled bile acid receptor) agonist, significantly improved the histologic features of NASH, resulted from recruitment of anti-inflammatory Ly6C^{low} monocytes to the liver, directly down-regulated the expression of Ly6C on bone-marrow derived monocytes and decreased production of pro-inflammatory cytokines by macrophages. In addition, INT-767 increased interleukin (IL)-10 production and enhanced hepatic expression of genes associated with alternatively activated macrophages. The data suggested INT-767 as a potential treatment target of NAFLD due to coordinating the immune phenotype of monocytes and macrophages[81]. In another study, INT-767 treatment markedly decreased cholesterol and TG levels in diabetic mice[82].

CONCLUSION

The data presented suggest that FXR plays crucial roles in mediating multiple target genes associated with bile acid, lipid and glucose metabolism and has beneficial effects on inflammation response, thus can partly interpret the pathogenesis of NAFLD. Accumulative data prove that targeting FXR may be beneficial in the prevention and treatment of NAFLD. However, some reports showed opposite results. For instance, the role of FXR in regulating HDL metabolism is still under debate, and need to be further evaluated. Some studies demonstrated different results, as FXR$^{-/-}$ mice had increased plasma HDL-cholesterol[44], and blockage of FXR activity also displayed reduced serum LDL levels and increased HDL levels[83], while activation of FXR by GW4064 suppressed apolipoprotein A-I transcription and reduced serum HDL levels[84]. On the other hand, FXR deficiency was shown to protect from excessive body weight gain in both genetic (*ob*/*ob*) and diet-induced obesity murine models and improve hyperglycemia and impaired glucose tolerance[85]. The same result also emerged in aging FXR deficient mice, and the reduced body weight gain is most likely explained by the increased energy expenditure[15]. In line with this, another study showed that activation of FXR with GW4064 was not useful for long term management of the metabolic syndrome, as it reduced the BA pool size and subsequently decreased energy expenditure, translating as weight gain and insulin resistance[86].

In summary, research on FXR has provided new opportunities to elucidate the pathogenesis of NAFLD and to develop effective treatment. Although activation of FXR by specific agonists could be an attractive pharmacological strategy for managing NAFLD, attention needs to be paid to several undesirable contradictory results, which remain to be elucidated. Since most evidence comes from preclinical studies, more clinical evidence is

urgently needed to establish treatments of FXR agonists for NAFLD.

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