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Review

Farnesoid X receptor: a potential therapeutic target in multiple organs

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Summary. Farnesoid X receptor (FXR), a member of the nuclear receptor family, is a common receptor found in the intestine and liver, and helps to maintain systemic metabolic homeostasis through regulating bile acid, glucose, lipid metabolism, and energy homeostatsis. In addition, FXR regulates the functions of various organs, such as liver, intestine, kidney, breast, pancreas, cardiovascular system and brain. FXR also plays a key role in regulation of gut-microbiota through mediating the various signaling pathways. Accordingly, FXR has become an attractive therapeutic target in a variety of diseases. This review combines classical and recent research reports to introduce the basic information about FXR and its important roles in various organs of the body.

Key words: Farnesoid X receptor, Bile acid, Metabolic homeostasis, Signaling pathways

Introduction

Farnesoid X receptor (FXR), also known as NR1H4, is a member of the nuclear receptor superfamily and was discovered in human and rat livers firstly (Forman et al., 1995). Two types of FXR are known, FXRα and FXRβ (Massafra et al., 2018). Four isoforms of FXRα (FXRα1, FXRα2, FXRα3, FXRα4) from four FXR transcripts were recognized in mammals (Zhang et al., 2003). These four isoforms are categorized according to organs and species. As shown in Table 1, in the human liver, the most abundant isoforms are FXRα1 and FXRα2, whereas four isoforms of FXR can be detected in the small intestine. FXRα3 and FXRα4 can be detected in the kidney and colon. The expression of various isoforms of FXR is somewhat different in mice (Wang et al., 2008a; Vaquero et al., 2013a). High levels of FXR are observed in the liver and ileum, and low levels of FXR are observed in the brain, lungs, pancreas, ileum, as well as the cardiovascular system (Lee et al., 2006; Wang et al., 2008b; Teodoro et al., 2011). Current research indicates that FXRα plays a major role in most metabolic homeostasis and disease regulations. Compared to FXRα, the distribution and function of FXRβ is still unclear (Wang et al., 2008a,b; Teodoro et al., 2011). FXR has a similar structure to that of most nuclear receptors, a DNA-binding domain and activation function 1 domain near the amino terminal. Analogously, a ligand binding domain and activation function 2 domain are at the carboxyl terminal. A hinge region connects with function 1 domain and function 2 domain (Wang et al., 2008a,b; Zwart et al., 2010; Vaquero et al., 2013a). When the ligand binds to the ligand-binding region of FXR, FXR in a heterodimeric form with the retinoic X receptor (RXR) or alone in a homodimeric form binds to the response element of the target gene promoter region to activate downstream target gene transcription (Zhang et al., 2011).

FXR plays an important role in several metabolic processes, such as bile acid (BA) metabolism, cholesterol metabolism, lipid metabolism and glucose metabolism by regulating target gene expression. FXR can influence the metabolism of BAs by up-regulating

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small heterodimer partner (SHP) and inhibiting cholesterol 7α-hydroxylase (CYP7A1) (Han, 2018). In addition, FXR affects lipid metabolism by suppressing CYP7A1, VLDLR and SREBP-1c, which can subsequently influence lipid absorption (Kim and Fang, 2018). Some studies indicated that FXR expression was inhibited in the liver of aged diabetic rats and restored via treatment of insulin (Rajani et al., 2018). As a negative regulator of Glucagon-like peptide-1 (7-36) amide (GLP-1), FXR inhibits GLP-1 secretion by interacting with Camp Response Element Binding Protein to regulate insulin secretion, suggesting that FXR is a key regulator of glucose control in diabetic patients (Rajani et al., 2018). In obesity and non-alcoholic fatty liver disease, FXR reduces gluconeogenesis by inhibiting phosphoenol-pyruvate carboxykinase and glucose-6-phosphatase and modulates glucose homeostasis (Teodoro et al., 2011; Gao et al., 2016; Dong et al., 2019). These findings mainly indicate that hepatic FXR as a monitor participates in glucose homeostasis.

Many FXR agonists have been reported. Natural agonists of FXR mainly include Cholic acid (CA), Chenodeoxycholic acid (CDCA), Lithocholic acid (LCA) and Deoxycholic acid (DCA) (Wang et al., 2008a,b; Gioiello et al., 2014). Moreover, natural agonists can be ordered in terms of their effectiveness: CDCA> LCA=DCA>CA. Apart from these natural agonists, synthetic agonists have been developed. It has been confirmed that GW4064 and 6-Ethylchenodeoxycholic acid are more powerful than bile acids in activating FXR (Maloney et al., 2000; Pellicciari et al., 2002). In recent years, several new FXR agonists and FXR antagonists have been gradually discovered and these ligands provide more possibilities for the functional research of FXR (Nishimaki-Mogami et al., 2006; Suzuki et al., 2008; Huang et al., 2014; Pellicciari et al., 2016; Tully et al., 2017; Al-Khaifi et al., 2018; Liu et al., 2018; Zheng et al., 2018; Fu et al., 2019) (Table 1).

This review discusses the regulation of FXR in various metabolic processes and some organs, including liver, intestine, pancreas, kidneys, breast, cardiovascular system, and brain (Fig. 1).

FXR in the liver

BAs, produced in the liver and metabolized by multiple enzymes (Han, 2018), play a crucial role in maintaining cholesterol level balance in the liver. Erroneous production of primary BAs or blocking BA circulation in the cholangiocytes can cause cholestasis, liver injury, fibrosis and cirrhosis (Jia et al., 2018). The functions of FXR in BA metabolism are helpful to reduce cholestasis and BA toxicity. CYP7A1 is a target gene of FXR, and activation of FXR suppresses hepatic CYP7A1 level, decreases the BA pool size and modifies the composition of BAs (Lefebvre et al., 2009). The previous report showed that FXR activation inhibits liver inflammation through suppressing NF-ϰB signaling *in vitro* and *in vivo* (Wang et al., 2008c). Auraptene may relieve cholestasis through activating FXR and repressing CYP7A1 to decrease BA biosynthesis (Wang et al., 2019a,b). Bile salt export pump (BSEP) is a regulator of BA canalicular export, which depends on the activity of FXR. Xiong et al. demonstrated emodin rescued intrahepatic cholestasis via upregulating FXR and BSEP (Xiong et al., 2019). In addition, Thompson et al. found that conditional knockdown of β-catenin in liver may activate FXR and decrease BA accumulation. β-catenin knockout in mice protected against liver fibrosis and inflammation after murine bile duct ligation (BDL). During cholestasis, β-catenin interfered with the nuclear localization of FXR and inhibited the combination of FXR and RXR and affected the bile flow subsequently (Thompson et al., 2018). Moreover, subsequent studies demonstrated that Sirtuin 1 (SIRT1) adjusts BA metabolism through regulating FXR. SIRThep-/- (SIRT1-knockout) mice displayed less liver injury and decreased significantly cholestasis compared with SIRToe (SIRT1-overexpressing) mice after BDL or nursing 0.1% 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DCC) (Blokker et al., 2019). Further exploration of the detailed mechanism between SIRT1 and FXR is necessary. Besides the pathways mentioned above, some proteins including MRP3/4, Ostα/β can bind to FXR to modulate bile acid transporters and then alleviate liver injury (Fernandez-Barrena et al., 2012; Guo et al., 2018; Zhang et al., 2018; Wang et al., 2019a,b). Overall, inhibition of BA accumulation by activating FXR/CYP7A1, FXR/BSEP, β-catenine/FXR, SIRT/FXR or other FXR pathways may relieve cholestasis in preclinical studies. Moreover, in phase III clinical trials and randomized double-blind phase II clinical trials, FXR agonist obeticholic acid (OCA) can reduce cholestasis and liver injury in patients with primary biliary cholangitis. However, the adverse events represented by pruritus were serious (Nevens et al., 2016; Kowdley et al., 2018). FXR provides an effective strategy to relieve cholestasis. Further clinical studies will be needed to verify the pharmacodynamics and safety of FXR agonists in patients with cholestasis or cholestatic liver injury.

Liver regeneration is an essential feature in repairing liver damage (Alvarez-Sola et al., 2018). Liver regeneration relies on the regulation of activation of FXR by BAs in a distinctive mechanism (Fan et al., 2015). FXR can promote regeneration after liver injury induced by carbon tetrachloride (CCl4) or partial hepatectomy. Meng et al. showed that FXR knockout mice have more serious functional deficiencies in hepatic repairing compared to WT mice (Meng et al., 2010). Similarly, FXR deficiency causes defect of liver regeneration after partial hepatectomy (Chen et al., 2010). Fan et al. reported that FXR may function as a cell protector to promote cell proliferation and attenuate hepatocyte death (Fan et al., 2015). In addition, several publications reported that Foxm1b is an age-related regulator in the repair of partial liver resection and liver

Table 1. Summary of related FXR information.

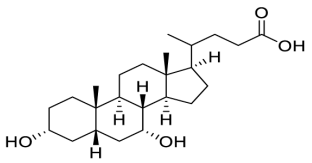
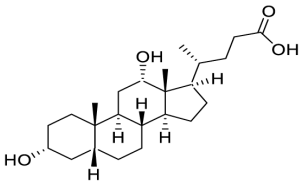
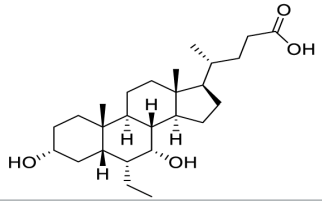
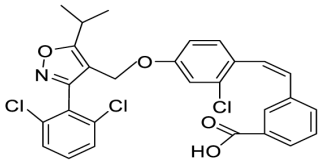
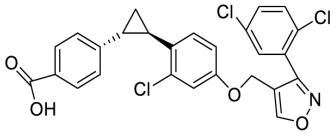
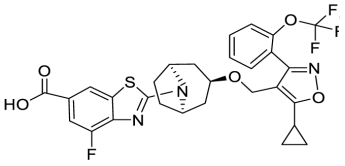
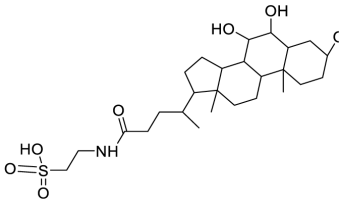
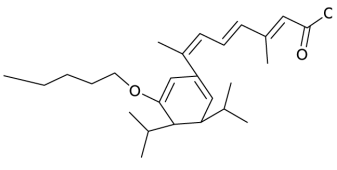
Gene name	FXR (NR1H4)		
Expression in tissues	Human: liver (FXRα1, FXRα2); kidneys and colon (FXRα3, FXRα4); small intestine (FXRα1, FXRα2, FXRα3, FXRα4); other organs (Low levels of FXR) Mouse: liver and small intestine (FXRα1, FXRα2, FXRα3, FXRα4)		
Agonists	Name	Structures	References
Steroidal agonists	CDCA		Wang et al., 2008a,b
	DCA		Gioiello et al., 2014
	OCA		Pellicciari et al., 2002
Nonsteroidal agonists	GW4064		Maloney et al., 2000
	Px-102		Al-Khaifi et al., 2018
	LJN452		Tully et al., 2017
Antagonists	T-β-MCA		Fu et al., 2019
	AGN34		Huang et al., 2014

Table 1. (Continued).

Tissues	Relevant Diseases	Common Treatment	References
Liver	Cholestasis	GW4064, CDCA	Thompson et al., 2018; Lefebvre et al., 2009
	NASH	OCA, BAR502, LMB763	Bowlus, 2016; Moscovitz et al., 2016; Gege et al., 2019; Carino et al., 2019; Chianelli et al., 2020
	Liver Injury	SP600125	Takahashi et al., 2017
Intestine	IBD	CDCA, DCA	Koutsounas et al., 2015; Joyce and Gahan, 2016; Tremblay et al., 2017
Kidney	Glomerulosclerosis	FXR agonists	Wickman and Kramer, 2013; Zammit et al., 2015; D'Agati et al., 2016
	Renal Fibrosis	EDP-305	Di Matteo et al., 2019
Cardiovascular System	Portal Hypertension	PX20606	Schwabl et al., 2017
	Atherosclerosis	Overexpress FXR	de Boer et al., 2017
	Myocardial Infarction	GW4064	Xia et al., 2018
Brain	Depression	Overexpress FXR	Huang et al., 2015; Chen et al., 2018
Malignant tumor	HCC	Px-102, Overexpress FXR	Deuschle et al., 2012; Koutsounas et al., 2012; Cariello, et al., 2017
	Colorectal Cancer	Overexpress FXR	Koutsounas et al., 2012; de Aguiar Vallim et al., 2013
	Pancreatic Cancer	DCA, Overexpress FXR	Ferrebee and Dawson, 2015; Giaginis et al., 2015; Rajani and Jia, 2018
	Breast Cancer	GW4064, Overexpress FXR	Huang et al., 2003; Swales et al., 2006; Koutsounas et al., 2012; Giaginis et al., 2017
	Leydig tumor	Overexpress FXR	Koutsounas et al., 2012
	Kidney cancer	FXR agonists	Masaoutis and Theocharis, 2019

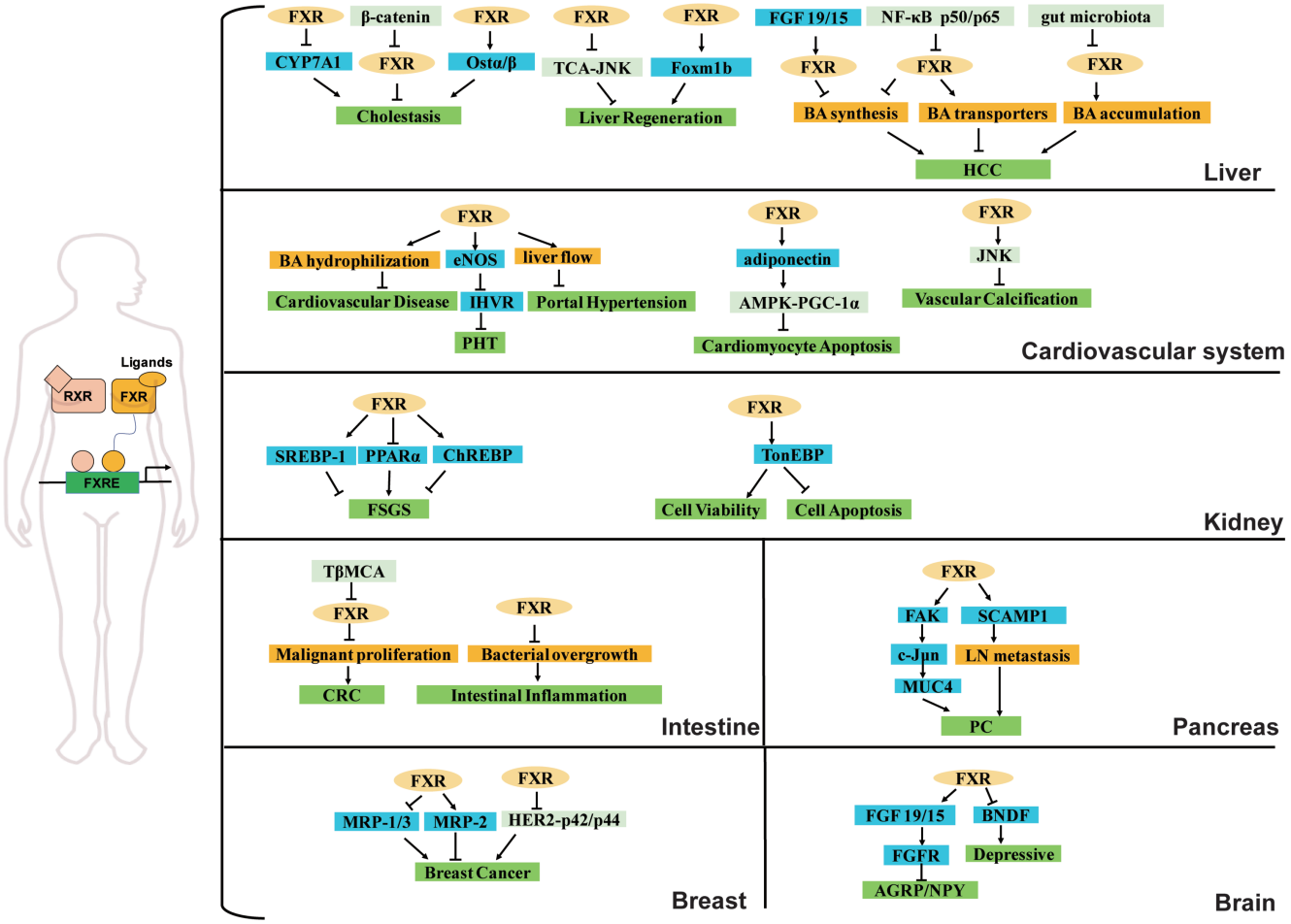


Fig. 1. FXR participates in the regulation of diseases in different tissues, including liver, intestine, pancreas, kidney, breast, cardiovascular system and brain. HCC, Hepatocellular carcinoma; PHT, portal hypertension; AGRP/NPY, a kind of hypothalamic neuron; CRC, colorectal cancer; PC, pancreatic cancer; FSGS, focal segmental glomerulosclerosis; ORG, Obesity-related glomerulopathy; IHVR, intrahepatic vascular resistance. →Induction; ⊣ Inhibition.

injury (Wang et al., 2001; Chen et al., 2010) and FXR directly regulates Foxm1b in aged mice to promote liver regeneration after partial hepatectomy (Chen et al., 2010). Moreover, pregnancy affects liver regeneration by reducing expression of FXR in mice (Moscovitz et al., 2016). Based on the above research, FXR shows protective efficacy in liver injury and partial liver resection. FXR-controlled BA signaling, and FXR/Foxm1b pathway might be necessary to maintain the self-regenerative capacity of the liver. These results suggest that FXR is critical for liver regeneration.

Nonalcoholic steatohepatitis (NASH) is a common human liver disease which can lead to chronic liver disease and eventually HCC (Asfari et al., 2020). BAR502, a steroidal ligand of FXR, can resume steatohepatitis and fibrosis in mice fed with a high-fat diet and can attenuate the development of NASH. In addition, liver histopathology features confirmed the efficacy of BAR502 (Carino et al., 2019). Thus, FXR may be a pivotal sensor in the diseases of lipid metabolism. FXR also plays a role in carbohydrate metabolism via regulating phosphoenolpyruvate carboxykinase (PEPCK) gene expression (Stayrook et al., 2005). FXR ligand OCA in high fat diet (HFD)-induced rabbits reduced TNF-α expression levels in liver and plasma, with a parallel increase of penile eNOS expression and responsiveness to acetylcholine (Vignozzi et al., 2014). In addition, in HFD-induced rabbits, INT-767, a dual ligand for FXR/TGR5, significantly counteracts HFD-induced liver and fat alterations, restoring insulin sensitivity and prompting preadipocyte differentiation toward a metabolically healthy phenotype (Comeglio et al., 2018). OCA, as a modified FXR agonist, was first approved in 2017 to be used in conjunction with UDCA for primary biliary cholangitis (PBS) patients. OCA significantly reduced serum alkaline phosphatase (ALP) levels, an important disease marker that correlates well with clinical outcomes of patients with PBC (Ali et al., 2015). Furthermore, OCA was used in the clinical trial for the treatment of NASH (Mudaliar et al., 2013). Data of NASH phase II clinical trials revealed that treatment of OCA for 72 weeks improved liver fibrosis compared to treatment of placebo (NeuschwanderTetri et al., 2015). However, potential risks to the cardiovascular system and severe pruritus could not be ignored (Bowlus, 2016; Gege et al., 2019). A new FXR agonist nidufexor (LMB763) has been evaluated in a preclinical study, which can inhibit liver inflammation and fibrosis in NASH mouse model. Also, a Phase II clinical trial is under way (Chianelli et al., 2020). Further insight into the safety and efficacy of more FXR agonists in clinical stages is necessary and urgent for NASH treatment.

FXR ligands are potential preclinical drugs in the treatment for Non-alcoholic fatty liver disease (NAFLD), diabetic nephropathy, diabetic cardiomyopathy and metabolic disease (Mudaliar et al., 2013; Zhang et al., 2016). Furthermore, FXR ligands have promising clinical efficiency in the treatment of other liver disorders such as primary biliary cirrhosis (PBC) (Eaton et al., 2019), primary sclerosing cholangitis (PSC) (Eaton et al., 2019) as well as human cholangiocarcinoma (Di Matteo et al., 2019). FXR-controlled BA signaling is a "hub" to regulate liver homeostasis. However, the development and application of FXR agonists in liver disease is still in the preclinical stage, the efficiency and safety of FXR ligands in most liver disease requires further clinical validation.

FXR in the intestine

BAs are considered to be one of the most important signaling molecules in the whole body including the intestine. BAs activate FXR to regulate the metabolism of energy and intestinal homeostasis (Joyce and Gahan, 2016). BAs in normal levels are beneficial to human body and imbalance of BA metabolism will cause diseases. Excessive accumulation of BAs can lead to intestinal diseases such as colorectal cancer (de Aguiar Vallim et al., 2013). For example, in the Lgr5-expressing intestinal cancer stem cells, tauro-β-muricholic acid, a kind of BAs, decreased the intestinal FXR function and induced malignant proliferation (Fu et al., 2019). FXR played an extremely important role in intestinal immunity diseases including small intestinal bacterial overgrowth and inflammatory bowel disease (IBD). FXR prevented the bacterial overgrowth by mediating the negative regulators iNOS, IL-18, type-C lectins Reg3b and Reg3g (Joyce and Gahan, 2016; Tremblay et al., 2017). Correspondingly, in the IBD models, FXR can attenuate intestinal inflammation and protect goblet cells from death (Gadaleta et al., 2011). Collectively, BAs in the normal levels protect the intestine from cancer and activate FXR to prevent the occurrence of cystic fibrosis and IBD. All the results mentioned above provide effective ideas to rescue intestinal diseases. FXR plays key roles in the regulation of the intestinal wall. Intestinal epithelial cell proliferation can be suppressed by hyodeoxycholic acid (HDCA) via FXR-PI3K/AKT signaling pathway, and the BA pool is changed by gut bacteria (Song et al., 2020). Also, OCA, as an FXR agonist, plays key roles in the prevention of epithelial injury and the preservation of intestinal architecture and permeability (Ceulemans et al., 2017). Besides, targeting FXR in the intestine specifically has shown remarkable physiological effects such as improvement of intestinal barrier function, glucose homeostasis and intestinal cholesterol turnover (van Zutphen et al., 2019). More studies are needed in order to understand the clinical efficacy of FXR ligands for enteropathy.

FXR and gut-microbiota

Recently, Sun et al. showed that metformin induced glucose metabolism via reducing *Bacteroides fragilis* in diabetic patients. In terms of mechanism, reduction of *Bacteroides fragilis* resulted in the increase of bile acid

glycorhodoxylic acid (FXR antagonist) and then inhibited the FXR signal pathway (Sun et al., 2018). In addition, activation of intestinal FXR by fexaramine can induce *Acetatifactor* and *Bacteroides* to regulate metabolism (Pathak et al., 2018). Diseases regulated by gut-microbiota are not limited in the gastrointestinal tract and exist in other organs (Duparc et al., 2017; Jia et al., 2018; Jiao et al., 2018). Friedma et al. reported that FXR ligand OCA increased Gram-positive bacteria through the regulation of BA synthesis (Friedman et al., 2018). However, the therapeutic effect of OCA on liver diseases via gut-microbiota deserves further exploration. In summary, the interaction between the FXR signal pathway and gut-microbiota may regulate the development of intestinal and liver diseases. Therefore, gut-microbiota-BAs-FXR axis is an important research target for future work.

FXR in the kidney

In recent years, many studies showed that FXR not only regulates BAs and energy metabolism but also participates in the regulation of nephrosclerosis, renal fibrosis and diabetic nephrotoxicity (Herman-Edelstein et al., 2018; Wang et al., 2018). Obesity-related glomerulopathy increases the burden on the kidney for renal reabsorption and glomerular filtration, and even results in focal segmental glomerulosclerosis (D'Agati et al., 2016). Activated FXR can improve the above symptoms through regulating BAs and fatty acids (Wickman and Kramer, 2013; Zammit et al., 2015; D'Agati et al., 2016). Based on the latest research, the function of FXR in renal fibrosis is becoming clear. FXR agonist EDP-305 can effectively alleviate macrophage infiltration and interstitial fibrosis in tubulointerstitial fibrosis model (Di Matteo et al., 2019). Zhang et al. reported that in the medullary collecting duct cells (MCDs), aquaporin 2 (AQP2) can significantly increase the concentration level of urine through combining the specific binding sites of FXR (Zhang et al., 2014). Recent studies showed that when MCDs are in a harsh environment, e.g., high osmotic pressure, overexpression of FXR can promote TonEBP expression and nuclear translocation to increase cell viability (Lee et al., 2011a,b; Xu et al., 2018). Hence, activation of FXR can regulate the BA metabolism or target genes to relieve glomerulopathy and multiple nephrosis. However, the studies about the function of FXR in kidney are mostly based on animal models or *in vitro*. More clinical studies are needed to confirm the therapeutic effect of FXR activation in renal disease.

FXR in the cardiovascular system

Previous studies confirmed that activation of FXR ameliorated cirrhotic portal hypertension in different models by decreasing total intrahepatic vascular resistance and hemodynamic effect, which is closely related to intrahepatic eNOS activity (Asrani and Kamath, 2013; Verbeke et al., 2014). PX20606 (FXR agonist) increased liver blood flow and reduced portal hypertension in the model of partial portal vein ligation (PPVL)/7 days or CCl4 /14 weeks (Schwabl et al., 2017). However, the clinical efficacy of activated FXR in cirrhotic portal hypertension still needs to be confirmed in patients. Besides, the composition of the BA pool is related to the cardiovascular disease (de Boer et al., 2017). In detail, FXR and FGF15/19 prevented against cardiovascular disease such as atherosclerosis by promoting hydrophilization of BAs in mouse models (de Boer et al., 2017). Furthermore, FXR plays a key role in cardiovascular remodeling. Activated FXR promoted angiogenesis and protected myocardial cells from inflammation. GW4064 promoted the expression of adiponectin and reduced cardiomyocyte apoptosis via AMPK-PGC-1α signaling, which improved the cardiac dysfunction after myocardial infarction (Xia et al., 2018). In addition, Miyazaki et al. indicated that FXR may function as a negative regulator of vascular calcification (Miyazaki-Anzai et al., 2010). As discussed above, activated FXR contributes to treatment of cirrhotic portal hypertension, atherosclerosis and myocardial infarction by influencing BA metabolism and several other signaling pathways. And the understanding of FXR functions can provide a novel perspective to treat these cardiovascular system diseases.

FXR in the brain

The roles of the BAs in the brain and other related organs are being increasingly recognized (Jia et al., 2020; Li et al., 2020). McMillin et al. reported that BA levels in the brain were doubled in a mouse model of hepatic encephalopathy induced by liver failure (McMillin et al., 2016). In addition to this aspect, FXR increased the expression of FGF19, which is able to cross the blood-brain barrier (BBB) and exists stably in the brain (Hsuchou et al., 2013). Furthermore, FGF19 injecting in arcuate nucleus of mice reduced AGRP/NPY activation and then improved glucose metabolism in obese mice (Marcelin et al., 2014). Therefore, FXR may be a therapeutic target of central type 2 diabetes by regulating the activity of AGRP/NPY neuron. Depression is a serious and common psychiatric disorder. Recent studies showed that FXR at high levels in the hippocampus helped to alleviate the phenotype of depressive patients (Huang et al., 2015; Chen et al., 2018). Currently, studies about FXR in brain diseases are deficient and further exploration is still needed.

FXR in cancer

FXR and liver cancer

HCC is one of the most common cancers worldwide. There are many causes of HCC such as alcoholism, hepatitis B/C infection, irregular growth of hepatocytes, liver injury, and cholestasis, especially the periodic

recurrence of chronic hepatitis (Wang et al., 2008b). Kong et al. found that liver injury was more serious in FXR deficiency mice than that in WT mice (Kong et al., 2019). FXR deficiency induces high BA levels, which can promote the development of HCC (Cariello et al., 2017). Recent research indicated that FXR can inhibit liver injury and liver cancer through antagonizing c-Jun-N-terminal kinase (JNK) pathway. Re-expressed FXR alleviated liver injury by inhibiting the expression of CCL2 and JNK in FXR-/- mice. Activated FXR inhibited JNK activity and then decreased the incidence of liver cancer by inducing superoxide dismutase 3 expression and reducing reactive oxygen species production in liver cancer cells (Wang et al., 2015; Takahashi et al., 2017). Conversely, treatment of JNK inhibitor and overexpression of FXR can effectively relieve liver injury and HCC (Takahashi et al., 2017). Imbalance of gut microbiota inhibits FXR expression and BA transport and induces hepatocyte apoptosis, inflammation, and HCC (Chiang, 2013; Jia et al., 2018). Thus, activated FXR can directly regulate liver injury and liver fibrosis and jointly maintain BA homeostasis through interacting with NF-κB or gut microbiota to alleviate HCC. Specifically, the association between gut microbiota and FXR needs to be further explored.

FXR and pancreatic cancer

The clinical manifestations of pancreatic cancer (PC) are jaundice and elevated alkaline phosphatase levels. Further pathogenesis is being gradually understood (Joshi et al., 2016). Lymph node (LN) metastasis is common for PC (Yang et al., 2013). DNA microarray analysis revealed that FXR was highly expressed in the tumor tissues from PC patients with LN metastasis (Yang et al., 2013). Moreover, FXR expression level was upregulated in pancreatic ductal adenocarcinoma (PDAC) compared to pericancerous tissues, and FXR expression was positively correlated with PDAC carcinogenesis accompanied with LN metastasis and invasion (Chen et al., 2019). Therefore, the expression level of FXR can be used as a prognostic marker of PDAC. Furthermore, Lee et al. showed that downregulation of FXR by siRNA inhibited cell migration and invasion in PC with LN metastasis to suppress cancer progression (Lee, et al., 2011a,b). Joshi et al. reported that activation of FXR induced MUC4 expression and pancreatic cancer development through FXR-FAK-c-Jun axis (Joshi et al., 2014, 2016 Lakshmanan et al., 2015). Based on the existing research, the possible reason why FXR displays a cancer-promoting role in PC is that FXR can activate genes and proteins related to malignant phenotype of PC (Hu et al., 2017). These results suggest that FXR antagonists provide a novel treatment direction for PC patients.

FXR and breast cancer

Activated FXR has protective efficacy for breast cancer. FXR increases the expression of multidrug resistance-associated protein 2 (MRP-2) to interfere with the growth of cancer cells (Huang et al., 2003; Swales et al., 2006). In MCF-7 TR1 cells, activated FXR inhibited breast cancer development by diminishing tyrosine kinase receptor (HER2) and blocking the HER2-p42/44(MAPK) signal pathway (Arpino et al., 2008; Giordano et al., 2011). Moreover, FXR has a positive regulation on cell apoptosis and shows negative regulation of cell invasion in MCF-7 and MDA-MB-231 cells (Zajchowski et al., 2001; Alasmael et al., 2016). These results indicate that activated FXR inhibits breast cancer progression mainly via interfering cancer cell growth. Previous studies reported that FXR inhibited the leptin signaling pathway and then attenuated the cancer-promoting activity in cancer-associated fibroblasts (Giordano et al., 2016). Moreover, recent findings suggested that FXR inhibited the growth and motility of breast cancer cells through altering the paracrine signaling repertoire (Barone et al., 2018). All the data suggest that activation of FXR can prevent the occurrence and deterioration of breast cancer. Therefore, FXR agonists may be potential therapeutic strategies for breast cancer treatment.

FXR and colon cancer

Fu et al. reported that selective activation of intestinal FXR can restrict abnormal Lgr5+ cell growth and curtail colorectal cancer (CRC) progression. This unexpected role for FXR in coordinating intestinal self-renewal with BA levels implicates FXR as a potential therapeutic target for CRC (Fu et al., 2019). FXR also exerts its cancer suppressor functions by antagonizing Wnt/β-catenin signal through FXR/β-catenin interaction in colorectal tumorigenesis (Yu et al., 2020). Besides, FXR can inhibit colon cancer cell proliferation and invasion by repressing MMP7 expression (Peng et al., 2019). These results suggest that FXR may be a potential target for treatment of CRC.

Future perspectives

Extensive studies on FXR structure, distribution and signaling pathways in various organs have been performed, suggesting that FXR may be a target for different diseases. FXR also plays key roles in the treatment of metabolic diseases and hepatocyte chemoprotection. FXR is identified as a regulator of insulin sensitivity and adipocyte function, thus FXR is a potential target in the treatment of obesity and Type 2 diabetes (Cariou et al., 2006). Also, FXR activated by OCA has a function in the treatment of bleomycin-induced pulmonary fibrosis and monocrotaline-induced pulmonary hypertension in rat model (Comeglio et al., 2019a,b). However the function of activated FXR in hepatocyte chemoprotection may lead to liver tumor chemoresistance in clinical treatment (Vaquero et al., 2013b). Potential toxic effects caused by FXR activation

are problems that must be considered. Chronic activation of FXR by specific exogenous agonist WAY-362450 leads to liver hypertrophy instead of proliferation of the liver. The mechanism of this process is that FXR directly targets Cyclin D1 in time-dependent and tissue-specific manners (Wu et al., 2019). BA-induced visceral hypersensitivity is mediated by FXR through FXR-NGF signaling pathway in mucosal mast cells in the bowel, and the beginning of this process is the activation of FXR by BAs in colon (Li et al., 2019). Insight into the improved safety and efficacy of FXR therapy at the clinical stage will develop promising treatment strategies for human disease.

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