Farnesoid X receptor-driven metabolic plasticity: Bridging physiological adaptation and malignant transformation in lipid handling (Review)

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Abstract. Metabolic reprogramming represents a hallmark of malignant tumors, manifested through progressive alterations in nutrient utilization patterns during oncogenesis. As fundamental constituents of biological membranes, essential components of signaling pathways, and critical energy substrates, lipids undergo comprehensive metabolic restructuring in neoplastic cells. This lipid remodeling confers enhanced adaptability to sustain uncontrolled proliferation while promoting aggressive migratory phenotypes. Farnesoid X receptor (FXR), a ligand-activated nuclear receptor responsive to bile acid (BA) derivatives and cholesterol metabolites, orchestrates key aspects of lipid homeostasis. Its regulatory network encompasses cholesterol/BA metabolism, fatty acid (FA) metabolism and plasma lipoprotein trafficking pathways. Emerging evidence positions FXR as a pleiotropic modulator in oncogenesis, with dysregulated expression patterns documented across multiple tumor lineages and premalignant lesions. This mechanistic understanding has propelled FXR-targeted therapeutics into the forefront of precision oncology development. The present review critically examines the FXR-lipid axis in lipid-enriched malignancies, with particular emphasis on its regulatory circuitry governing BA flux and FA turnover.

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1. Introduction

During malignant transformation from normal to neoplastic tissues, tumors progressively develop distinct metabolic adaptations to sustain their proliferative demands. In numerous solid malignancies, dysregulated lipid homeostasis emerges as a pathogenic driver or pathognomonic feature, exemplified by hepatocellular carcinoma (HCC), colorectal adenocarcinoma, breast cancer and clear cell renal cell carcinoma (ccRCC). This metabolic rewiring positions lipid metabolism regulators as promising therapeutic targets, with nuclear receptors constituting a major crucial class of lipid-sensing molecules.

As ligand-activated transcription factors, nuclear receptors interact with various cellular metabolites including steroid hormones, vitamins and lipids. Through recruitment of transcriptional co-regulators, these molecular sensors orchestrate precise gene expression programs (1). Farnesoid X receptor (FXR), initially described in 1995 as a retinoid X receptor (RXR)-interacting partner, exemplifies this family (2). Though first identified in rat hepatic, renal and adrenal tissues (2), FXR's designation as an orphan receptor persisted until 1999 when physiological bile acid (BA) concentrations were shown to activate it through ligand binding (2,3). Subsequent investigations establish FXR's central role in cholesterol homeostasis through the regulation of BA synthesis enzymes, notably cholesterol 7α hydroxylase, the rate-limiting enzyme of BA synthesis (3,4). Expanding beyond hepatobiliary functions, clinical investigations reveal FXR's modulatory effects on systemic lipid profiles through molecular control of fatty acid (FA) synthesis, transport pathways and β-oxidation processes. Thus, FXR-mediated signal transduction is closely associated with multiple metabolic disorders, including obesity, diabetes, atherosclerosis and non-alcoholic fatty liver disease (NAFLD) (5-7).

The emerging paradigm of tumor metabolic reprogramming, combined with FXR's pivotal functions in the

gut-liver axis has led to intense investigations into nuclear receptor-targeted therapeutics. This review mainly focuses on FXR's multifaceted roles in lipid metabolism regulation and its involvement in lipid-rich tumor progression, providing conceptual frameworks for advancing nuclear receptor-targeted therapeutic strategies.

2. FXR

Structure of FXR. The nuclear receptor superfamily is categorized into two classes based on DNA-binding properties: One class function as homodimers, while another class forms heterodimers with RXR for DNA interaction (4). FXR belongs to the latter class and shares structural homology with other members, including the retinoic acid receptor, the thyroid hormone receptor and the vitamin D_3 receptor (4). The structure of nuclear receptors typically encompasses five domains: The amino terminal transcriptional activation function-1, a DNA binding domain, a hinge region, a ligand binding domain (LBD) and the carboxyl terminal activation function-2 (AF-2). This architecture facilitates RXR-mediated heterodimerization, as illustrated in Fig. 1A-C (1,8). FXR is originally cloned from rats using degenerate primers corresponding to the semi-conserved DNA-binding domain of the nuclear receptor (4). Early functional characterization reveals weak farnesol-induced activation; however, the absence of endogenous ligands under physiological conditions initially classified FXR as an orphan nuclear receptor. A paradigm shift occurred in 1999 when endogenous BAs were demonstrated to robustly activate FXR at physiological concentrations, triggering downstream transcriptional responses. This discovery propels extensive investigations into FXR's regulatory roles in BA homeostasis and hepato-enteric pathophysiology. Structurally, FXR's LBD mirrors the characteristic three-layered helical sandwich observed across nuclear receptors, which was resolved in 2003 (Fig. 1C) (9,10). Of particular functional significance is, H12, which harbors AF-2 and establishes hydrophobic interactions with H3 and H4, stabilizing co-activator binding through LXXLL motif engagement at the LBD interface (9,10). In contrast to most ligands, BAs occupy the FXR LBD binding site in an opposite direction, and there are two sites binding to the LXXLL motif simultaneously. This distinctive orientation enhances binding affinity compared with single-motif co-activators. Comprehensive structural analyses of FXR have been systematically documented in prior crystallographic studies (11,12).

Subtypes and polymorphism of FXR. Two FXR genes have been identified: FXRα and FXRβ. In rodents, rabbits and dogs, FXRβ has been shown to be activated by lanosterol, while in humans and primates, it constitutes a non-functional pseudogene (13). Human physiology specifically expresses four functional FXRα isoforms (FXRα1-4) differentiated by their amino-terminal domains, as illustrated in Fig. 1D (14). This is due to differential promoter usage and alternative exon splicing patterns. A four-amino acid residue insertion MYTG in the hinge region leads to the difference between FXRα1/α3 and α2/α4, which potentially impacts receptor functionality. In addition, tissue- and species-specific expression profiles are observed in these isomers. Murine models demonstrate predominant hepatic and intestinal co-expression of both FXR subtypes, whereas renal tissue preferentially expresses FXRβ and adrenal glands favor FXRα (15). Human expression patterns similarly mirror this compartmentalization, with hepatocytes predominantly expressing FXRα1/α2 isoforms, while enterocytes show preferential FXRα3/α4 expression (16). Furthermore, there is also evidence that dynamic regulation of FXR isoform expression is closely associated with the metabolic progress and physiological states (17-19).

Genetic polymorphisms in nuclear receptor superfamily members (vitamin D receptor, peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), small heterodimer partner (SHP), hepatocyte nuclear factor-1-α and hepatocyte nuclear factor-4α (HNF4α) establish disease predisposition through phenotypic modulation (20-27). Clinical investigations implicate FXR genetic variation in hepatobiliary pathologies, exemplified by four novel heterozygous FXR variants (-1g>t, M1V, W80R, M173T) identified in intrahepatic cholestasis of pregnancy (28). The amino terminus contains two ATG parts (M1 and M5), which could be identified as translational initiation site. M1 plays the initiation role in humans, in addition, -1g>t and M1V mutations impair protein expression and reduce transcriptional activation of ileal BA binding protein (IBABP)/bile salt export pump (BSEP) promoters, suggesting compromised translational efficiency. M173T similarly affects IBABP and BSEP promoter activation.

A study on FXR polymorphism in different races conducted by Marzolini *et al* (20) found several meaningful single nucleotide polymorphisms compared with an FXR reference sequence from GenBank, including G-1T, C643T (H215Y) and G646T (A216S). Furthermore, two synonymous polymorphisms (C783T, 261N; 1341T, 447H) are included in the aforementioned study as well, whose locations predict amino acid differences within the hinge region of FXR. The expression of SHP and organic anion transporting polypeptide, two FXR target genes, was significantly decreased in liver carrying FXR (G-1T) compared with FXR (-1G). However, BSEP, another FXR target gene, is unassociated with an FXR polymorphism. This differential regulation suggests target gene-specific modulation mechanisms by FXR genetic variants, highlighting the complexity of receptor-target gene interactions.

FXR response element (FXRE) and ligands. As reviewed, FXR shares its structural homology with classical nuclear receptors in its ability to form heterodimers with RXR, subsequently binding DNA to transcriptionally activate downstream target genes. The cognate DNA recognition, initially characterized as FXRE, is subsequently designated the BA response element, due to its activation by endogenous BA ligands (4). The canonical FXRE configuration comprises a conserved (AGGTCA) hexamer arranged as an inverted repeat with single nucleotide spacing (IR1) (29), representing both the most prevalent and highest affinity DNA binding configuration for nuclear receptor dimers (29,30). In addition, there are other FXRE, such as IR0, IR8 (31), ER8 (32) and DR1 (33). Some of the FXRE sites are tissue-specific, and a study of Chip-Seq in murine treated with GW4064 showed only 11% of the sites were shared between the liver and intestine (34).

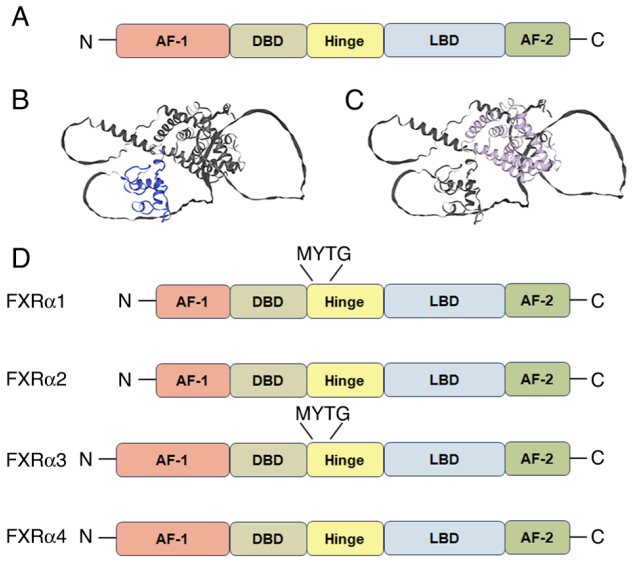

Figure 1. Model diagram and structure diagram of FXR. (A) Model diagram of FXR Structural domain. (B) Model structure of FXR(FXR-DBD) (UniProtKB AC Q96RI1). (C) Model structure of FXR(FXR-LBD) (UniProtKB accesion no: Q96RI1). (D) Human four FXRα isoforms. AF-1, amino terminal transcriptional activation function-1; DBD, DNA binding domain; LBD, ligand binding domain; AF-2, carboxyl terminal transcriptional activation function-2.

Farnesoid derivatives are intermediates of mevalonate pathway metabolism and can activate FXR at supra-physiological dose concentrations (4). BAs, the natural ligand of FXR, activate FXR at physiological concentrations. Comparative analyses revealed chenodeoxycholic acid (CDCA) as the most potent endogenous agonist, exhibiting activity superior to deoxycholic acid, lithocholic acid (LCA) and cholic acid (2). However, a mechanistic exploration of FXR's roles in sterol homeostasis has been constrained by available pharmacological tools. While CDCA serves as the archetypal endogenous ligand, its extensive interactions with BA chaperone proteins, metabolism into LCA and non-specific cellular effects render it suboptimal for experimental applications. These limitations motivated the development of GW4064, a synthetically optimized FXR agonist demonstrating superior specificity and pharmacological stability (2). Of note, multiple FXR-targeted therapeutics have advanced through clinical development pipelines for cholestatic and metabolic disorders including primary biliary cholangitis, primary sclerosing cholangitis and non-alcoholic steatohepatitis (NASH) (Table I). Paralleling agonist development, novel modulatory agents exhibiting distinct activation profiles relative to CDCA and GW4064 are emerging, with comparative pharmacodynamic characteristics outlined in Table II.

Physiological functions of FXR. The regulation of FXR *in vivo* is complex, and its physiological effects include several categories: i) It maintains BA pool homeostasis, and reduces BA concentration in the liver by increasing BA output and reducing BA synthesis; ii) it reduces blood lipid levels and regulates plasma lipoproteins; iii) it exerts liver protection and regeneration; iv) it regulates glucose metabolism and gluconeogenesis (35); v) it regulates blood vessel clotting and anticoagulation molecules (36,37); and vi) it is involved in urine volume regulation and anti-renal fibrosis (38,39).

3. FXR and lipid metabolism

FXR and FA. FA homeostasis is governed by a balance between uptake and elimination, with disruptions in this equilibrium contributing to metabolic pathogenesis. In this section, the regulatory roles of FXR in FA transport, *de novo* synthesis and catabolism were systematically evaluated (Fig. 2).

FXR and FA uptake/transport. Cellular FA internalization is mediated by specialized transporters, notably CD36, caveolins (CAVs) and the FA transport protein (FATP) family (40).

CD36 (SR-B2/FAT) is a membrane-spanning glycoprotein facilitating absorption of long-chain FAs and oxidized low-density lipoprotein (LDL) uptake (40). A mechanistic study demonstrated that hepatic CD36 overexpression exacerbates FA influx in NAFLD murine models, whereas its genetic silencing alleviates steatosis-associated lipid deposition (41). As a transcriptional target of PPARs and other nuclear receptors (40), CD36 expression has been shown to be modulated by pregnane X receptor-mediated transcriptional activation, driving hepatic triglyceride (TG) accumulation through enhanced lipid uptake (42). Small heterodimer partner is an atypical nuclear receptor that lacks DNA-binding domain, which is regarded as the target gene of FXR. GW4064 dose-dependently suppresses CD36 effectively reversing hepatic steatosis in diet-induced obese mice (43). Complementary evidence from diosgenin mechanistic studies confirms FXR/SHP-mediated CD36 downregulation as an anti-steatotic pathway (44). These findings collectively established FXR/SHP/CD36 as a pivotal regulatory node in FA homeostasis.

CAVs are essential components of caveolae (one site of endocytosis) involved in several biological functional processes, such as vesicle formation and lipid droplet formation. CAV-1 has been extensively investigated in prior studies. Preclinical investigations have revealed CAV-1 upregulation within mitochondrial inner membranes and lipid droplets of choline deficiency-induced fatty liver models (45), while CAV-1 knockout mice have been shown to exhibit attenuated hepatic lipid storage capacity (46), implicating its necessity for physiological lipid storage. Further characterization of CAV-1(-/-) mice reveals compromised PPARα signaling, manifested by downregulated carnitine palmitoyl-transferase (CPT) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha. These perturbations were found to be correlated with mitochondrial dysfunction and to impair FA β-oxidation (47). In summary, CAV-1 deficiency concurrently disrupts FXR signaling and BA metabolism, suggesting its dual regulatory role-modulating both anabolic and catabolic pathways-analogous to multifaceted functions of CD36.

The FATP family represents another critical determinant of transmembrane FA flux. Motojima *et al* (48) reported FATP is upregulated in the liver of mice threated with the PPAR activator Wy14643. FATP-mediated lipid metabolic reprogramming has been extensively characterized in oncogenesis (49). FATP2 displays hepatorenal expression, whereas FATP5 exhibits liver-specific localization (50). A previous study on knockout FATP2 or FATP5 mice found that FA

Table I. FXR agonists in clinical trials.

FXR Agonists	Condition/disease	Clinical trials ID	Phase of study
OCA/ INT-747	PBC	NCT02308111	IV
	PBC	NCT01473524	III
	Biliary acid diarrhea	NCT01585025	II
	PSC	NCT02177136	II
	NAFLD/NASH	NCT01265498	II
	NASH	NCT02633956	II
	NASH	NCT02548351	III
	NASH	NCT03439254	
	Barrett's esophagus	NCT04939051	II
	Hepatic steatosis and familial partial lipodystrophy	NCT02430077	II
EDP-305	PBC	NCT03394924	II
	NASH	NCT03421431	II
	NASH	NCT04378010	II
MET409	NASH/type 2 diabetes	NCT04702490	II
TERN-101	NASH	NCT04328077	II
Cilofexor/GS-9674	PSC	NCT03890120	III
	PSC	NCT02943460	II
	PSC	NCT02943447	II
	NASH	NCT02781584	II
Tropifexor/LJN452	PBC	NCT02516605	II
	NASH	NCT04065841	II
	NASH	NCT02855164	II
Px-104	NAFLD	NCT01999101	II
EYP001a	NASH	NCT03812029	II
Nidufoxor/ LMB763	Diabetic nephropathy	NCT03804879	II
	NASH	NCT02913105	II

PBC, primary biliary cholangitis; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; PSC, primary sclerosing cholangitis.

uptake was reduced and hepatic steatosis was reversed (51). Interestingly, when PPARα agonist was administered to ApoE (-/-) FXR (-/-) mice, Lee *et al* (52) observed that despite lipid reduction which resulted in NAFLD and atherosclerosis alleviated, the expression of FATP1 and CD36 was upregulated. This suggests that FATP family members may not simply promote lipid accumulation, but enhance lipid transport to drive intracellular lipid metabolism pathways.

FXR and synthesis of FAs. FXR inhibits the *de novo* synthesis of FAs. During the *de novo* synthesis of FAs in the body, acetyl-CoA carboxylase (ACC) can carboxylate acetyl CoA to form malonyl CoA, which is a rate-limiting enzymatic step in this pathway. Experimental evidence demonstrates ACC's pivotal metabolic role. ACC (-/-) mice have a lower weight than the wild-type (WT) group, and using ACC inhibitors to treat mice induced by diet could upregulate FA oxidation (FAO) and inhibit FA synthesis, thus leading to NAFLD relief (53). In addition, sterol regulatory element binding protein 1 (SREBP-1) and carbohydrate reaction element binding protein (ChREBP) are also essential transcriptional regulators in the lipid synthesis pathway. In an ob/ob mouse model of obesity and insulin resistance, the expression of SREBP-1 and ChREBP were significantly increased, and the dual or selective inhibition of these factors effectively alleviated the liver steatosis of the model mice (54,55).

In FXR deficient mice, SREBP-1, FA synthase (FASN) and stearoyl-CoA desaturase-1 were significantly upregulated, indicating that FXR might inhibit the synthesis of FA to improve liver steatosis (56). On the contrary, CA administration significantly downregulated SREBP-1 and its transcriptional targets, while impairing lipogenic capacity in murine hepatocytes (57). As one of the key target genes of FXR, the role of SHP has been investigated. Mechanistic investigations have revealed that SHP mediated SREBP-1c promoter regulation. CDCA-induced SHP upregulation has been shown to be inversely correlated with SREBP-1c target gene suppression. CA or GW4064 could attenuate serum TGs along with sterol regulatory element-binding protein 1 (SREBP1) decreases in SHP (+/+) mice; however, this was absent in SHP (-/-) mice, establishing the FXR/SHP axis as a dual regulator of FA transport and lipogenesis through SREBP-1c modulation.

ChREBP has been shown to regulate glucose-induced fat production. Under hyperglycemic conditions, ChREBP combines with Max-like protein and ChREBP to form two

Table II. FXR modulates.

First author/s, year	Compounds	Regulation of target genes	Receptor selectivity	(Refs.)
Urizar *et al*, 2002; Burris *et al*, 2005	Guggulsterone	HepG2: BSEP ↑, SHP ↓ Caco-2: IBABP ↓	FXR, PXR, GR, MR, AR, PR, ER	(131,132)
Bijsmans *et al*, 2015	Mometasone furoate	HepG2: IL-8, CXCL12, MCP-1 ↓ Reduced recruitment of p65 to IL-8, CXCL12	FXR, GR	(133)
Dussault *et al*, 2013	AGN-34	HepG2: CYP7A1 ↓ Caco-2: IBABP ↓	FXR, RXR	(134)
Chang *et al*, 2016	Xanthohumol	In KK-ay mice: SREBP1, stearoyl-CoA desaturase-, PEPCK, G6Pase ↓	FXR, CAR, GABAA	(135)
Liu *et al*, 2010	Oleanoic acid	HepG2: BSEP ↓	FXR, PAPPA, CAR, PXR	(136)
Fang *et al*, 2015	Fexaramine	Intestinal specificity; SHP, FGF19, IBABP, OSTA/B ↑	FXR	(137)
Pellicciari *et al*, 2016	TC-100	Intestinal specificity; FGF15, SHP, ANG1 ↑	FXR	(138)
Jin *et al*, 2015	Ivermectin	Intestinal specificity; FXR ↑	FXR, CAR, LXRα, PXR	(139)
Li *et al*, 2012	EGCG	Intestinal specificity; SHP, FGF15 ↑	FXR	(140)

HepG2, a hepatoma cell line; Caco-2, a colorectal adenocarcinoma cell line; FXR, farnesoid X receptor; PXR, pregnane X receptor; RXR, retinoid X receptor; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; AR, androgen receptor; ER, estrogen receptor.

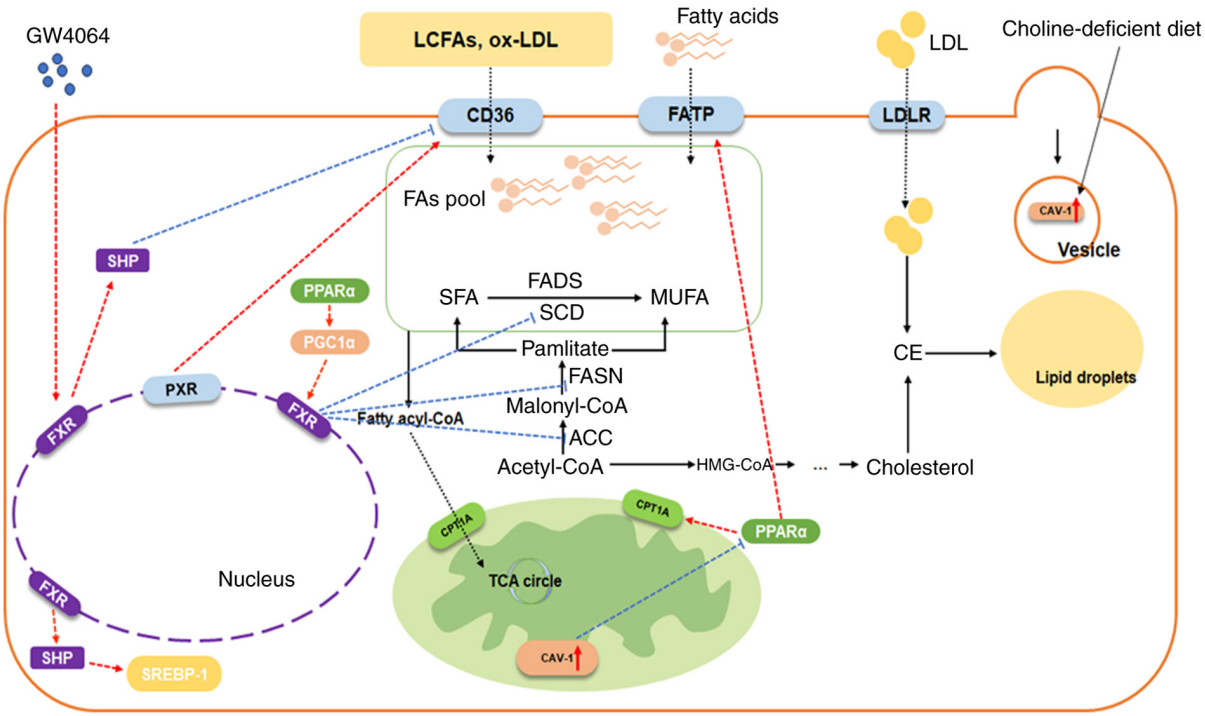

Figure 2. Regulation of FXR and FA metabolism. The regulatory relationship indicates the regulation of adjacent molecules, arrow-headed lines mean a promotion/activation, while flat-headed lines mean an inhibition. FA, fatty acid; LCFA, long-chain FAs; FXR, Farnesoid X receptor; SHP, small heterodimer partner; PPARα, peroxisome proliferator-activated receptors α; SREBP-1, sterol regulatory element binding protein 1; PGC1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PXR, pregnane X receptor; FADS, FA desaturase; SCD, stearoyl-CoA desaturase; SFA, saturated FA; MUFA, monounsaturated FA; FASN, FA synthase; ACC, acetyl-CoA carboxylase; CAV-1, caveolin-1; FATP, FA transport protein; LDL, low-density lipoprotein; LDLR, LDL receptor; CPT1A, carnitine O-palmitoyl transferase 1 A; TCA, tricarboxylic acid; ox-oxidized.

box-like motifs, therefore promoting the expression of its target genes, such as liver-type pyruvate kinase (LPK), FASN and ACC1, driving enhanced FA and TG biosynthesis (58). Given that FXR is negatively associated with the expression of LPK, FASN and ACC, Caron *et al* (59) hypothesized that FXR interfered with the transcriptional activity of ChREBP. Fasting-refeeding studies revealed that INT-747, a synthetic FXR agonist, significantly attenuated

high-carbohydrate-induced increase in mRNA expression of LPK in WT mice, with parallel observations in IHH and HepaRG human hepatocytes. FXR did not affect ChREBP nuclear translocation, but decreased transcription coactivator binding to L4L3 region of LPK promoter to release ChREBP, meanwhile inducing the recruitment of silencing mediator of retinoid and thyroid hormone receptor (a transcriptional corepressor) leading to a prevention of the FXR-dependent repression of LPK at a high glucose concentration. This mechanism could be extended to other ChREBP target genes under hyperglycemic conditions, collectively reducing the generation of acetyl-CoA, suppressing *de novo* lipogenesis, and potentially ameliorating NAFLD pathogenesis.

In addition, due to the enterohepatic cycle of BA metabolism, the fibroblast growth factor (FGF) family members have also been extensively investigated. The expression and excretion of fibroblast growth factor-15/19 are induced by FXR in the intestine. The intestinal activation of FXR stimulates the secretion of FGF-19, which negatively regulates cholesterol 7α hydroxylase (CYP7A1) transcription after binding to FGF4/klothoβ (60). FGF-19 inhibits insulin-induced FA synthesis by i) decreasing the activity of SREBP-1c; ii) enhancing STAT3 signaling and iii) downregulating PGC1β. Furthermore, the FGF19/SHP/SREBP-1c axis suppresses lipogenic enzyme expression while promoting FAO through ACC2 downregulation (61).

FXR and FAO. In FA metabolism, FA from acetyl-CoA and malonyl-CoA, and FFA from TGs are catalyzed by fatty acyl-CoA synthetase to form fatty acyl-CoA, which is the main step in FA β-oxidation. Products are then transferred into the mitochondria by carnitine CPT1a for the subsequent step. Accumulating evidence demonstrates FXR's regulatory role in facilitating this metabolic cascade.

Previous research on FXR-mediated FA transport has revealed functional interplay with PPARα. The PPAR family is part of the nuclear receptor sup-family, including PPAR-α, PPAR-β/δ and PPAR-γ. PPARs serve as primary regulators of glucose and lipid homeostasis, establishing them as therapeutic targets for metabolic disorders and oncogenesis. Experimental evidence indicates that PPARα-deficient mice develop pronounced hepatic steatosis (62), while FXR (-/-) ob/ob mice exhibit significant PPARα downregulation (63). These observations suggest the potential FXR-mediated regulation of FA β-oxidation through PPARα-dependent mechanisms. Substantiating this hypothesis, Pineda Torra *et al* (64) found that the incubation of a human HepG2 cell line with CDCA or GW4064 led to a significant induction of PPARα in a transcriptional level. Through mutation analysis, they found αFXRE in the human PPARα promoter. In addition, induction of human PPARα by CDCA enhanced the expression of PPARα target gene CPT1, which was not observed in mice. This indicated that the underlying mechanism might be species-specific, which is worth investigating further. In addition, FXR could activate the transcription of liver carboxylesterase 1, which enhanced FA β-oxidation through PPARα (65). While reviewing the previous article, it was also found that the FXR/SHP axis may induce the AMPK-ACC-CPT1α mechanism to promote FA β-oxidation (66).

Peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) contributes to the regulation of certain transcription factors, such as PPARα and -γ as the coactivator, thus modulating several genes in metabolic pathways (67). In a study on the pharmacological effect and mechanism of Nuciferine, it was found that Nuciferine could attenuate hepatic steatosis in HFD/STZ-induced diabetic mice through the PPARα/PGC1α pathway (68). In addition, FXR is activated by PGC1α, which promotes PGC1α-mediated FA oxidation (69). In conclusion, FXR tended to promote FA β-oxidation in the majority of studies.

FXR with cholesterol/Bas. Cholesterol undergoes hepatic biosynthesis with subsequent conversion to BAs; this constitutes its principal metabolic fate. BAs are divided into free BAs and conjugated acids in structure, or primary BAs and secondary BAs in source. Given the established role of FXR in regulating BA homeostasis, this section focuses on its contribution to cholesterol metabolite dynamics and enterohepatic BA cycling (Fig. 3).

Synthesis of Bas. Cholesterols could be catalyzed by CYP7A1 into 7α hydroxycholesterol, then undergo a series of complicated enzymatic reactions, finally being transformed into primary free BAs, such as CA and CDCA, or combined with the corresponding glycine or taurine to produce primary conjugated acids to discharge into the intestine. CYP7A1 functions as the key enzyme of the classic BA synthesis pathway (70). 12α-hydroxylase (CYP8B1) determines the ratio of CA and CDCA.

SHP, the target gene of FXR, can inhibit the expression of CYP7A1 by blocking the trans-activation of the liver activator liver receptor homolog-1 (LRH-1) and HNF4α (71,72). In addition, FXR can also reduce BA synthesis by inhibiting CYP8B1, and the mechanism is similar (70,73).

Transport of Bas. Following synthesis and conjugation with glycine or taurine, BAs are secreted into bile canaliculi through BSEP, and then enter the gallbladder for storage. Nutrient-responsive gallbladder contraction initiates bile release into the duodenal lumen. In the distal small intestine, BAs are reabsorbed into the blood through apical sodium-dependent BA transporter. Next, in intestinal epithelial cells, they are reabsorbed by IBABP and organic solute transporter alpha/beta (OSTα/β) into portal circulation. Hepatocyte reuptake completes this enterohepatic cycling mechanism that is essential for maintaining BA pool homeostasis. Almost all of these transporters involved in the enterohepatic circulation of BAs are regulated by FXR (74,75). Others include multidrug-resistant associated protein 2 (MRP2) (76), and multidrug-resistant P-glycoprotein 3 (77), which promote hepatic BA outflow.

FXR and plasma lipoprotein. Plasma lipoprotein is the blood component that transports plasma lipids. It was reviewed independently to elucidate the link between FXR and blood lipid (Fig. 4). This part actually has a crosstalk with the FA metabolism and cholesterol metabolism. Very low-density lipoprotein (VLDL), synthesized primarily in hepatocytes, mediates the hepatic export of TG and cholesterol to peripheral tissues. Upon entering circulation, nascent VLDL acquires apolipoprotein C (apoC) from high-density lipoprotein (HDL), where apoC-II activates endothelial lipoprotein lipase (LPL) to hydrolyze VLDL-associated TG. Through progressive lipid exchange with HDL, VLDL undergoes remodeling into

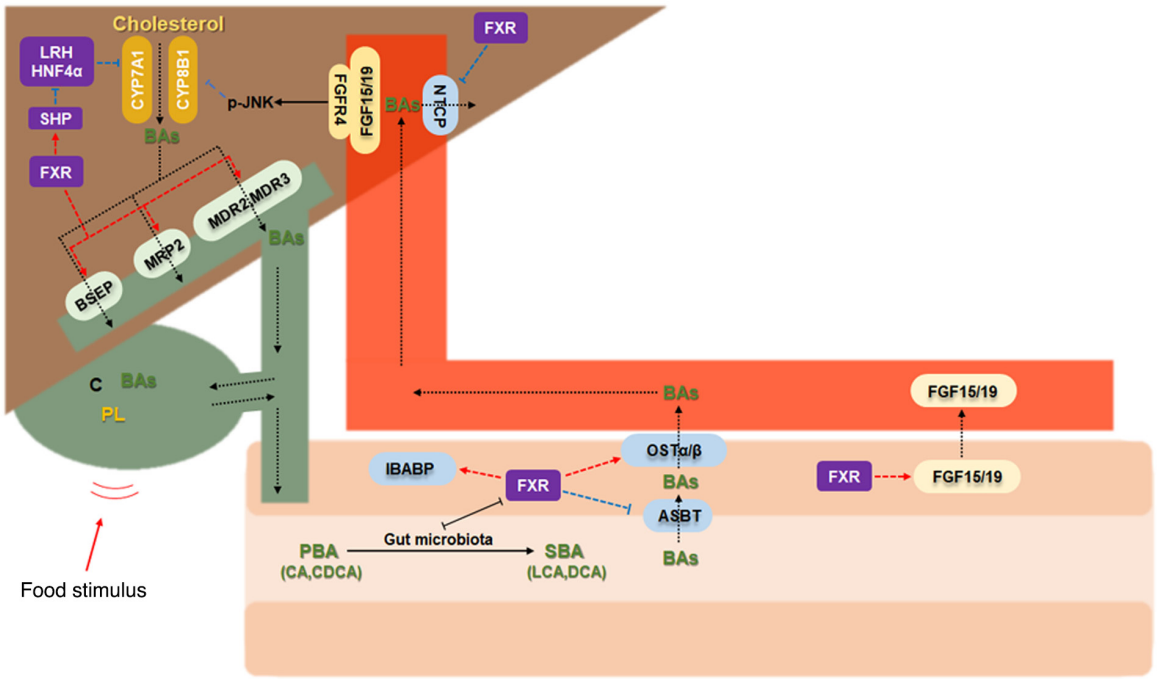

Figure 3. Regulation of FXR and bile acids. The regulatory relationship indicates the regulation of adjacent molecules, arrow-headed lines mean a promotion/activation, while flat-headed lines mean an inhibition. FXR, farnesoid X receptor; SHP, small heterodimer partner; BSEP/ABC11, bile salt export pump; HNF4α, hepatocyte nuclear factor-4-alpha; IBABP, ileal bile acid binding protein; CYP7A1, cholesterol 7α hydroxylase; CYP8B1, cytochrome P450 8B1; MRP2, multidrug-resistant associated protein 2; MDR2/3, multidrug-resistant P-glycoprotein 2/3; FGF-15/19, fibroblast growth factor-15/19; PBA, primary bile acids; SBA, secondary bile acids; OSTα/β, organic solute transporter α/β; ASBT, apical sodium-dependent bile acid transporter; NTCP, sodium taurocholate co-transporting polypeptide; CA, cholic acid; CDCA, chenodeoxycholic acid; LCA, lithocholic acid; DCA, deoxycholic acid.

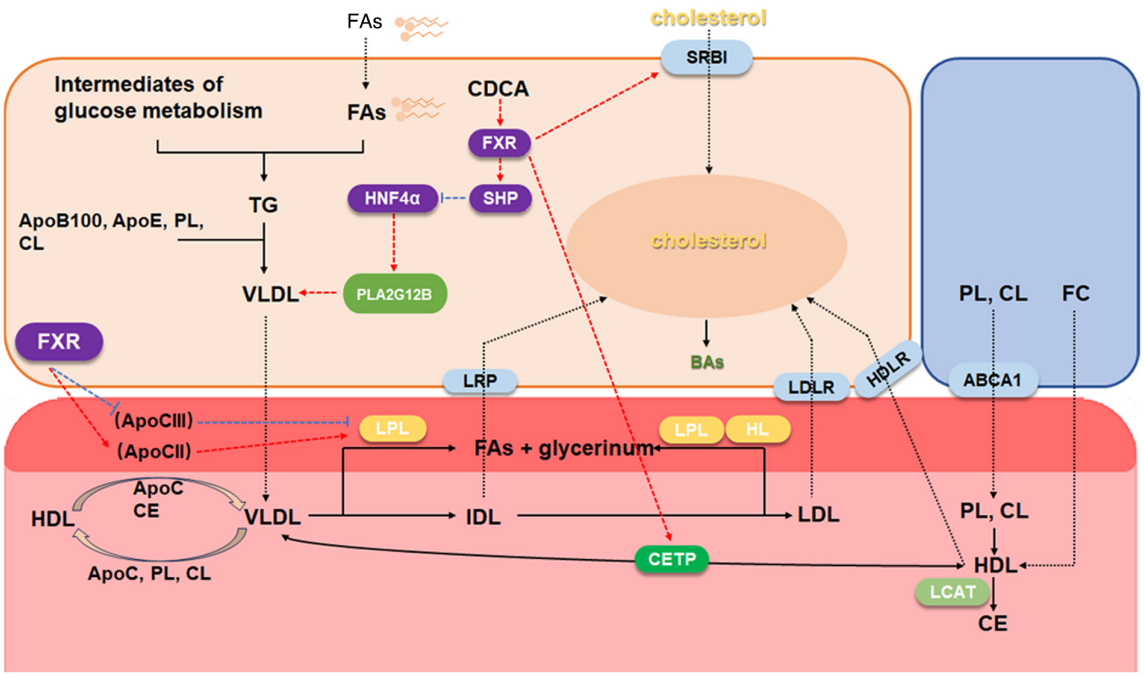

Figure 4. Regulation of FXR and plasma lipoprotein. The regulatory relationship indicates the regulation of adjacent molecules, arrow-headed lines mean a promotion/activation, while flat-headed lines mean an inhibition. FXR, farnesoid X receptor; SHP, small heterodimer partner; FA, fatty acid; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate density lipoprotein; LDL, low-density lipoprotein; CETP, cholesterol ester transfer protein; LCAT, phosphatidylcholine-cholesterol acyltransferase; LPL, lipoprotein lipase; HL, hepatic lipase; PL, phospholipid; CL, cardiolipin; FC, free cholesterol.

cholesterol-enriched LDL, with circulating VLDL and LDL levels serving as established clinical biomarkers for the evaluation of dyslipidemia.

Clinical investigations indicated that pharmacologic FXR activation significantly reduces serum TGs, while aggravating liver cholesterol accumulation and atherogenic

serum lipoprotein profiles (high LDL level) in FXR-deficient models (6,78). Consistently, CDCA was found to be associated with decreased serum TG and VLDL production in patients with hyperlipidemia, while colestyramine (BA chelating agent) exhibited the opposite trends (79). The antilipidemic action of CDCA involves multiple regulatory axes. One is the FXR/SHP/HNF4α axis (80). Hirokane *et al* (80) found that, following the treatment of HepG2 cells with CDCA, the expression of microsomal TG transfer protein (MTP) and apoB are attenuated as HNF-4 is suppressed by SHP. Similarly, FXR/SHP/HNF4α can also reduce VLDL by partially inhibiting the expression of phospholipase A2 group XIIB, a mediator of VLDL (81). From the aforementioned studies, the role of apoC II and LPL were reported. The former activates LPL, and then the latter hydrolyzes TG, leading to TGs clearing. ApoC III is also a component of various lipoproteins, which is known as the inhibitor of LPL, meanwhile affecting hepatic lipase, therefore impairing the conversion of VLDL to IDL and LDL (82). FXR can promote TG clearing by inducing hepatic apoC-II and inhibiting apoC-III and angiopoietin-like protein 3 (83,84). CDCA could lead to FXR combined promoter of apoC-II, but this does not exist in FXR-deficient mice.

HDL is mainly synthesized in the liver and partly in the small intestine, which is responsible for reverse cholesterol transport-the process of shuttling peripheral cholesterol to hepatic tissues for biliary excretion or direct intestinal elimination. Lipid transfer proteins, particularly phospholipid transfer protein (PLTP) and cholesteryl ester transfer protein (CETP), govern lipoprotein remodeling through phospholipid and cholesterol exchange between VLDL and HDL particles. FXR activation by CDCA elevates PLTP activity and induces CETP expression through ApoE-mediated pathways (85,86), thereby modulating lipoprotein redistribution. Scavenger receptor class B type I (SRBI), a key HDL receptor parallel to CD36 in lipid metabolism, demonstrates FXR-dependent upregulation in murine with CA-containing diet, whereas FXR deficiency abrogates this dietary response, establishing SRBI as a regulatory node in FXR-mediated HDL homeostasis.

FAs, cholesterol and plasma lipoproteins are inextricably linked and convert each other, leading to the crosstalk between metabolic mechanisms, which enables a more comprehensive study of the role of FXR in lipid metabolism and BA circulation.

4. FXR and lipid-rich tumors

Obesity constitutes one of the risk factors for cancer. Patients with elevated lipid levels tend to have a higher propensity to develop tumors. Gastrointestinal tumors, such as liver and colon cancer, are typical examples. There are also certain tumors, such as ccRCC, with intracellular accumulation of a significant amount of lipid droplets as a typical pathological feature, distinct from other subtypes. This section focuses on these lipid-associated malignancies, elucidating FXR's pivotal regulatory mechanisms in tumorigenesis and progression to inform novel therapeutic strategies.

FXR and digestive system cancer

Liver cancer. The liver is the central hub for both lipid and BA metabolism. Lipid homeostasis imbalance, alcohol, viral infection, inflammation and cholestasis are all high-risk factors for hepato-carcinogenesis. As aforementioned, the regulation of FXR orchestrates numerous biological protective processes in the liver, with its deficiency resulting in poor prognosis. Studies have shown that FXR-null mice exhibit a significantly elevated incidence of HCC (87,88). This observation is consistent with clinical data showing the reduced FXR expression in human HCC tissues being associated with multiple malignant pathological characteristics, such as large tumor size, advanced Barcelona Clinic Liver Cancer stage, poor differentiation and absence of encapsulation (89). Of note, organ-specific FXR modulation appears to exert different effects to those of systemic FXR perturbation. An American study found that ~20% of mice with liver-specific FXR deficiency developed HCC, which is well below the 90% of mice with global FXR knockouts (90). Furthermore, the tumor-modulating effects of FXR suggest tissue specificity. Kong *et al* (91) reported that hepatocyte-specific FXR deficiency was resistant to spontaneous HCC development, but susceptible to CA-induced hepato-carcinogenesis. The results of another study showed that intestine-specific FXR reactivation could impair the spontaneous development of HCC (92). These findings underscored the critical role of systemic BA homeostasis regulated by FXR in HCC pathogenesis, while highlighting pro- or anti-tumorigenic functions of tissue-specific FXR.

The role of FXR/SHP axis in the segments of lipid metabolism and BAs synthesis, including FXR/SHP/CD36, FXR/SHP/SREBP1 and FXR/SHP/HNF4α has been summarized; however, the relationship between FXR and SHP is not just linear. FXR (-/-) and SHP (-/-) could result in tumorigenesis independently. As a strong induced target, SHP could affect HCC in the liver of FXR (-/-) mice. Li *et al* (93) engineered FXR (-/-)/SHP^{Tg} mice to explore the contribution of SHP. Their investigation revealed that SHP overexpression reduced HCC proliferation while enhancing apoptosis, without altering tumor incidence or dimensions. Although SHP partially rescued FXR (-/-)-induced hepato-carcinogenesis, it failed to inhibit JAK2/STAT3 pathway activation, suggesting a complex crosstalk between inflammatory signaling and the FXR/SHP axis during HCC development.

While cholestasis constitutes a recognized HCC risk factor, recent evidence indicated that different BA species exhibit differential carcinogenic potential, with hydrophobic BAs demonstrating particular oncogenic properties (94). Chronic liver diseases, such as cirrhosis and non-alcoholic steatohepatitis, frequently exhibit compromised BA homeostasis due to diminished hepatic BA transporter expression and impaired FXR signaling, creating permissive microenvironments for HCC progression (71,72,74,75,94). As a BA-causing efflux and FXR target gene, BSEP deficiency contributed to cholestasis and HCC development. In addition to conventional regulatory mechanisms, limited studies have shown that FXR subtypes affect BSEP transcription. Chen *et al* (17) found that FXRα2 exhibited a stronger transactivation activity of human BSEP than FXRα1. Proinflammatory cytokines, such as IL-6 and TNF-α, were elevated in HCC tissues. When Huh7 was treated by these inflammatory cytokines, the ratio of FXR α1/FXR α2 was increased, while it was decreased following BSEP treatment (17). The aforementioned study showed that FXR subtypes affect bile content, and thus the development of HCC.

On the other hand, FXR deficiency results in lipid accumulation and attenuates FAO. Pharmacological FXR activation has been shown to have a therapeutic potential in preclinical models of HCC, notably ameliorating NAFLD and NASH. NAFLD pathophysiology features elevated hepatic and circulating TG levels (95) and is converted to NASH if not well controlled. Clinical evidence has revealed the consistent FXR downregulation in both pediatric and adult NAFLD/NASH cohorts, as compared with simple obesity or healthy hepatic tissue (96,97). The FXR agonist obeticholic acid has been identified to be effective to NASH (98); however, there have been some adverse reactions, prompting the intensive development of next-generation FXR modulators. To address these concerns, multiple FXR agonists in NAFLD and NASH have been explored (99-102). Lipocalin 13 (LCN13), recently identified as an FXR-regulated hepatoprotective factor, mitigates steatosis through the dual modulation of lipogenesis suppression and FA β-oxidation enhancement. Its transcriptional downregulation in patients with NASH, coupled with FXR-dependent activation, positions LCN13 as both a novel FXR target and a promising therapeutic candidate (103).

Beyond BA homeostasis and lipid modulation, emerging mechanisms delineated in the study by Huang *et al* (104) implicated FXR in hepatic regeneration, injury resolution, anti-inflammatory signaling and direct neoplastic regulation. Crucially, these pathways have exhibited extensive crosstalk, with collaborative interactions ultimately driving hepato-carcinogenesis.

Colorectal cancer (CRC). Due to its role in BA circulation and gut microbiota, the development of intestinal tumors involves a complex interaction with the FXR's expression and activity. Beyond the direct regulation of BA synthesis/transport machinery, FXR-mediated pathological mechanisms extend to bidirectional crosstalk with microbial communities and immunomodulatory pathways.

The gut microbes have profound effects on BA metabolism by promoting the decoupling, dehydrogenation and dihydroxylation of primary BAs in the distal small intestine and colon, thereby increasing the chemical diversity of Bas (105). Gut microbes and FXR, as two factors in BA regulation, also interact with each other through the change of BA pool. Sayin *et al* (105) analyzed the differences in BAs between germ-free (GF) and conventionally raised (CONV-R) mice. The BAs' composition spectrum showed organic differences between two groups, and the BAs' pool of CONV-R was reduced by 71±2%. Further intestinal segment analysis revealed the effect of the presence of intestinal microbes on the BAs' profiles of different intestinal segments; that is, the modification of BAs by microorganisms. Given FXR's role in BA balance, they explored the activities of FXR and found that FXR, SHP and FGF15 are upregulated in distal ileum of CONV-R mice compared with the GF group. Furthermore, the upregulation of SHP, FGF15 and IBABP was eliminated when $FXR^{-/-}$ mice were rederived as GF. These findings revealed that the effect of gut microbes on BAs is induced by FXR. In patients with CRC, 16s rRNA shows multiple mucosal microbes increased, including the genera *Bacteroides*, *Curto bacterium* and *Campylobacter* (106). In addition, these microbes have a stronger ability to produce DCA, which inhibits FXR and promotes CRC. Consistent with this, the low expression of FXR was observed in a different CRC study, meanwhile researchers found that FXR was negatively correlated with the PI3K pathway and EMT (107). By contrast, FXR deficiency results in the of BA profiles, which then affects gut PH and, ultimately, enterotoxigenic *Bacteroides Fragilis* (ETBF) mucosal colonization, contributing to the development of CRC (108).

Immune microenvironment alterations emerge through dual mechanisms. One reason for that is microbial imbalance. *Bacteroides fragilis* toxins, produced by ETBF, have a carcinogenic effect on colonic epithelial cells. It can induce mucosal Th17 response, which in turn selectively leads to the activation of the NF-κB pathway (109,110). In addition, Guo *et al* (108) demonstrated that BA levels affect IgA concentrations, which serve as the first line of defense for intestinal immunity. Secretory IgA is increased in the high-BA group, and decreased in the low-BA group. This change of immune environment also plays a synergistic role in the colonization of intestinal microbiota and CRC. Another reason for that was that FXR directly influences immune cell function and inflammation resolution. Colitis-associated cancer (CAC) is a subtype of CRC associated with inflammatory bowel disease (IBD). Macrophages are located in the intestinal epithelium sublaminar propria, mediating the inflammatory response to foreign substances, playing a role in defense, clearance and antigen presentation. Previous studies have shown that the occurrence of inflammation impaired BA homeostasis, and the activation of FXR exerted a protective effect on the intestine (111,112). Compared with healthy tissues, FXR and downstream gene expression was decreased in CAC tissues, while proinflammatory factors were significantly increased. These cytokines resulted in the upregulation of Paneth and goblet cell markers, promoting organoid budding and branching, which suggests that the stemness of intestinal stem cells was promoted, therefore contributing to CAC. Since it has been previously suggested that FXR reduces IL-17 and IFN, and Th17 cells secreting inflammatory cytokines have been shown to be associated with CAC mouse models, Dong *et al* (111) explored the effect of FXR agonist Fexaramine D on tumor progression. The results revealed that FXR activation enhanced the polarization and maturation of macrophages, which further led to the activation of Th17 cells (111). Furthermore, inflammation drove an increase in innate lymphoid cells (ILC) in IBD, particularly ILC3. The activation of FXR not only blocked the activation of IL-17a and IL-17f in ILC but also regulated the maturation and differentiation of ILC (112).

Collectively, intestinal carcinogenesis emerges from dynamic FXR-mediated crosstalk between BA metabolism, microbial ecology, barrier integrity and immune surveillance. As a primary regulator of BA homeostasis, FXR represents both biomarker and therapeutic target in CRC development, with pharmacological activation holding promise for intercepting microbiome-driven malignancy progression.

FXR and breast cancer. According to data from the World health Organization (http://gco.iarc.who.int), breast cancer ranks first in incidence and mortality among all cancer types in women. Estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2) status constitute critical determinants of metastatic progression, with osseous

metastasis being the most frequent dissemination pattern. FXR has been found to be expressed in primary breast cancers with bone metastases and plays an important role in osteo-mimetism of tumor cells to result in the osteo-tropism of breast cancer (113). Mechanistic investigations by Silva *et al* (114) revealed that bone-derived sodium deoxycholate enhanced the metastatic potential of MDA-MB-231 cells through FXR upregulation and nuclear translocation-an effect abrogated by Z-guggulsterone-mediated FXR inhibition (114,115). However, another study showed that FXR activators CDCA and GW4064 resulted in the apoptosis of MCF-7 and MDA-MB-468 cell lines (116). Of note, FXR's oncogenic role exhibits concentration-dependent duality. A low DCA concentration (10 μmol/l) promotes metastasis, while a high DCA (100-150 μmol/l) causes apoptosis (114). Furthermore, it has been shown that the mRNA expression of SHP, MRP2 and IBABP is induced in breast cancer lines following treatment with a low concentration of GW4060 (3 μmol/l) (116). The study by Alasmael *et al* (117) also supported that the activation of FXR induces apoptosis, without increasing the migration potential. Discrepancies between these studies likely reflect methodological variations in FXR activation thresholds and cellular context dependencies (117).

For ER-α-positive breast cancer, tamoxifen (tam) is the first-line endocrine therapy. However, drug resistance often occurs on account of $HER2^+$. Therefore, the combination of endocrine therapy and targeted therapy is the optimal treatment for patients with HR^+HER2^+ breast cancer. Targeting HER2 is more critical. Giordano *et al* (118) found that the activation of FXR by GW4064 and CDCA inhibited the growth of a tam-resistant MCF-7 TR1 cell line. Their results demonstrated that CDCA reduced HER2 expression and impaired EGF-mediated HER2 and p42/44 MAPK phosphorylation. This suggested that the inhibition of HER2/MAPK through FXR may offer a new therapy direction for HR^+HER2^+ breast cancer.

Additional pathophysiological interactions emerge through leptin signaling modulation (119). GW4064 inhibits the growth, migration and invasion of breast cancer induced by leptin, affecting tumor-promoting activities of cancer-associated fibroblasts. The underlying mechanism showed that FXR increased the expression of suppressor of the cytokine signaling 3, leading to the inhibition of leptin signaling and downregulation of its target genes.

These findings suggest that targeting FXR may provide a new direction for breast cancer treatment but should take into consider the biological context and dose effects.

FXR and urinary system cancer

Kidney cancer. RCC is the most common type of kidney cancer, with ccRCC accounting for 60-70%. This histological subtype displays characteristic metabolic aberrations manifested by cytoplasmic lipid droplet and glycogen accumulation. In a multi-omics investigation, Strauss *et al* (120) stratified patients with ccRCC into non-progressing (NP) and low-risk tumors progressing within a 5-years average follow-up (P) cohorts based on tumor behavior during a 5-year surveillance period. Comparative proteomic profiling revealed an elevated expression of LXR/RXR- and FXR/RXR-related proteins in the NP cohort compared with the P cohort (121). One functional validation study demonstrated that FXR knockdown suppressed ACHN cell proliferation, although this antitumor effect was absent in HK-2 proximal tubule cells (121). These findings were consistent with those of Huang *et al* (122), who reported FXR upregulation in specimens of patients with ccRCC and cell lines. FXR may influence cell cycle through the cyclin E2/cyclin dependent kinase 2 pathway. In conclusion, these results showed that FXR could affect the development of ccRCC.

Most studies agree that the accumulation of FAs and cholesterol leads to tumor progression, while its oxidative metabolism inhibits tumor growth in ccRCC. Emerging evidence positions FXR as a key metabolic regulator in ccRCC, characterized by the upregulation of its transcriptional targets CD36 and ACC alongside carnitine palmitoyl-transferase 1A downregulation (123). Another FA transport molecule, CAV-1, is upregulated and has been identified as a promising therapeutic target (124). This apparent divergence from the canonical FXR/SHP/CD36 and FXR/CAV-1 liver signaling pathways raises thought-provoking questions about organ-specific metabolic regulation, potentially reflecting the liver's unique lipid homeostatic dominance.

SRBI promotes the influx of HDL into ccRCC, resulting in the accumulation of cholesterol in ccRCC, which is conducive to the growth of tumor cells (125). When inhibiting SRBI, the proliferation of ccRCC is impaired (126). The expression levels of SRBI and FXR are parallel in the liver (127). The evolving understanding of renal vs. hepatic FXR signaling highlights fundamental differences in organ-specific lipid regulatory networks.

Collectively, current evidence reveals a dualistic role for FXR activation in ccRCC progression, simultaneously modulating pro- and anti-tumorigenic pathways. The intricate crosstalk between FXR-mediated lipid/cholesterol metabolism and renal oncogenesis remains inadequately characterized, necessitating systematic investigation.

Prostate cancer (PCa). High cholesterol is a risk factor for PCa. Beyond BA synthesis, cholesterol serves as the metabolic precursor for sex hormone biosynthesis, particularly androgens that drive PCa pathogenesis. While androgen receptor (AR/NR3C4) has been found associated with lipid metabolism (128), emerging evidence reveals complex regulatory cross-talk with nuclear receptors, including LXR and FXR, acting as metabolic counterbalances. Two mechanistic studies demonstrated that pharmacological FXR activation suppresses PCa proliferation through phosphatase and tensin homolog deleted on chromosome ten upregulation and SREBP1 downregulation (129,130). In addition, CDCA and GW4064, FXR activators, both inhibit the expression of UGT2B15/17 and their combination with androgens. This means FXR activators regulate androgen metabolism in PCa as well. Despite growing evidence implicating FXR in cholesterol and FA metabolic reprogramming through SREBP1 modulation, the precise mechanistic interplay between these pathways in PCa pathobiology remains incompletely characterized and warrants systematic investigation.

5. Conclusion and perspectives

For most solid tumors, surgery is the first line of treatment. The emergence of targeted drugs has brought the dawn of precision

treatment of tumors, but the invasive nature of surgery, the resistance of targeted drugs and the recurrence of tumors have brought new challenges, which require researchers to explore the potential targets of tumor therapy from a new angle. An increasing number of studies are focused on the key regulatory molecules of metabolic reprogramming. For lipid-rich tumors, lipids play a significant role in the process of pathological changes and become one of the important driving factors for the transition from pretumor to tumor stage. Thus, lipid metabolism is a good breakthrough, and there are already a large number of small molecule drugs targeting this aspect. In addition, lipid-lowering agents, such as statins, have been used in clinical cohorts of cancer patients to investigate the effect of serum lipid level on tumor progression.

The present review showed that the interaction between FXR and lipid metabolism involves a multifaceted regulatory network of BA-cholesterol axes, FAs and lipoproteins, with profound implications for lipid-rich tumors. The role of FXR in lipid metabolism can be summarized as follows: First, FXR is activated by physiological ligand CDCA or synthetic agonists (such as GW4064), which inhibits LRH-1/HNF4α through SHP-dependent inhibition, thereby inhibiting CYP7A1 and CYP8B1, and limiting BA synthesis. At the same time, it upregulates BSEP and OSTα/β, coordinates BA outflow and prevents cholestasis and lipid overload. Secondly, on the one hand, FXR antagonizes fat production by inhibiting SREBP-1c and ChREBP, thereby downregulating FASN and ACC1. On the other hand, it enhances FAO through PPARα activation and CPT1A induction, thereby controlling FA flux. Thirdly, FXR inhibits MTP/apoB through SHP/HNF4α, thereby reducing VLDL secretion, and promotes HDL-mediated cholesterol reverse transport for plasma lipoprotein remodeling through PLTP and SRBI. In the tumors listed, FXR plays both pro- and antitumor roles, depending on the heterogeneity of the tumor.

Overall, the present review summarized the relationship between FXR, lipids and tumors from the perspective of lipid metabolic reprogramming, suggesting that FXR may be one of the potential targets for tumor therapy, which provides new implications for tumor therapy from the perspective of tumor metabolic tendency.

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Authors' contributions

YNS reviewed previous research on FXR, drafted the manuscript and drew the figures. HJL and KS revised the manuscript and helped with literature review. QHX revised the manuscript critically for important intellectual content. The implementation of this study was aided by the participation of all authors. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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