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Advances in Research on PNPLA3 in Non-alcoholic Fatty Liver Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease and a significant cause of hepatocellular carcinoma, defined by the presence of ≥5% hepatic steatosis in patients without a significant history of alcohol consumption or other liver diseases. The prevalence of NAFLD is increasing annually and is expected to become one of the major global health issues. If not diagnosed and treated promptly, NAFLD can lead to liver fibrosis, cirrhosis, and liver cancer. Therefore, elucidating the mechanisms of NAFLD development is of great significance for its diagnosis and treatment. The patatin-like phospholipase domain-containing protein 3 gene (PNPLA3) encodes a protein with triglyceride hydrolase activity. This research has confirmed that PNPLA3 plays a crucial role in NAFLD, closely associated with liver lipid metabolism, inflammatory response, and liver fibrosis. This paper reviews the role and potential mechanisms of PNPLA3 in NAFLD, aiming to provide new therapeutic strategies and diagnostic directions for the pathogenesis of this disease.

Keywords

Non-alcoholic fatty liver disease; PNPLA3; mechanism of action

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases and has become a global public health issue. The incidence of NAFLD is rising annually and is prevalent worldwide [1]. In China, NAFLD has become the most common disease, particularly with a significant increase in incidence among young people [2]. NAFLD is currently defined as a spectrum of diseases characterized by the presence of steatosis in more than 5% of hepatocytes, associated with metabolic risk factors, excluding excessive alcohol consumption or other chronic liver diseases [3]. It is a complex metabolic disease caused by intricate interactions between genetics, host metabolism, and the environment [4]. NAFLD is primarily divided into non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) based on histological features. However, as the disease progresses, it can lead to liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [5]. As a metabolic disease, NAFLD is mainly associated with metabolic syndrome conditions such as obesity and diabetes [6]. Initially, NAFLD was believed to develop through a "two-hit" hypothesis, where insulin resistance caused the first hit, leading to hepatic steatosis, followed by oxidative stress as the second hit, inducing inflammation and hepatocyte death, ultimately resulting in disease [7]. However, the recent "multiple-hit" hypothesis provides a more comprehensive understanding of NAFLD pathogenesis [8]. Overall, the mechanisms underlying NAFLD are not yet fully understood, posing a challenge for treatment and necessitating further research to develop targeted therapeutic strategies to control disease progression.

The risk of developing NAFLD varies significantly among individuals and is determined by environmental and genetic susceptibility. Genome-wide association studies have revealed a robust relationship between PNPLA3 gene variants and NAFLD [9]. The patatin-like phospholipase domain-containing (PNPLA) family has nine members,

playing a role in regulating adipocyte differentiation, with PNPLA3 inhibiting protein synthesis through its close association with lipid droplets [10]. PNPLA3 is expressed in various tissues and organs, such as the liver, retina, skin, and spleen, with the highest expression in the liver [11]. the PNPLA3-I148M variant (rs738409) is closely associated with hepatic steatosis and can lead to the progression of NAFLD [12]. The PNPLA3-I148M variant can escape ubiquitin-mediated degradation under fasting conditions and inhibit ATGL activity by sequestering the ATGL cofactor α/β-hydrolase domain-containing protein 5 (ABHD5), thereby influencing NAFLD susceptibility [13].

Given the association of PNPLA3 with the development and progression of NAFLD, it holds significant potential for therapeutic interventions. This review aims to summarize the role and mechanisms of PNPLA3 in NAFLD, providing new insights for the development of novel therapeutic targets.

1. Overview of PNPLA3

The PNPLA3 gene is located on human chromosome 22 and encodes a membrane-bound protein composed of 481 amino acids, which is highly expressed in liver tissues [14]. The PNPLA3 protein has a conserved patatin-like phospholipase domain at its N-terminus, which possesses lipase and lipid acyl hydrolase activities. The PNPLA3 variant (rs738409) involves a cytosine-to-guanine substitution, resulting in an amino acid change from isoleucine to methionine at position 148 [15]. This variant is significantly associated with the development of NAFLD, leading to increased synthesis of fatty acids and triglycerides in the liver and affecting triglyceride hydrolysis [16]. The genotypes of PNPLA3 rs738409 primarily include CC, CG, and GG types. Studies have found that carriers of the G allele of PNPLA3 rs738409 have a higher risk of developing liver fibrosis compared to non-carriers [17]. Additionally, research suggests that the PNPLA3 rs738409 C>G variant (wild-type to mutant) promotes the progression of NAFLD to liver fibrosis and even cirrhosis, resulting in irreversible liver damage [18].

2. Mechanisms of PNPLA3 in Influencing NAFLD

Research has shown that lipid metabolism, inflammatory responses, liver fibrosis, and insulin resistance can all promote the development and progression of NAFLD. Hepatic lipid accumulation, in conjunction with insulin resistance, oxidative stress, mitochondrial dysfunction, and genetic susceptibility, collectively contribute to NAFLD progression. This can eventually lead to hepatitis, liver fibrosis, cirrhosis, and hepatocellular carcinoma, resulting in multiple impacts on the liver [19].

2.1 PNPLA3 and Lipid Metabolism

Hepatic steatosis is the first stage in the development of NAFLD, with triglyceride accumulation in fat leading to disease progression. Studies have found that PNPLA3 (148M) promotes hepatic steatosis by accumulating on liver lipid droplets. The ubiquitin-proteasome system and autophagy pathways help degrade PNPLA3, thereby reversing hepatic steatosis [20], This finding is consistent with results from rodent experiments [21]. Therefore, targeting PNPLA3 to reduce hepatic triglyceride levels could be a strategy to control NAFLD progression. PNPLA3-I148M induces morphological changes in the Golgi apparatus, increasing lipid droplet-Golgi contact points, resulting in lipid droplet accumulation [22]. Additionally, the ER-α binding site within the PNPLA3 enhancer drives the upregulation of PNPLA3 I148M, affecting lipid metabolism [23]. PNPLA3 typically mediates triglyceride remodeling, and this function is impaired in carriers of PNPLA3 I148M [24], significantly reducing the hydrolysis rate of [^{3}H]triglycerides during lipolysis [25]. Furthermore, the interaction between CGI-58 and PNPLA3 affects triglyceride hydrolysis by lipase, promoting steatosis [26]. In animal models, we found that PNPLA3 expression levels in hepatocytes are correlated with the expression levels of lipogenesis-related genes such as ME1, SPOT14, and SCD1 [27].

2.2 PNPLA3 and Inflammatory Response

Liver inflammation is a key mechanism in the pathogenesis of NAFLD, triggered by both internal factors (such as mitochondrial dysfunction and endoplasmic reticulum stress) and external factors (such as the gut). Cellular and molecular response mechanisms can induce chronic inflammatory responses that promote liver inflammation and potentially lead to persistent inflammation and disease progression [28, 29]. Hepatocyte injury activates Kupffer cells, leading to the production of inflammatory cytokines and chemokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which cause liver cell damage. IL-6 is involved in tissue homeostasis and metabolism, and its excessive activation is related to the pathogenesis of inflammatory diseases [30], Blocking IL-6 signaling can inhibit NAFLD progression [31]; nhibiting IL-6 activity reduces the susceptibility of PNPLA3 to NAFLD.

Additionally, CXC chemokines are key mediators of leukocyte infiltration in liver diseases [32], and IL-8 induced by PNPLA3 triggers hepatic inflammatory responses, accelerating NAFLD progression [33]. Reducing PNPLA3 levels can lead to reduced liver inflammation, potentially due to lower levels of chemokines attracting fewer inflammatory cells [34].

2.3 PNPLA3 and Liver Fibrosis

Liver fibrosis is considered a major determinant of mortality in NAFLD patients, with hepatic stellate cell activation causing hepatocyte damage and ultimately leading to fibrosis[35].PNPLA3 levels increase as liver fibrosis progresses from mild to severe, and it is closely associated with the staging of liver fibrosis and the expression of α-SMA in liver tissues [36]. PNPLA3-I148M promotes fibrosis progression by causing mitochondrial dysfunction in the LX-2 hepatic stellate cell line through cholesterol accumulation [13]. A retrospective study found that the GG genotype of PNPLA3 rs738409 polymorphism in hepatitis C patients is associated with hepatic steatosis and fibrosis [37], consistent with recent research findings [38]. In mouse models, we found that inhibiting PNPLA3 reduces liver fibrosis, potentially related to collagen breakdown caused by inhibition of tissue metalloproteinase family members [39]. The PNPLA3 rs738409 G allele promotes fibrosis development by activating specific fibrogenic pathways and affects fibrosis severity through portal inflammation [40].

3. Discussion

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, encompassing a spectrum of conditions including non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC). The prevalence of NAFLD is steadily increasing, with an estimated global prevalence of approximately 25% [41]. In addition to liver-related diseases, NAFLD also increases the risk of type 2 diabetes (T2DM), cardiovascular diseases, and chronic kidney disease [42]. The currently favored theory regarding the pathogenesis of NAFLD is the "multiple-hit" hypothesis, which suggests that various factors interact to form a vicious cycle of "hepatic steatosis-metabolic dysregulation-inflammation-insulin resistance-worsening hepatic metabolic dysregulation" within the liver [43].

The risk of developing NAFLD and its associated complications varies greatly among individuals, influenced by the interaction between environmental factors and a polygenic host background. The I148M PNPLA3 variant has been identified as a major common genetic determinant of NAFLD [44], associated with the risk of NAFLD in both adults and children [45]. PNPLA3 is a lipid droplet protein primarily expressed in the liver and adipose tissue. Its biological function involves transferring unsaturated fatty acids from triglycerides to phospholipids, a function impaired by the PNPLA3 I148M variant [46]. PNPLA3 is a lipid droplet protein primarily expressed in the liver and adipose tissue. Its biological function involves transferring unsaturated fatty acids from triglycerides to phospholipids, a function impaired by the PNPLA3 I148M variant [39], and even slowing the progression of renal injury [47]. Incorporating PNPLA3 into risk stratification models can improve the accuracy of NAFLD prediction. Although PNPLA3 is involved in every stage of NAFLD disease progression, its underlying pathophysiological mechanisms remain unclear. Further basic experimental and clinical research is needed to evaluate the role of PNPLA3 in NAFLD and to provide more targeted therapeutic strategies.

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