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Targeting nuclear receptors for the treatment of fatty liver disease

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ABSTRACT

Ligand-activated nuclear receptors, including peroxisome proliferator-activated receptor alpha (PPARα), pregnane X receptor, and constitutive androstane receptor, were first identified as key regulators of the responses against chemical toxicants. However, numerous studies using mouse disease models and human samples have revealed critical roles for these receptors and others, such as PPARβ/δ, PPARγ, farnesoid X receptor (FXR), and liver X receptor (LXR), in maintaining nutrient/energy homeostasis in part through modulation of the gut-liver-adipose axis. Recently, disorders associated with disrupted nutrient/energy homeostasis, e.g., obesity, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD), are increasing worldwide. Notably, in NAFLD, a progressive subtype exists, designated as non-alcoholic steatohepatitis (NASH) that is characterized by typical histological features resembling alcoholic steatohepatitis (ASH), and NASH/ASH are recognized as major causes of hepatitis virus-unrelated liver cirrhosis and hepatocellular carcinoma. Since hepatic steatosis is basically caused by an imbalance between fat/energy influx and utilization, abnormal signaling of these nuclear receptors contribute to the pathogenesis of fatty liver disease. Standard therapeutic interventions have not been fully established for fatty liver disease, but some new agents that activate or inhibit nuclear receptor signaling have shown promise as possible therapeutic targets. In this review, we summarize recent findings on the roles of nuclear receptors in fatty liver disease and discuss future perspectives to develop promising pharmacological strategies targeting nuclear receptors for NAFLD/NASH.

Contents

Abbreviations: ABC, ATP-binding cassette transporter; ACACA, acetyl-CoA carboxylase α; ACACB, acetyl-CoA carboxylase β, ACLY, ATP citrate lyase; ACADM, medium-chain acyl-CoA dehydrogenase; ACOX1, acyl-CoA oxidase 1; AFB1, aflatoxin B1; AMPK, adenosine monophosphate-activated protein kinase; ALD, alcoholic liver disease; ALT, alanine aminotransferase; ASH, alcoholic steatohepatitis; αSMA, α-smooth muscle actin; BA, bile acid; CAR, constitutive androstane receptor; CCl_4, carbon tetrachloride; CDCA, chenodeoxycholic acid; CPT1A, carnitine palmitoyl-CoA transferase 1α; CTLN2, adult-onset type II citrullinemia; CYP, cytochrome P450; CYP7A1, cholesterol 7α hydroxylase; DR, direct repeat; DSS, dextran sulfate sodium; FA, fatty acid; FABP, fatty acid-binding protein; FASN, fatty acid synthase; FGF, fibroblast growth factor; Fra, Fos-related antigen; FSP27, fat-specific protein 27; FXR, farnesoid X receptor; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL, high-density lipoprotein; Hes6, hairy and enhancer of split 6; HSC, hepatic stellate cell; IBD, inflammatory bowel disease; IL, interleukin; LXR, liver X receptor; MCD, methionine- and choline-deficient; MCP1, monocyte chemoattractant protein 1; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor kappa B; NRF2, nuclear factor erythroid 2; OCA, obeticholic acid; OST, organic solute transporter; PGC1α, PPARγ coactivator 1α; PD, pancreaticoduodenectomy; PP, peroxisome proliferator; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor; SHP, small heterodimer partner; SLC25A20, carnitine-acylcarnitine translocase; SREBP, sterol-regulatory element-binding protein; TAG, triacylglycerol; TLR, Toll-like receptor; TNFα, tumor necrosis factor α; TZD, thiazolidinedione; WAT, white adipose tissue.

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1. Introduction

1.1. Liver as a main regulator of whole-body metabolism

Liver is the largest solid organ in the body playing a crucial role in maintaining energy homeostasis through metabolism of various nutrients. For example, the main symptoms and signs of acute liver failure are jaundice (impaired bilirubin conjugation/excretion), bleeding tendency (impaired synthesis of coagulation factors), and consciousness disturbance (impaired detoxification of ammonia and other neurotoxic metabolites). Patients having liver cirrhosis often exhibit impaired glucose metabolism (insulin resistance and diabetes), protein/amino acid metabolism (decreased albumin and branched-chain amino acids and increased aromatic amino acids), and lipid metabolism (hypocholesterolemia). These clinical findings mirror a key role of the liver in whole-body metabolism.

Infection with hepatotropic viruses and parasites, autoimmunity, intake of ethanol and certain drugs/medications, and exposure to occupational and environmental toxicants cause liver damage. In Asia, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are among the main causes for chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). Recent advances in antiviral therapies, such as nucleoside analogues for HBV and pegylated interferon/ribavirin and direct-acting antiviral agents for HCV, have improved the quality of life and survival for HBV- or HCV-infected patients. Further improvements in preventive/therapeutic strategies will lead to reduced incidence and mortality of patients having hepatitis virus-related diseases.

Metabolic derangements also cause chronic liver disease, such as fatty liver disease, glycogen storage disease, and hemochromatosis. Fatty liver disease refers to a pathological spectrum ranging from lipid accumulation in hepatocytes (steatosis) to the development of accompanying hepatocyte degeneration (ballooning, Mallory-Denk body) and hepatic inflammation (steatohepatitis), eventually leading to liver fibrosis/cirrhosis, portal hypertension, decompensated liver failure, and HCC (Cohen, Horton, & Hobbs, 2011). Although the mechanism of fatty liver disease may vary according to the etiologies, the liver pathology is often indistinguishable. Therefore, fatty liver diseases are classified according to their etiology/cause, i.e., long-term excess ethanol consumption [alcoholic liver disease/steatohepatitis (ALD/ASH)], overnutrition, visceral obesity, and metabolic syndrome without ethanol intake [non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH)], occupational/environmental chemical exposure [toxicant-associated fatty liver disease/steatohepatitis], and others (e.g., drug-induced steatohepatitis and steatohepatitis following gastrointestinal surgery).

1.2. NAFLD/NASH - emerging liver disease

The worldwide spread of sedentary lifestyle and diet westernization has increased a prevalence of NAFLD in many countries among wider generations. In Japan, approximately 30% of Japanese upon annual health checkups were found to have NAFLD (Kojima, Watanabe, Numata, Ogawa, & Matsuzaki, 2003; Eguchi et al., 2012), which extrapolates to an estimated 20 million NAFLD patients nationwide. The prevalence of NAFLD in junior high school students was also estimated as approximately 4% in certain areas of Japan (Tsuruta et al., 2010). NAFLD is associated with obesity, insulin resistance, diabetes, hypertension, dyslipidemia, atherosclerosis, and systemic inflammation, representing hepatic manifestation of metabolic syndrome. Although it remains controversial whether NAFLD is a cause or a result of glucose intolerance and insulin resistance, a prospective study demonstrated higher risk of diabetes and cardiovascular events in non-diabetic humans with NAFLD compared with those without NAFLD (Heianza et al., 2014). Additionally, liver with significant steatosis is more susceptible for hepatotoxicants and retards/impairs regeneration following partial hepatectomy (Kele et al., 2013). Therefore, NAFLD is considered as a detrimental condition necessitating appropriate therapeutic interventions.

Dr. Ludwig, a pathologist in Mayo Clinic, proposed a term non-alcoholic steatohepatitis (NASH) in 1980 (Ludwig, Viggiano, McGill, & Oh, 1980). He described 20 non-alcoholic patients having histological findings as compatible with ASH, such as fatty changes, focal necrosis, ballooned hepatocytes with Mallory-Denk bodies, lobular inflammation, and perisinusoidal/perivenular fibrosis. Clinically, most of these patients were obese and 25% had diabetes. At present, NAFLD is classified into two categories according to liver pathology: non-alcoholic fatty liver (NAFL, previously designated as simple steatosis) and NASH. NASH is defined by the presence of hepatocyte ballooning, lobular inflammation, and/or fibrosis in addition to macrovesicular steatosis, and NAFL is characterized as macrovesicular steatosis without ballooned hepatocytes (Hashimoto, Tokushige, & Ludwig, 2015). This pathology-based classification stems from the concept that NASH can progress into advanced liver fibrosis and the prognosis is poorer than that of NAFL and exhibited the clinical outcome different from NAFL. Indeed, in our NASH cases with obesity, diabetes, hypertension, and dyslipidemia, ballooned hepatocytes were detected in the initial biopsied samples, in which liver fibrosis apparently progressed in 5 years (Fig. 1). Matteoni et al. identified that the outcomes of cirrhosis and liver-related death were more frequent in NAFLD patients with ballooned hepatocytes than in those without ballooned hepatocytes (Matteoni et al., 1999). Others reported that the survival of NASH patients, but not NAFL patients, was significantly lower than an age- and sex-matched reference population (Ekstedt et al., 2006). Based on these findings, the notion that NASH is a serious and progressive type of NAFLD has generally been accepted. The diagnosis of NASH and evaluation of histological severity of NAFLD are performed by the pathological findings of the liver, but liver biopsy is somewhat invasive and costly. Additionally, sampling errors and differences in diagnostic accuracy between independent pathologists can sometimes be problematic. Therefore, less invasive and more accurate strategies to discriminate between NAFL and NASH and predict actual steatosis/inflammation/fibrosis instead of liver biopsy have been evaluated (Fujimori et al., 2016; Hatta et al., 2010; Kitabatake et al., 2017; Matsubara et al., 2012; Tanaka, Ichijo, et al., 2006; Tanaka, Tanaka, et al., 2006; Tanaka, Matsubara, Krausz, Patterson, & Gonzalez, 2012; Tsutsui et al., 2010). Recent studies demonstrated that the presence of fibrosis, but not hepatocyte ballooning, was a determinant of poor prognosis in NAFLD patients (Angulo et al., 2015; Loomba & Chalasani, 2015). Indeed, such a case of NAFLD with careful 27-year follow-up was examined (Nagaya et al., 2008). This patient was diagnosed as having NAFL at the first liver biopsy but gradually developed into cirrhosis and HCC over 20 years. This case teaches us that NAFL is not always benign. Additionally, HCC may occur from NAFL regardless of the absence of advanced fibrosis, past HBV infection, and regular ethanol consumption (Kimura et al., 2017). Although key factors affecting clinical course and outcome of NAFLD and methods to predict fibrosis progression and HCC development have not been identified, attenuating steatosis, hepatic injury, and inflammation and inhibiting fibrosis progression are promising strategies to improve the prognosis of NAFLD/NASH patients.

Understanding NAFLD/NASH pathogenesis is mandatory for developing novel therapeutic intervention strategies. Insulin resistance and

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