FEBS Letters

Lipid sensing nuclear receptors involved in the pathogenesis of fatty liver disease

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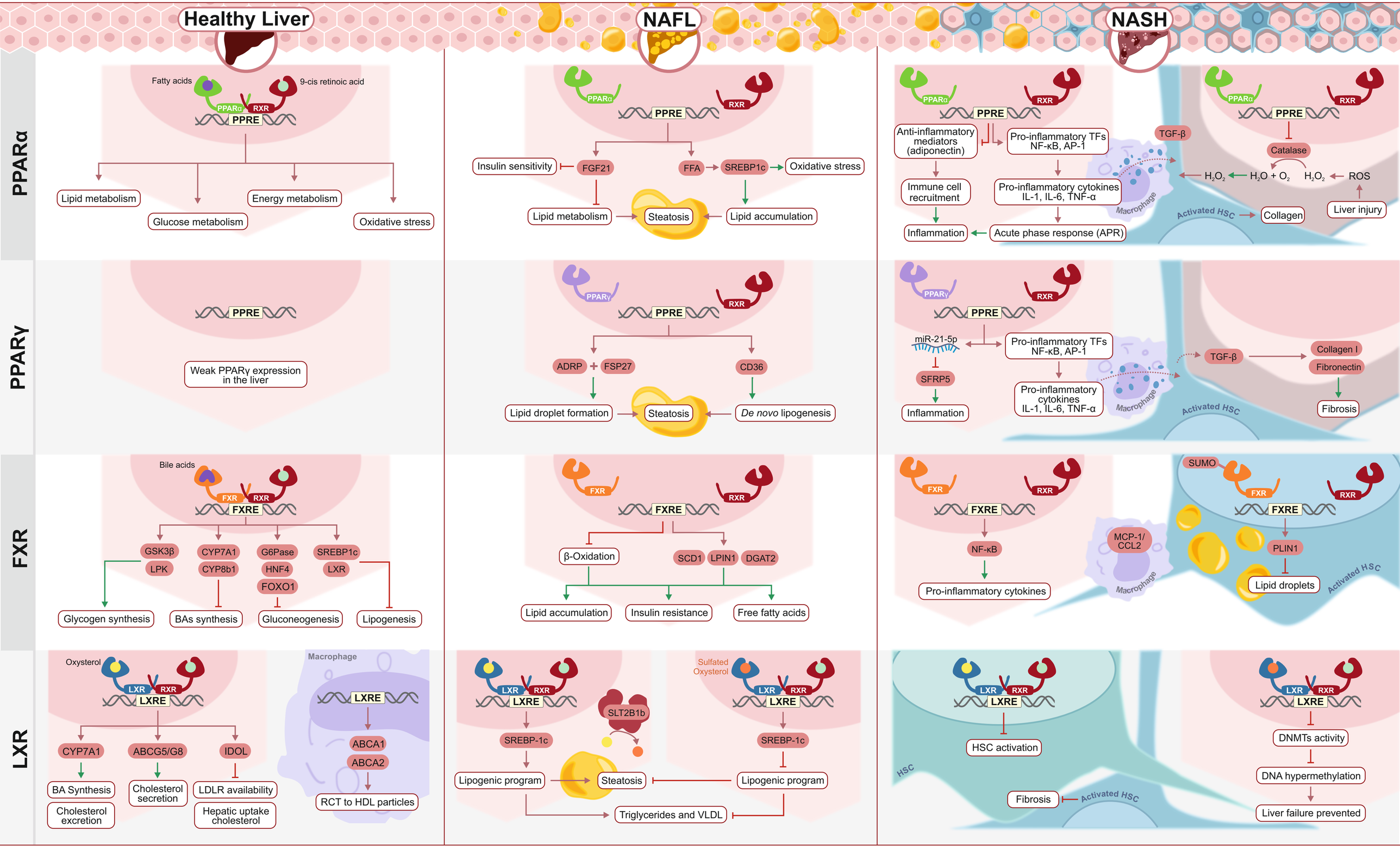
GRAPHICAL Review



 doi: 10.1002.1873-3468.14818

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GRAPHICAL Review

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is a progressive liver disease sometimes referred to as the "hepatic manifestation of the metabolic syndrome" [1], that starts with excess lipid accumulation (NAFLD) or steatosis. Advanced stages are characterized by inflammation and liver injury, defined as non-alcoholic steatohepatitis (NASH) [2]. NAFLD affects approximately 30% of adults worldwide, with about 1 in 5 NAFLD patients developing NASH [3]. NASH and fibrosis are risk factors for serious long-term outcomes, including cirrhosis, hepatocellular carcinoma, and death. NASH is closely associated with metabolic syndrome, obesity, type 2 diabetes, and cardiovascular diseases [4]. Currently, there are few therapeutic options, and lifestyle adjustments are often the recommended treatment. Over the past years, nuclear receptors have appeared as promising drug targets for metabolic diseases like NAFLD. This review focuses on members of the ligand-binding nuclear receptor superfamily that bind to DNA hormone response elements as heterodimers with the common partner RXR. Specifically, here we highlight PPARα, PPARγ, FXR, and LXRα/β with their central roles in regulating lipid and glucose metabolism, based on studies in preclinical models.

Peroxisome proliferator-activated receptor alpha (PPARα)

Hepatic PPARs are involved in lipid and glucose metabolism, energy balance, inflammation, and fibrogenesis [5]. The three isotypes PPARα, PPARβ/δ, and PPARγ are activated endogenously by eicosanoids and dietary fatty acids. Since the role of PPARβ/δ in NAFLD context is still under investigation [6] and clinical trials including PPARβ/δ either as selective or dual agonist were interrupted or discontinued [7], we focus on PPARα and PPARγ, which are currently investigated as the main targets for NAFLD progression and treatment. Among these isoforms, PPARα expression is highest in hepatocytes. In healthy liver tissue, PPARα regulates fatty acid transport, peroxisomal and mitochondrial ß-oxidation, and ketogenesis. It may reduce steatosis by upregulating lipolysis [8]. In NASH, PPARα may have anti-inflammatory properties via trans-repression of pro-inflammatory transcription factors like NF-κB or AP-1, which activate cytokine production [9]. Furthermore, PPARα upregulates antioxidant enzymes such as catalase, which neutralize reactive oxygen species to keep stellate cells in a quiescent state, thereby potentially preventing liver fibrosis [10].

Peroxisome proliferator-activated receptor gamma (PPARγ)

In addition, hepatic expression of PPARγ increases with NAFLD progression [11, 12]. PPARγ transcriptionally activates lipid uptake and fatty acid synthesis to induce lipid accumulation [13]. In NASH, PPARγ may also reduce inflammatory responses by alleviating hepatic inflammation via miR-21-5p/SFRP5 signaling [14] and regulating macrophage polarization [15], keeping hepatic stellate cells inactive. Concurrently, it may decrease collagen I synthesis, which halts NASH progression towards fibrosis [16]. This observation is consistent with an increased susceptibility to developing fibrosis in HSC (hepatic stellate cell)-specific PPARγ knockout mice [17].

Compound	Therapeutic benefits and side effects	ClinicalTrial.gov ID
Pemafibrate (PPARα agonist)	No significant change in liver fat content	NCT03350165 Phase 2
Pioglitazone (PPARγ agonist, partial PPARα agonist)	Improved markers of hepatic steatosis and fibrosis	NCT05521633 Phase 3
Lobeglitazone (PPARγ agonist, partial PPARα agonist)	Improved steatosis	NCT02285205 Phase 4
Saroglitazar (PPARα and PPARγ dual agonist)	Resolution of NASH and improved fibrosis	NCT05011305 Phase 2
Lanifibranor (Pan-PPAR agonist)	Resolution of NASH and improved fibrosis	NCT04849728 Phase 3 (NATiV3)

Farnesoid X Receptor (FXR)

FXR is highly expressed in the liver and in other tissues. In response to its endogenous ligands, bile acids, FXR regulates bile acid homeostasis, glucose utilization, and lipid metabolism [18]. Activation of FXR affects glucose homeostasis by decreasing gluconeogenesis and by enhancing glycogen synthesis, while inhibiting *de novo* lipogenesis. Simultaneously, FXR promotes triglyceride clearance and fatty acid oxidation in the liver, leading to reduced cholesterol, lipid, and LDL levels [19, 20]. It might also play a role in suppressing inflammation by reducing the expression of chemokines like MCP-1/CCL2 [20]. FXR impact on fibrosis, particularly in hepatic stellate cells, is still debated. Recent research indicates that activated stellate cells may inhibit the response to FXR agonists by enhanced SUMOylation of the receptor itself. However, combining SUMOylation inhibitors with FXR agonist treatment has shown promising results in reducing fibrotic markers [21].

Compound	Therapeutic benefits and side effects	Metabolic effects	ClinicalTrial.gov ID
Obeticholic acid (OCA) (agonist)	Improved fibrosis HDL decrease, LDL increase Pruritus	Weight loss AST/ALT levels improvement	NCT02548351 Phase 3 (REGENERATE)
MET409 (agonist)	Hepatic fat content reduction HDL decrease, LDL increase Pruritus	Weight loss ALT reduction	NCT04702490 Phase 1b
Tropifexor (agonist)	Hepatic fat content reduction Pruritus	Weight loss ALT/GTT reduction	NCT02855164 Phase 2 a/b (FLIGHT-FXR)
Vonafexor (agonist)	Hepatic fat content reduction Pruritus	Hepatic enzyme improvement Weight loss Visceral obesity reduction	NCT03812029 Phase 2a (LIVIFY)

Liver X Receptor (LXR)

There are two major subtypes, LXRα and LXRβ, with LXRα being the predominant form in the liver [22]. They are activated by oxysterols, and exert potent effects on cholesterol homeostasis. LXRs stimulate bile acid synthesis, promoting cholesterol excretion by the liver [23], and activate reverse cholesterol transport in peripheral cells [24], overall inhibiting atherosclerosis [25]. They also induce fatty acid biosynthesis, mainly by the induction of *SREBP-1c* expression [26]. Accordingly, treatment with synthetic LXR agonists induces hepatic steatosis and increases circulating levels of triglycerides and VLDL [27]. The sulfated forms of oxysterol (such as Larsucosterol) are inhibitors of LXRs. When the enzyme catalyzing this sulfation reaction (SLT2B1b) is overexpressed in the liver of mice supplemented with oxysterols, the expression of downstream targets of LXRα is substantially reduced, as are hepatic lipid content and circulating lipids [28]. Moreover, the effects of LXRs on NASH are still controversial: activation of LXRs may suppress markers of fibrosis in hepatic stellate cells *ex vivo*, while LXR double knock-out animals are more susceptible to developing liver fibrosis in response to different insults, suggesting that LXRs might impair the progression of steatosis to more advanced phases of liver disease [29].

Compound	Therapeutic benefits and side effects	ClinicalTrial.gov ID
Oltipraz (antagonist)	Significantly reduced liver fat content	NCT01373554 Phase 2

Final remark

Over the last years, the RXR heterodimer partners PPARα, PPARγ, FXR, and LXR have emerged as key players in glucose and lipid homeostasis in healthy livers, with several studies highlighting their importance during NASH progression and pathogenesis. Therefore, targeting these receptors may have high therapeutic potential in the future. As a closing remark, it is appropriate to underline that fatty liver disease is addressed here with the classical acronym NAFLD, albeit the awareness that the use of MAFLD abbreviation is actively debated in the scientific community.

Abbreviations

AP-1, Activator Protein-1; BA, Bile Acids; CCL2, Chemokine Ligand 2; FA, Fatty Acids; FXR, Farnesoid X Receptor; HSC, Hepatic Stellate Cell; IL-1ß, Interleukin-1ß; IL-6, Interleukin-6; LDL, Low Density Lipoprotein; LXR, Liver X Receptor; MCP-1, Monocyte Chemoattractant Protein-1; NAFLD, Non-Alcoholic Fatty Liver Disease; NASH, Non-Alcoholic SteatoHepatitis; NF-kB, Nuclear Factor kB; NR, Nuclear Receptor; PPAR, Peroxisome Proliferator-Activated Receptor; ROS, Reactive Oxygen Species; RXR, Retinoid X Receptor; SREBP-1c , Sterol Regulatroy Element-Binding Protein 1c; TAG , Triacylglycerol; T2DM, Type 2 Diabetes Mellitus; VLDL, Very-Low-Density Lipoprotein.

Acknowledgements

We thank the German Research Foundation DFG (UH 275/6-1-ID 457050056, TRR333 BATEnergy ID 450149205, TRR205 Adrenal Gland ID 314061271 and CRC1064 Chromatin Dynamics ID 213249687) for their continuous support. Our gratitude goes to Sybille Regn and Ivonne Guderian for their contributions. We apologize to all authors whose work could not be cited due to space constraints.

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 doi: 10.1002.1873-3468.14818