Nuclear Receptors as Drug Targets in Cholestatic Liver Diseases

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KEYWORDS

• Cholestatic liver disease • Nuclear receptors • Cholestasis • Bile acids

KEY POINTS

- Nuclear receptors (NRs) regulate ligand-activated transcription factor networks of genes for the elimination and detoxification of potentially toxic biliary constituents accumulating in cholestasis.
- Activation of several NRs also modulates fibrogenesis, inflammation, and carcinogenesis as sequels of cholestasis.
- Impaired NR signaling may be involved in the pathogenesis of cholestasis and genetic variants of NR-encoding genes are associated with susceptibility and progression of cholestatic disorders.
- NRs represent attractive targets for pharmacotherapy of cholestatic disorders, because their activation may orchestrate several key processes involved in the pathogenesis of cholestatic liver diseases.
- Several already available drugs may exert their beneficial effects in cholestasis via NR activation (eg, ursodeoxycholic acid via glucocorticoid receptor and pregnane X receptor; rifampicin via pregnane X receptor; fibrates via PPARα; budesonide via glucocorticoid receptor) and novel therapeutic developments target NRs (obeticholic acid - farnesoid X receptor).

INTRODUCTION

Cholestasis may be best defined as an impairment of bile flow whereby bile reaches the duodenum in insufficient amounts.[1] The cause of different cholestatic diseases

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is quite diverse, comprising hereditary and acquired diseases caused by genetic and environmental factors (discussed in previous articles in this volume). Independent of their cause, the main features of cholestatic liver disorders include an accumulation of cholephils such as bile acids (BAs) in the liver and systemic circulation.[2] The accumulation of potentially toxic BAs leads to hepatocellular damage followed by inflammation and fibrosis, and, finally, depending on the disease severity and duration, may culminate in liver cirrhosis and hepatocellular or cholangiocellular cancer. To handle potentially toxic cholephils under physiologic and pathologic conditions, the liver possesses a complex network of nuclear receptor (NR)-regulated pathways that coordinate BA homeostasis and bile secretion to limit their concentrations and prevent hepatic as well as systemic accumulation. NRs are ligand-activated transcription factors that regulate a broad range of key hepatic processes[3] in addition to hepatobiliary excretory function, such as hepatic glucose and lipid metabolism, inflammation, regeneration, fibrosis, and tumorigenesis.[4] On activation by ligands, NRs change their conformation, which in turn facilitates the recruitment of coactivators and dissociation of corepressors and enables DNA binding and stimulation of gene transcription.[5] The recruitment of cofactors fine tunes the regulation of transcription by NRs.[6] The most relevant BA-activated NRs for regulation of hepatobiliary homeostasis, bile secretion, and, thereby understanding and treating cholestasis, include the farnesoid X receptor (FXR, NR1H4),[7] pregnane X receptor (PXR, NR1I2),[8,9] and vitamin D receptor (VDR, NR1I1).[10] Apart from BAs, other biliary constituents such as bilirubin can also activate NRs, such as the constitutive androstane receptor (CAR, NR1I3). Furthermore, other nuclear receptors such as glucocorticoid receptor (GR, NR3C1) and fatty acid-activated peroxisome proliferator-activated receptors (PPARs), in particular PPARα (NR1C1) and PPARγ (NR1C3) as regulators of inflammation, fibrosis, and energy homeostasis, may also impact on biliary homeostasis and cholestatic liver injury. Because of their capability to control hepatic metabolism, NRs have emerged as promising therapeutic targets in many liver diseases, including cholestatic disorders. In this article, the principal role of NRs in the pathogenesis of various cholestatic disorders and how they may serve as drug targets in the management of cholestatic patients are discusssed.

NUCLEAR BA RECEPTOR FXR AND ITS BIOLOGY

FXR has been identified as a main nuclear BA receptor,[7,11,12] controlling synthesis and uptake of BAs as well as stimulating their elimination from liver. FXR is predominantly expressed in organs involved in BA transport and/or metabolism, such as liver, ileum, kidney, and adrenal glands.[13–15] As many other NRs, it exerts its transcriptional activity by heterodimer formation with another NR retinoid X receptor (RXR, NR2B1).[13,16] To initiate gene transcription, the FXR-RXR heterodimer binds to so-called inverted repeat 1 (IR-1) within the promoter sequence of target genes.[17] Four FXRα isoforms coded as FXRα1-4 have been described,[18] which have identical DNA-binding domain but may differ in gene regulation because of differences in ligand-dependent recruitment of coactivator/corepressor proteins, heterodimer formation with RXR, or DNA binding.[15,19,20]

The central role of FXR encompasses the regulation of the enterohepatic circulation and intracellular load of BAs (**Fig. 1**). By inhibition of the basolateral uptake transporter sodium/taurocholate cotransporting polypeptide, solute carrier family 10, member 1 (NTCP; SLC10A1) and upregulation of the canalicular export transporter bile salt export pump (BSEP; ABCB11) in hepatocytes, FXR reduces