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The role of fibroblast growth factor 21 in the pathogenesis of non-alcoholic fatty liver disease and implications for therapy☆

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) includes a cluster of liver disorders ranging from simple fatty liver to non-alcoholic steatohepatitis (NASH) and cirrhosis. Due to its liver and vascular complications, NAFLD has become a public health problem with high morbidity and mortality. The pathogenesis of NAFLD is considered a "multi-hit hypothesis" that involves lipotoxicity, oxidative stress, endoplasmic reticulum stress, a chronic inflammatory state and mitochondrial dysfunction. Fibroblast growth factor 21 (FGF21) is a member of the fibroblast growth factor family with multiple metabolic functions. FGF21 directly regulates lipid metabolism and reduces hepatic lipid accumulation in an insulin-independent manner. Several studies have shown that FGF21 can ameliorate the "multi-hits" in the pathogenesis of NAFLD. The administration of FGF21 reverses hepatic steatosis, counteracts obesity and alleviates insulin resistance in rodents and nonhuman primates. Using several strategies, we show that the reversal of simple fatty liver and NASH is mediated by activation of the FGF21 signaling pathway. In this review, we describe the molecular mechanisms involved in the onset and/or progression of NAFLD, and review the current literature to highlight the therapeutic procedures associated with the FGF21 signaling pathway for simple fatty liver and NASH, which are the two most important types of NAFLD.

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; FGF21, fibroblast growth factor 21; SREBP-1c, sterol regulatory element-binding protein-1c; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; SCD1, stearoyl-CoA desaturase 1; ChREBP, carbohydrate response element binding protein; PKC, protein kinase C; ERK, extracellular regulated protein kinases; ROS, reactive oxygen species; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein; JNK, c-jun N-terminal kinase; IκB, inhibitor of nuclear factor-κB; NF-κB, nuclear factor-κB; CHOP, CCAAT enhancer binding protein homologous protein; FGFR, fibroblast growth factor receptor; PPARα, peroxisome proliferator activated receptor α; AMPK, AMP-activated protein kinase; SIRT1, sirtuin 1; PPARγ, peroxisome proliferators-activated receptor γ; UCP-1, uncoupling protein 1; UCP-2, uncoupling protein 2; PI3K, phosphatidylinositol 3-kinase; ATF4, activating transcription factor 4; OLETF, Otsuka Long Evans Tokushima Fatty; GLP-1, glucagon-like peptide-1; MCAD, medium-chain acyl-CoA dehydrogenase.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) includes a cluster of liver disorders ranging from simple fatty liver to non-alcoholic steatohepatitis (NASH) to cirrhosis [1]. A sedentary lifestyle along with excessive energy intake contributes to obesity, insulin resistance and NAFLD [1]. NAFLD is a public health problem with high morbidity and mortality due to its liver and vascular complications [1]. The current therapies are limited to reducing weight and improving insulin sensitivity with drugs or lifestyle interventions, such as dietary changes and physical activity, which have uncertain therapeutic effects [1].

Fibroblast growth factor 21 (FGF21) is a member of the fibroblast growth factor family with multiple metabolic functions [2]. The administration of FGF21 reverses hepatic steatosis, counteracts obesity, and alleviates insulin resistance and dyslipidemia in both rodents and nonhuman primates. These findings support its development as a novel therapy for the treatment of NAFLD and other metabolic disorders [3–9]. In this review article, we describe the molecular mechanisms involved in the onset and/or progression of NAFLD. Furthermore, we review the current literature to highlight the therapeutic procedures associated with the FGF21 signaling pathway for simple fatty liver and NASH, which are the two most important types of NAFLD.

2. The Pathogenesis of NAFLD

The pathogenesis of NAFLD has been modified to the "multi-hit hypothesis" from the "two-hit hypothesis" [10]. The "first-hit" is known as hepatic lipid accumulation/steatosis, which is the initial histological characteristic of NAFLD [11]. Insulin resistance causes an imbalance of fatty acid metabolism of hepatocytes and further contributes to hepatic steatosis [10]. Under physiological conditions, insulin suppresses the lipolysis of white adipose tissue and hepatic gluconeogenesis and also promotes hepatic lipogenesis by stimulating the transcription of sterol regulatory element-binding protein-1c (SREBP-1c). SREBP-1c is a master regulator of lipogenesis that regulates the transcription of acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) and stearoyl-CoA desaturase 1 (SCD1) [12,13]. However, in some insulin-resistant states, including obesity, type 2 diabetes and metabolic syndrome, lipolysis and hepatic gluconeogenesis are not inhibited by insulin. However, insulin retains the ability to effectively promote hepatic lipogenesis [14]. Elevated lipolysis of white adipose tissue increases plasma free fatty acids and enhances gluconeogenesis. These changes result in hyperglycemia and further increase de novo lipogenesis by stimulating carbohydrate response element binding protein (ChREBP) [14]. In NAFLD patients, approximately 60% of hepatic lipid accumulation is derived from the re-esterification of plasma free fatty acids. 26% occurs by de novo lipogenesis and 14% is derived from dietary fatty acids [15]. Additional lipids are deposited in the liver and simple fatty liver histologically manifests as steatosis with more than 5% hepatic lipid accumulation [11].

The exposure and overload of fatty acid harm hepatocytes by intracellular accumulation of lipid intermediates, such as diglycerides and ceramides, which is defined as lipotoxicity [16]. The lipids and intermediates induce endoplasmic reticulum stress and mitochondrial dysfunction directly or via activation of Toll-like receptors 2 and 4 [16]. Ceramides activate protein kinase C (PKC), inhibit Akt and increase protein phosphatase 2A levels. The increase in protein phosphatase 2A levels contributes to mitochondrial dysfunction and endoplasmic reticulum stress [17]. In addition, the accumulation of lipids and intermediates activates p38 mitogen-activated protein kinase, extracellular regulated protein kinases (ERK) and c-Jun. The activation of these pathways further exacerbates insulin resistance [18]. Elevated fatty acid β-oxidation increases reactive oxygen species (ROS) and activates oxidative stress [16]. The hepatic lipid accumulation and intracellular stresses activate the transcription and release of pro-inflammatory factors, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) [19,20]. A sedentary lifestyle in conjunction excessive energy intake promotes obesity and dysfunction of white adipose tissue. White adipose tissue secretes more TNF-α and IL-6 and reduces the secretion of adiponectin [20]. The elevated circulating levels of pro-inflammatory cytokines and reduced anti-inflammatory factors cause a chronic low-grade inflammatory state that is recognized as an important pathogenic mechanism of NAFLD [20,21].

These "hits" further deteriorate insulin resistance and initiate inflammatory signaling pathways and apoptosis cascades [10]. TNF-α activates c-Jun N-terminal kinase (JNK), PKC and inhibitor of nuclear factor-κB (IκB), which inhibits insulin signal and triggers inflammatory pathways [20]. TNF-α also activates de novo ceramide synthesis by stimulating sphingomyelinase [22]. IL-6 stimulates Janus kinase activation and induces the phosphorylation of signal transducters and activators of transcription to increase the transcription of the suppressor of cytokine signaling and promote insulin resistance [23]. An increase of ROS levels and oxidative stress triggers the ROS–PKC–nuclear factor-κB (NF-κB) pathway and further activates inflammatory signaling pathways that stimulate the infiltration of inflammatory cells [10,20]. Endoplasmic reticulum stress also stimulates cell apoptosis through both CCAAT enhancer binding protein homologous protein (CHOP)-induced and JNK-mediated mitochondria-dependent apoptosis pathways [24,25].

Hepatocytes with excess lipid accumulation are susceptible to subsequent "multi-hits", including oxidative stress, endoplasmic reticulum stress, a chronic inflammatory state and mitochondrial dysfunction. These changes lead to the infiltration of inflammatory cells, activation of inflammatory signaling pathways and hepatocytes apoptosis. Additionally, these changes promote the progression from simple fatty liver to NASH [10] (Fig. 1). Previous studies have shown more than 25% of NASH patients will develop cirrhosis within 10 years, and a few patients will develop end-stage liver disease and hepatocellular carcinoma [26]. Thus, NASH is a turning point from benign to irreversible lesions including cirrhosis and hepatocellular carcinoma [26].

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