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**Columns:** **REVIEW**

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

Xu JY *et al*. Recent insights into FXR in NAFLD

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**Abatract**

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.

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**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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**IN****TRODUCTION**

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 and NASH cluster 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 was since 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, hyperglycermia, 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 causing further liver damage. Studies have showed 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 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 releases 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 ~5% of them escapes from reabsorption per cycle and expels from the body in the fece[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, inflammatory, necrosis, and eventually fibrosis and cirrhosis[28,29], which are key roles of the pathogenesis of NAFLD and NASH. 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 stimulate 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) involve in hepatic cholesterol uptake. Increased LDLR and CD-36 expression, and decreased SR-BI expression are detected in NAFLD and NASH, which correlated 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 regulate 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 account 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: hepatic uptake of fatty acid, lipoprotein and glucose; *de novo* TG synthesis; TG degradation and FAO; and 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), 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 display elevated TG synthesis, due to increased expression of SREBP-1c[14]. FXR activation effectively prevents hepatic TG accumulation, the underlying mechanisms may due to FXR-mediated SHP activation, thus suppress the expression of SREBP-1c and its lipogenic target genes[18]. Among this, other mechanisms independent of the FXR-SHP-SREBP-1c pathway may also contribute to FXR-mediated TG homeostasis[25].

FXR also demonstrates 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 angiopoetin-like 3 expression, thus activate lipoprotein lipase (LPL)-mediated lipolysis of TG rich lipoproteins[56]. Peroxisome proliferator-activated receptor alpha (PPARα) is a key regulator of FAO, 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 shows that hepatic carboxylesterase 1 (CES1) plays a key role in regulating both normal and FXR-controlled lipid homeostasis. Over-expression 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 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 deceased levels of hepatic inflammation markers such as keratinocyte derived chemokine (mKC), MCP-1, VCAM-1, *et*c, 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-қB) 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. And whether FXR agonist attenuates hepatic inflammation and fibrosis in mouse NASH model through 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. XR-mediated miR-29a up-regulation in hepatic stellate cells (HSCs) leads to decreased amounts of extracellular matrix, 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), 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, researches have addressed the role 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 effect 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, *via* decreasing PEPCK and G6pase, GW4064 improved hyperinsulinemia and hyperglycemia as well[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 expressions of PPARγ2, adiponectin, adiponectin receptor 2 (adipoR2) in 3T3-L1 preadipocytes and adipoR2 in HepG2 cells, indicating that FXR agonist has the therapeutic potential on 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, Number: 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 murine model of ALD[75]. Furthermore, treatment 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 Ly6Clow 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)-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 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 agonist could be an attractive pharmacological strategy for managing NAFLD, attentions need to be paid to several undesirable contradictory results, which remain to be elucidated. Since most evidence come from preclinical studies, more clinical evidence is urgently needed to establish treatments of FXR agonists for NAFLD.

**REFERENCES**

1 **Kwok R**, Tse YK, Wong GL, Ha Y, Lee AU, Ngu MC, Chan HL, Wong VW. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease--the role of transient elastography and plasma cytokeratin-18 fragments. *Aliment Pharmacol Ther* 2014; **39**: 254-269 [PMID: 24308774 DOI: 10.1111/apt.12569]

2 **Sanyal AJ**. NASH: A global health problem. *Hepatol Res* 2011; **41**: 670-674 [PMID: 21711426 DOI: 10.1111/j.1872-034X.2011.00824.x]

3 **Wong RJ**, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. *Hepatology* 2013; [PMID: 24375711 DOI: 10.1002/hep.26986]

4 **Lin XF**, Shi KQ, You J, Liu WY, Luo YW, Wu FL, Chen YP, Wong DK, Yuen MF, Zheng MH. Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study. *Mol Biol Rep* 2014; **41**: 2989-2997 [PMID: 24449368 DOI: 10.1007/s11033-014-3157-y]

5 **El Azeem HA**, Khalek el-SA, El-Akabawy H, Naeim H, Khalik HA, Alfifi AA. Association between nonalcoholic fatty liver disease and the incidence of cardiovascular and renal events. *J Saudi Heart Assoc* 2013; **25**: 239-246 [PMID: 24198448 DOI: 10.1016/j.jsha.2013.07.004]

6 **Targher G**, Chonchol M, Zoppini G, Abaterusso C, Bonora E. Risk of chronic kidney disease in patients with non-alcoholic fatty liver disease: is there a link? *J Hepatol* 2011; **54**: 1020-1029 [PMID: 21145850 DOI: 10.1016/j.jhep.2010.11.007]

7 **Bhatia LS**, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? *Eur Heart J* 2012; **33**: 1190-1200 [PMID: 22408036 DOI: 10.1093/eurheartj/ehr453]

8 **Bonapace S**, Valbusa F, Bertolini L, Pichiri I, Mantovani A, Rossi A, Zenari L, Barbieri E, Targher G. Nonalcoholic fatty liver disease is associated with aortic valve sclerosis in patients with type 2 diabetes mellitus. *PLoS One* 2014; **9**: e88371 [PMID: 24505484 DOI: 10.1371/journal.pone.0088371]

9 **Lefebvre P**, Cariou B, Lien F, Kuipers F, Staels B. Role of bile acids and bile acid receptors in metabolic regulation. *Physiol Rev* 2009; **89**: 147-191 [PMID: 19126757 DOI: 10.1152/physrev.00010.2008]

10 **Thomas C**, Pellicciari R, Pruzanski M, Auwerx J, Schoonjans K. Targeting bile-acid signalling for metabolic diseases. *Nat Rev Drug Discov* 2008; **7**: 678-693 [PMID: 18670431 DOI: 10.1038/nrd2619]

11 **Parks DJ**, Blanchard SG, Bledsoe RK, Chandra G, Consler TG, Kliewer SA, Stimmel JB, Willson TM, Zavacki AM, Moore DD, Lehmann JM. Bile acids: natural ligands for an orphan nuclear receptor. *Science* 1999; **284**: 1365-1368 [PMID: 10334993]

12 **Wang YD**, Chen WD, Moore DD, Huang W. FXR: a metabolic regulator and cell protector. *Cell Res* 2008; **18**: 1087-1095 [PMID: 18825165 DOI: 10.1038/cr.2008.289]

13 **Laffitte BA**, Kast HR, Nguyen CM, Zavacki AM, Moore DD, Edwards PA. Identification of the DNA binding specificity and potential target genes for the farnesoid X-activated receptor. *J Biol Chem* 2000; **275**: 10638-10647 [PMID: 10744760]

14 **Yang ZX**, Shen W, Sun H. Effects of nuclear receptor FXR on the regulation of liver lipid metabolism in patients with non-alcoholic fatty liver disease. *Hepatol Int* 2010; **4**: 741-748 [PMID: 21286345 DOI: 10.1007/s12072-010-9202-6]

15 **Bjursell M**, Wedin M, Admyre T, Hermansson M, Böttcher G, Göransson M, Lindén D, Bamberg K, Oscarsson J, Bohlooly-Y M. Ageing Fxr deficient mice develop increased energy expenditure, improved glucose control and liver damage resembling NASH. *PLoS One* 2013; **8**: e64721 [PMID: 23700488]

16 **Kong B**, Luyendyk JP, Tawfik O, Guo GL. Farnesoid X receptor deficiency induces nonalcoholic steatohepatitis in low-density lipoprotein receptor-knockout mice fed a high-fat diet. *J Pharmacol Exp Ther* 2009; **328**: 116-122 [PMID: 18948497 DOI: 10.1124/jpet.108.144600]

17 **Ma K**, Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. *J Clin Invest* 2006; **116**: 1102-1109 [PMID: 16557297 DOI: 10.1172/JCI25604]

18 **Watanabe M**, Houten SM, Wang L, Moschetta A, Mangelsdorf DJ, Heyman RA, Moore DD, Auwerx J. Bile acids lower triglyceride levels via a pathway involving FXR, SHP, and SREBP-1c. *J Clin Invest* 2004; **113**: 1408-1418 [PMID: 15146238 DOI: 10.1172/JCI21025]

19 **Cipriani S**, Mencarelli A, Palladino G, Fiorucci S. FXR activation reverses insulin resistance and lipid abnormalities and protects against liver steatosis in Zucker (fa/fa) obese rats. *J Lipid Res* 2010; **51**: 771-784 [PMID: 19783811 DOI: 10.1194/Jlr.M001602]

20 **Zhang S**, Wang J, Liu Q, Harnish DC. Farnesoid X receptor agonist WAY-362450 attenuates liver inflammation and fibrosis in murine model of non-alcoholic steatohepatitis. *J Hepatol* 2009; **51**: 380-388 [PMID: 19501927 DOI: 10.1016/j.jhep.2009.03.025]

21 **Day CP**, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology* 1998; **114**: 842-845 [PMID: 9547102 DOI: S0016508598003564]

22 **Nomura K**, Yamanouchi T. The role of fructose-enriched diets in mechanisms of nonalcoholic fatty liver disease. *J Nutr Biochem* 2012; **23**: 203-208 [PMID: 22129639 DOI: 10.1016/j.jnutbio.2011.09.006]

23 **Mantena SK**, King AL, Andringa KK, Eccleston HB, Bailey SM. Mitochondrial dysfunction and oxidative stress in the pathogenesis of alcohol- and obesity-induced fatty liver diseases. *Free Radic Biol Med* 2008; **44**: 1259-1272 [PMID: 18242193 DOI: 10.1016/j.freeradbiomed.2007.12.029]

24 **Lanktree MB**, Johansen CT, Joy TR, Hegele RA. A translational view of the genetics of lipodystrophy and ectopic fat deposition. *Prog Mol Biol Transl Sci* 2010; **94**: 159-196 [PMID: 21036325 DOI: 10.1016/S1877-1173(10)94006-4]

25 **Li Y**, Jadhav K, Zhang Y. Bile acid receptors in non-alcoholic fatty liver disease. *Biochem Pharmacol* 2013; **86**: 1517-1524 [PMID: 23988487 DOI: 10.1016/j.bcp.2013.08.015]

26 **Rizzo G**, Renga B, Mencarelli A, Pellicciari R, Fiorucci S. Role of FXR in regulating bile acid homeostasis and relevance for human diseases. *Curr Drug Targets Immune Endocr Metabol Disord* 2005; **5**: 289-303 [PMID: 16178789]

27 **Li T**, Chiang JY. Bile Acid signaling in liver metabolism and diseases. *J Lipids* 2012; **2012**: 754067 [PMID: 21991404 DOI: 10.1155/2012/754067]

28 **Allen K**, Jaeschke H, Copple BL. Bile acids induce inflammatory genes in hepatocytes: a novel mechanism of inflammation during obstructive cholestasis. *Am J Pathol* 2011; **178**: 175-186 [PMID: 21224055 DOI: 10.1016/j.ajpath.2010.11.026]

29 **Hofmann AF**. The continuing importance of bile acids in liver and intestinal disease. *Arch Intern Med* 1999; **159**: 2647-2658 [PMID: 10597755]

30 **Chiang JY**. Bile acid metabolism and signaling. *Compr Physiol* 2013; **3**: 1191-1212 [PMID: 23897684 DOI: 10.1002/cphy.c120023]

31 **Goodwin B**, Jones SA, Price RR, Watson MA, McKee DD, Moore LB, Galardi C, Wilson JG, Lewis MC, Roth ME, Maloney PR, Willson TM, Kliewer SA. A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. *Mol Cell* 2000; **6**: 517-526 [PMID: 11030332 DOI: 10.1016/S1097-2765(00)00051-4]

32 **Chiang JY**. Bile acid regulation of gene expression: roles of nuclear hormone receptors. *Endocr Rev* 2002; **23**: 443-463 [PMID: 12202460 DOI: 10.1210/er.2000-0035]

33 **Chen Q**, Jiang Y, An Y, Zhao N, Zhao Y, Yu C. Soluble FGFR4 extracellular domain inhibits FGF19-induced activation of FGFR4 signaling and prevents nonalcoholic fatty liver disease. *Biochem Biophys Res Commun* 2011; **409**: 651-656 [PMID: 21616061 DOI: 10.1016/j.bbrc.2011.05.059]

34 **Inagaki T**, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG, Luo G, Jones SA, Goodwin B, Richardson JA, Gerard RD, Repa JJ, Mangelsdorf DJ, Kliewer SA. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metab* 2005; **2**: 217-225 [PMID: 16213224 DOI: 10.1016/j.cmet.2005.09.001]

35 **Song KH**, Li T, Owsley E, Strom S, Chiang JY. Bile acids activate fibroblast growth factor 19 signaling in human hepatocytes to inhibit cholesterol 7alpha-hydroxylase gene expression. *Hepatology* 2009; **49**: 297-305 [PMID: 19085950 DOI: 10.1002/hep.22627]

36 **Eloranta JJ**, Kullak-Ublick GA. The role of FXR in disorders of bile acid homeostasis. *Physiology (Bethesda)* 2008; **23**: 286-295 [PMID: 18927204 DOI: 10.1152/physiol.00020.2008]

37 **Geier A**, Wagner M, Dietrich CG, Trauner M. Principles of hepatic organic anion transporter regulation during cholestasis, inflammation and liver regeneration. *Biochim Biophys Acta* 2007; **1773**: 283-308 [PMID: 17291602 DOI: 10.1016/j.bbamcr.2006.04.014]

38 **Pollheimer MJ**, Fickert P, Stieger B. Chronic cholestatic liver diseases: Clues from histopathology for pathogenesis. *Mol Aspects Med* 2014; **37C**: 35-56 [PMID: 24141039 DOI: 10.1016/j.mam.2013.10.001]

39 **Kast HR**, Goodwin B, Tarr PT, Jones SA, Anisfeld AM, Stoltz CM, Tontonoz P, Kliewer S, Willson TM, Edwards PA. Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. *J Biol Chem* 2002; **277**: 2908-2915 [PMID: 11706036 DOI: 10.1074/jbc.M109326200]

40 **Boyer JL**, Trauner M, Mennone A, Soroka CJ, Cai SY, Moustafa T, Zollner G, Lee JY, Ballatori N. Upregulation of a basolateral FXR-dependent bile acid efflux transporter OSTalpha-OSTbeta in cholestasis in humans and rodents. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G1124-G1130 [PMID: 16423920 DOI: 10.1152/ajpgi.00539.2005]

41 **Musso G**, Gambino R, Cassader M. Cholesterol metabolism and the pathogenesis of non-alcoholic steatohepatitis. *Prog Lipid Res* 2013; **52**: 175-191 [PMID: 23206728 DOI: 10.1016/j.plipres.2012.11.002]

42 **Enjoji M**, Yasutake K, Kohjima M, Nakamuta M. Nutrition and nonalcoholic fatty liver disease: the significance of cholesterol. *Int J Hepatol* 2012; **2012**: 925807 [PMID: 22550592 DOI: 10.1155/2012/925807]

43 **Sinal CJ**, Tohkin M, Miyata M, Ward JM, Lambert G, Gonzalez FJ. Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. *Cell* 2000; **102**: 731-744 [PMID: 11030617 DOI: S0092-8674(00)00062-3]

44 **Lambert G**, Amar MJ, Guo G, Brewer HB, Gonzalez FJ, Sinal CJ. The farnesoid X-receptor is an essential regulator of cholesterol homeostasis. *J Biol Chem* 2003; **278**: 2563-2570 [PMID: 12421815 DOI: 10.1074/jbc.M209525200]

45 **Van Rooyen DM**, Larter CZ, Haigh WG, Yeh MM, Ioannou G, Kuver R, Lee SP, Teoh NC, Farrell GC. Hepatic free cholesterol accumulates in obese, diabetic mice and causes nonalcoholic steatohepatitis. *Gastroenterology* 2011; **141**: 1393-1403, 1403.e1-5 [PMID: 21703998 DOI: 10.1053/j.gastro.2011.06.040]

46 **Langhi C**, Le May C, Kourimate S, Caron S, Staels B, Krempf M, Costet P, Cariou B. Activation of the farnesoid X receptor represses PCSK9 expression in human hepatocytes. *FEBS Lett* 2008; **582**: 949-955 [PMID: 18298956 DOI: 10.1016/j.febslet.2008.02.038]

47 **Li G**, Thomas AM, Williams JA, Kong B, Liu J, Inaba Y, Xie W, Guo GL. Farnesoid X receptor induces murine scavenger receptor Class B type I via intron binding. *PLoS One* 2012; **7**: e35895 [PMID: 22540009 DOI: 10.1371/journal.pone.0035895]

48 **Malerød L**, Sporstøl M, Juvet LK, Mousavi SA, Gjøen T, Berg T, Roos N, Eskild W. Bile acids reduce SR-BI expression in hepatocytes by a pathway involving FXR/RXR, SHP, and LRH-1. *Biochem Biophys Res Commun* 2005; **336**: 1096-1105 [PMID: 16168958 DOI: 10.1016/j.bbrc.2005.08.237]

49 **Ma Y**, Huang Y, Yan L, Gao M, Liu D. Synthetic FXR agonist GW4064 prevents diet-induced hepatic steatosis and insulin resistance. *Pharm Res* 2013; **30**: 1447-1457 [PMID: 23371517 DOI: 10.1007/s11095-013-0986-7]

50 **Li T**, Matozel M, Boehme S, Kong B, Nilsson LM, Guo G, Ellis E, Chiang JY. Overexpression of cholesterol 7α-hydroxylase promotes hepatic bile acid synthesis and secretion and maintains cholesterol homeostasis. *Hepatology* 2011; **53**: 996-1006 [PMID: 21319191 DOI: 10.1002/hep.24107]

51 **Jiang ZG**, Robson SC, Yao Z. Lipoprotein metabolism in nonalcoholic fatty liver disease. *J Biomed Res* 2013; **27**: 1-13 [PMID: 23554788 DOI: 10.7555/JBR.27.20120077]

52 **Horton JD**, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest* 2002; **109**: 1125-1131 [PMID: 11994399 DOI: 10.1172/JCI15593]

53 **Xiong X**, Wang X, Lu Y, Wang E, Zhang Z, Yang J, Zhang H, Li X. Hepatic steatosis exacerbated by endoplasmic reticulum stress-mediated downregulation of FXR in aging mice. *J Hepatol* 2014; **60**: 847-854 [PMID: 24333182 DOI: 10.1016/j.jhep.2013.12.003]

54 **Li X**, Li Y, Yang W, Xiao C, Fu S, Deng Q, Ding H, Wang Z, Liu G, Li X. SREBP-1c overexpression induces triglycerides accumulation through increasing lipid synthesis and decreasing lipid oxidation and VLDL assembly in bovine hepatocytes. *J Steroid Biochem Mol Biol* 2014; **143C**: 174-182 [PMID: 24565561 DOI: 10.1016/j.jsbmb.2014.02.009]

55 **Trauner M**, Claudel T, Fickert P, Moustafa T, Wagner M. Bile acids as regulators of hepatic lipid and glucose metabolism. *Dig Dis* 2010; **28**: 220-224 [PMID: 20460915 DOI: 10.1159/000282091]

56 **Fuchs M**. Non-alcoholic Fatty liver disease: the bile Acid-activated farnesoid x receptor as an emerging treatment target. *J Lipids* 2012; **2012**: 934396 [PMID: 22187656 DOI: 10.1155/2012/934396]

57 **Pineda Torra I**, Claudel T, Duval C, Kosykh V, Fruchart JC, Staels B. Bile acids induce the expression of the human peroxisome proliferator-activated receptor alpha gene via activation of the farnesoid X receptor. *Mol Endocrinol* 2003; **17**: 259-272 [PMID: 12554753 DOI: 10.1210/me.2002-0120]

58 **Cyphert HA**, Ge X, Kohan AB, Salati LM, Zhang Y, Hillgartner FB. Activation of the farnesoid X receptor induces hepatic expression and secretion of fibroblast growth factor 21. *J Biol Chem* 2012; **287**: 25123-25138 [PMID: 22661717 DOI: 10.1074/jbc.M112.375907]

59 **Xu J**, Lloyd DJ, Hale C, Stanislaus S, Chen M, Sivits G, Vonderfecht S, Hecht R, Li YS, Lindberg RA, Chen JL, Jung DY, Zhang Z, Ko HJ, Kim JK, Véniant MM. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. *Diabetes* 2009; **58**: 250-259 [PMID: 18840786 DOI: 10.2337/db08-0392]

60 **Seo JA**, Kim NH. Fibroblast growth factor 21: a novel metabolic regulator. *Diabetes Metab J* 2012; **36**: 26-28 [PMID: 22363918 DOI: 10.4093/dmj.2012.36.1.26]

61 **Ge X**, Yin L, Ma H, Li T, Chiang JY, Zhang Y. Aldo-keto reductase 1B7 is a target gene of FXR and regulates lipid and glucose homeostasis. *J Lipid Res* 2011; **52**: 1561-1568 [PMID: 21642744 DOI: 10.1194/jlr.M015859]

62 **Xu J**, Li Y, Chen WD, Xu Y, Yin L, Ge X, Jadhav K, Adorini L, Zhang Y. Hepatic carboxylesterase 1 is essential for both normal and farnesoid X receptor-controlled lipid homeostasis. *Hepatology* 2014; **59**: 1761-1771 [PMID: 24038130 DOI: 10.1002/hep.26714]

63 **Lu Y**, Ma Z, Zhang Z, Xiong X, Wang X, Zhang H, Shi G, Xia X, Ning G, Li X. Yin Yang 1 promotes hepatic steatosis through repression of farnesoid X receptor in obese mice. *Gut* 2014; **63**: 170-178 [PMID: 23348961 DOI: 10.1136/gutjnl-2012-303150]

64 **Wang YD**, Chen WD, Wang M, Yu D, Forman BM, Huang W. Farnesoid X receptor antagonizes nuclear factor kappaB in hepatic inflammatory response. *Hepatology* 2008; **48**: 1632-1643 [PMID: 18972444 DOI: 10.1002/hep.22519]

65 **Inagaki T**, Moschetta A, Lee YK, Peng L, Zhao G, Downes M, Yu RT, Shelton JM, Richardson JA, Repa JJ, Mangelsdorf DJ, Kliewer SA. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. *Proc Natl Acad Sci U S A* 2006; **103**: 3920-3925 [PMID: 16473946 DOI: 10.1073/pnas.0509592103]

66 **Xu Z**, Huang G, Gong W, Zhou P, Zhao Y, Zhang Y, Zeng Y, Gao M, Pan Z, He F. FXR ligands protect against hepatocellular inflammation via SOCS3 induction. *Cell Signal* 2012; **24**: 1658-1664 [PMID: 22560881 DOI: 10.1016/j.cellsig.2012.04.015]

67 **Peng X**, Wu W, Zhu B, Sun Z, Ji L, Ruan Y, Zhou M, Zhou L, Gu J. Activation of farnesoid X receptor induces RECK expression in mouse liver. *Biochem Biophys Res Commun* 2014; **443**: 211-216 [PMID: 24291500 DOI: 10.1016/j.bbrc.2013.11.082]

68 **Jia X**, Naito H, Yetti H, Tamada H, Kitamori K, Hayashi Y, Wang D, Yanagiba Y, Wang J, Ikeda K, Yamori Y, Nakajima T. Dysregulated bile acid synthesis, metabolism and excretion in a high fat-cholesterol diet-induced fibrotic steatohepatitis in rats. *Dig Dis Sci* 2013; **58**: 2212-2222 [PMID: 23824403 DOI: 10.1007/s10620-013-2747-1]

69 **Li J**, Zhang Y, Kuruba R, Gao X, Gandhi CR, Xie W, Li S. Roles of microRNA-29a in the antifibrotic effect of farnesoid X receptor in hepatic stellate cells. *Mol Pharmacol* 2011; **80**: 191-200 [PMID: 21511916 DOI: 10.1124/mol.110.068247]

70 **Lee CG**, Kim YW, Kim EH, Meng Z, Huang W, Hwang SJ, Kim SG. Farnesoid X receptor protects hepatocytes from injury by repressing miR-199a-3p, which increases levels of LKB1. *Gastroenterology* 2012; **142**: 1206-1217.e7 [PMID: 22265968 DOI: 10.1053/j.gastro.2012.01.007]

71 **Williamson RM**, Price JF, Glancy S, Perry E, Nee LD, Hayes PC, Frier BM, Van Look LA, Johnston GI, Reynolds RM, Strachan MW. Prevalence of and risk factors for hepatic steatosis and nonalcoholic fatty liver disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetes Care* 2011; **34**: 1139-1144 [PMID: 21478462 DOI: 10.2337/dc10-2229]

72 **Zhang Y**, Lee FY, Barrera G, Lee H, Vales C, Gonzalez FJ, Willson TM, Edwards PA. Activation of the nuclear receptor FXR improves hyperglycemia and hyperlipidemia in diabetic mice. *Proc Natl Acad Sci U S A* 2006; **103**: 1006-1011 [PMID: 16410358 DOI: 10.1073/pnas.0506982103]

73 **Zhang L**, Wang YD, Chen WD, Wang X, Lou G, Liu N, Lin M, Forman BM, Huang W. Promotion of liver regeneration/repair by farnesoid X receptor in both liver and intestine in mice. *Hepatology* 2012; **56**: 2336-2343 [PMID: 22711662 DOI: 10.1002/hep.25905]

74 **Nomoto M**, Miyata M, Yin S, Kurata Y, Shimada M, Yoshinari K, Gonzalez FJ, Suzuki K, Shibasaki S, Kurosawa T, Yamazoe Y. Bile acid-induced elevated oxidative stress in the absence of farnesoid X receptor. *Biol Pharm Bull* 2009; **32**: 172-178 [PMID: 19182371 DOI: JST.JSTAGE/bpb/32.172]

75 **Wu W**, Zhu B, Peng X, Zhou M, Jia D, Gu J. Activation of farnesoid X receptor attenuates hepatic injury in a murine model of alcoholic liver disease. *Biochem Biophys Res Commun* 2014; **443**: 68-73 [PMID: 24269813 DOI: 10.1016/j.bbrc.2013.11.057]

76 **Mencarelli A**, Renga B, Distrutti E, Fiorucci S. Antiatherosclerotic effect of farnesoid X receptor. *Am J Physiol Heart Circ Physiol* 2009; **296**: H272-H281 [PMID: 19028791 DOI: 10.1152/ajpheart.01075.2008]

77 **Xin X**, Zhong M, Zhang S, Peng Y, Zhu W, Zhang Y. [Effects of farnesoid X receptor agonist on adiponectin and its receptors]. *Nan Fang Yi Ke Da Xue Xue Bao* 2014; **34**: 109-112 [PMID: 24463129]

78 **Gadaleta RM**, van Erpecum KJ, Oldenburg B, Willemsen EC, Renooij W, Murzilli S, Klomp LW, Siersema PD, Schipper ME, Danese S, Penna G, Laverny G, Adorini L, Moschetta A, van Mil SW. Farnesoid X receptor activation inhibits inflammation and preserves the intestinal barrier in inflammatory bowel disease. *Gut* 2011; **60**: 463-472 [PMID: 21242261 DOI: 10.1136/gut.2010.212159]

79 **Fiorucci S**, Rizzo G, Antonelli E, Renga B, Mencarelli A, Riccardi L, Orlandi S, Pruzanski M, Morelli A, Pellicciari R. A farnesoid x receptor-small heterodimer partner regulatory cascade modulates tissue metalloproteinase inhibitor-1 and matrix metalloprotease expression in hepatic stellate cells and promotes resolution of liver fibrosis. *J Pharmacol Exp Ther* 2005; **314**: 584-595 [PMID: 15860571 DOI: 10.1124/jpet.105.084905]

80 **Mudaliar S**, Henry RR, Sanyal AJ, Morrow L, Marschall HU, Kipnes M, Adorini L, Sciacca CI, Clopton P, Castelloe E, Dillon P, Pruzanski M, Shapiro D. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. *Gastroenterology* 2013; **145**: 574-582.e1 [PMID: 23727264 DOI: 10.1053/j.gastro.2013.05.042]

81 **McMahan RH**, Wang XX, Cheng LL, Krisko T, Smith M, El Kasmi K, Pruzanski M, Adorini L, Golden-Mason L, Levi M, Rosen HR. Bile acid receptor activation modulates hepatic monocyte activity and improves nonalcoholic fatty liver disease. *J Biol Chem* 2013; **288**: 11761-11770 [PMID: 23460643 DOI: 10.1074/jbc.M112.446575]

82 **Rizzo G**, Passeri D, De Franco F, Ciaccioli G, Donadio L, Rizzo G, Orlandi S, Sadeghpour B, Wang XX, Jiang T, Levi M, Pruzanski M, Adorini L. Functional characterization of the semisynthetic bile acid derivative INT-767, a dual farnesoid X receptor and TGR5 agonist. *Mol Pharmacol* 2010; **78**: 617-630 [PMID: 20631053 DOI: 10.1124/mol.110.064501]

83 **Urizar NL**, Liverman AB, Dodds DT, Silva FV, Ordentlich P, Yan Y, Gonzalez FJ, Heyman RA, Mangelsdorf DJ, Moore DD. A natural product that lowers cholesterol as an antagonist ligand for FXR. *Science* 2002; **296**: 1703-1706 [PMID: 11988537 DOI: 10.1126/science.1072891]

84 **Claudel T**, Sturm E, Duez H, Torra IP, Sirvent A, Kosykh V, Fruchart JC, Dallongeville J, Hum DW, Kuipers F, Staels B. Bile acid-activated nuclear receptor FXR suppresses apolipoprotein A-I transcription via a negative FXR response element. *J Clin Invest* 2002; **109**: 961-971 [PMID: 11927623 DOI: 10.1172/JCI14505]

85 **Prawitt J**, Abdelkarim M, Stroeve JH, Popescu I, Duez H, Velagapudi VR, Dumont J, Bouchaert E, van Dijk TH, Lucas A, Dorchies E, Daoudi M, Lestavel S, Gonzalez FJ, Oresic M, Cariou B, Kuipers F, Caron S, Staels B. Farnesoid X receptor deficiency improves glucose homeostasis in mouse models of obesity. *Diabetes* 2011; **60**: 1861-1871 [PMID: 21593203 DOI: 10.2337/db11-0030]

86 **Watanabe M**, Horai Y, Houten SM, Morimoto K, Sugizaki T, Arita E, Mataki C, Sato H, Tanigawara Y, Schoonjans K, Itoh H, Auwerx J. Lowering bile acid pool size with a synthetic farnesoid X receptor (FXR) agonist induces obesity and diabetes through reduced energy expenditure. *J Biol Chem* 2011; **286**: 26913-26920 [PMID: 21632533 DOI: 10.1074/jbc.M111.248203]

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