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Review Article

An Overview of Lipid Metabolism and Nonalcoholic Fatty Liver Disease

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The occurrence of nonalcoholic fatty liver disease (NAFLD) is associated with major abnormalities of hepatic lipid metabolism. We propose that lipid abnormalities directly or indirectly contribute to NAFLD, especially fatty acid accumulation, arachidonic acid metabolic disturbance, and ceramide overload. The effects of lipid intake and accumulation on NAFLD and NAFLD treatment are explained with theoretical and experimental details. Overall, these findings provide further understanding of lipid metabolism in NAFLD and may lead to novel therapies.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases in Western countries, and its prevalence is increasing worldwide [1, 2]. Recently, the prevalence of NAFLD was reported to be higher in South America and Asia than in Europe and USA [3]. The spectrum of NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), which is caused by excessive caloric intake without

excessive alcohol consumption [4]. Fatty liver development without heavy drinking is generally called nonalcoholic fatty liver (NAFL) [5]. NASH is the intensified form of NAFL, which is associated with inflammation and different degrees of fibrosis [5, 6]. Nearly 10%–25% of patients with NASH may develop cirrhosis [7]. However, in some patients, NASH can progress to hepatocellular carcinoma without significant cirrhosis [8]. NASH is projected to be the leading cause of liver transplantation in USA by 2020, which is due to increasing disease prevalence and ineffective treatment [9].

Recent studies on the relationship between NAFLD and lipid disorders have demonstrated that disruption of the lipid metabolism balance in the liver causes lipid accumulation and consequently, hepatotoxicity, and NAFLD [10–12]. Dyslipidemia manifests as an increase in plasma free fatty acids (FFA), oxidized low-density lipoprotein (ox-LDL), and triglycerides (TGs), which cause inflammation, oxidative stress, lipotoxicity, and liver damage [11, 12]. Dyslipidemia can occur at all stages of NAFLD and aggravate the NAFLD process. Few studies have emphasized on the role of ceramide and arachidonic acid metabolism in the development of NAFLD. Therefore, we reviewed the metabolic pathways contributing to the pathogenesis of NAFLD by elaborating the role of fatty acid (FA), ceramide, and arachidonic acid as well as studying lipid uptake and potential treatments.

2. Factors Influencing NAFLD

Weight gain and obesity are primary risk factors for the development of fatty liver. Further evidence suggests that diet composition, particularly carbohydrates, has an important role in the progression of disease to NASH and fibrosis [6].

2.1. Obesity and NAFLD. Obesity refers to the excessive accumulation of body fat due to the imbalance of cellular lipogenic and lipolytic activities [13]. The incidence of obesity has been increasing worldwide for the past two decades; the prevalence in South America, Middle East, Asia, the United States, and Europe was reported to be 31%, 32%, 27%, 24%, and 23%, respectively [14–16]. In addition, the morbidity of NAFLD is increasing [17]. Although the awareness emphasis on healthy lifestyle is increasing, obesity remains a public health problem, leading to many preventable complications such as NAFLD [5]. A study indicated that 80% of NAFLD patients are obese (body mass index (BMI) > 30 kg/m²) as well as the large amount of visceral adipose tissue (VAT) in morbidly obese (BMI > 40 kg/m²) individuals which leads to high morbidity of NAFLD [18]. Ciupińska-Kajor et al. reported that morbid obesity is associated with a higher incidence of more advanced fibrosis and confirmed that severe fibrosis and cirrhosis are common to a greater extent in morbidly obese patients with NAFLD [19]. Therefore, NAFLD treatments are focused on weight loss through lifestyle changes, antiobesity drugs, and bariatric surgery [20].

2.2. High-Carbohydrate Diet Intake and NAFLD. Excessive carbohydrate intake is closely associated with the occurrence of NAFLD. It has been demonstrated that a high-carbohydrate diet pattern characterized by high intake of fruits, cakes, ice cream, soft drinks, and candied fruits is positively associated with the prevalence of NAFLD [21]. The higher risk of NAFLD due to fruits, sugared beverages, and snacks may be because these foods contain large amounts of sugars such as fructose and sucrose that have been associated with the pathophysiology of NAFLD. Among the three most important carbohydrates (glucose, fructose, and sucrose), fructose and sucrose have some influence on the epidemiology of NAFLD. Fructose is the main component of sweeteners, and its intake has tripled over the past decade

[22]. It can cause liver damage through a variety of mechanisms [23]. In fact, several epidemiological and experimental studies have supported the potential pathogenic effects of increased fructose consumption [24, 25]. Different animal models have been studied to explore the mechanism of fructose-induced NAFLD. In humans, excess fructose intake is associated with elevated plasma TG level and hepatic lipid deposition [26]. A study demonstrated that high-calorie foods (65% sucrose foods) for 8 weeks resulted in obesity, insulin resistance, and macrovesicular steatosis in C57BL/6 mice [27]. Hence, targeting excessive fructose and sucrose consumption that cause NAFLD, dietary guidelines have recommended to limit added sugars (primarily sucrose and high-fructose corn syrup (HFCS)) in the diet to a maximum 5%–10% of daily calories [28, 29].

3. Lipid Uptake in the Normal Liver and in NAFLD

The process of lipid uptake in the liver in both physiological and pathological conditions is mediated through liver FA binding protein (FABP1) and CD36. Abnormal protein regulation may lead to excessive hepatic accumulation of nonesterified FAs (NEFAs) and TG, causing cytotoxicity and resulting in NAFLD.

3.1. CD36-Mediated Lipid Uptake. CD36 is the major receptor involved in long-chain FA transport and TG storage and is expressed in several cells such as macrophages and monocytes [30] and tissues such as the liver, heart, and adipose [31]. It recognizes modified lipoproteins such as ox-LDL, promotes lipid-laden foam cell formation [32], and modulates events associated with lipid utilization. Recently, CD36 was found to play a crucial role in the liver by participating in FA uptake and storage and secretion of TG [33]. CD36 mediates FFA uptake in various tissues, and FA uptake has a significant role in hepatic steatosis; thus, abnormalities in CD36 may lead to hepatic steatosis [34]. The majority of NEFAs in the blood are bound to carrier proteins (mainly albumin), and their uptake requires dissociation from CD36-mediated carrier proteins [35]. Excessive hepatic accumulation of NEFAs and TG leads to cytotoxicity, resulting in NAFLD progression. Li et al. indicated that CD36 is the negative regulator of lipophagy in liver cells [36]. It has been reported that CD36 expression is significantly upregulated in hepatic tissues of NAFLD patients [37] and overexpression of CD36 in the liver increases TG accumulation and causes hepatic steatosis progression [38]. The localization of CD36 on the plasma membrane of liver cells was significantly higher in NASH patients than that in patients with normal liver and those with simple steatosis [39]. In the livers of mice with NASH, increased CD36 palmitoylation and CD36 localization on the plasma membrane of hepatocytes were observed. In addition, inhibition of CD36 palmitoylation protected mice from developing NASH [39]. Briefly, CD36 expression is increased in the liver of NAFLD patients, which leads to abnormal liver function and systemic abnormalities, including inflammation, hepatocyte damage, hepatic lipid accumulation, and fibrosis.

3.2. FABP1-Mediated Lipid Uptake. FABP1 or L-FABP is the first discovered member of the FABP family, with high concentrations in the liver, intestine, and kidney. In addition to CD36, FABP1 mediates the uptake, transport, and metabolism of long-chain FAs and other lipid ligands in cells [40]. It is a soluble protein commonly found in rodents (26% cytosolic protein; 200–400 μM) and humans (7%–10% cytosolic protein; 700–1,000 μM). Recent studies using cell and mice models have verified that FABP1 is the key regulator of lipid metabolism and steatosis in the liver [41]. In vitro studies revealed that FA uptake was significantly increased with FABP1 overexpression and was significantly decreased with FABP1 antisense ribonucleic acid (RNA) expression [42]. A Western diet of high saturated fat and high cholesterol could prevent diet-induced obesity and hepatic steatosis in FABP1^{-/-} mice, which reflected changes in the kinetics of saturated FA (SFA) utilization [42]. Human genetic variant of *L-FABP* gene is linked to abnormal lipid metabolism [42]. Studies have indicated that FFA-induced hepatic steatosis and liver injury can be improved by inhibiting FABP1 expression [41]. Downregulation of FABP1 has been identified as the new mechanism for preventing hepatic steatosis and liver injury [41]. Overall, similar to CD36, FABP1 overexpression can lead to abnormal liver functions such as dyslipidemia and hepatic steatosis.

4. Lipid Abnormalities in the Liver

Abnormal lipid accumulation in the liver is the pathophysiological feature of NAFLD [43]. Lipid abnormalities are of many types. This study mainly focuses on the FA-induced hepatotoxicity, arachidonic acid metabolism and inflammation, and hepatic ceramide overload and hepatic injury.

4.1. FA Accumulation and Hepatotoxicity. Lipotoxicity is defined as abnormal cellular lipid composition that leads to the accumulation of toxic lipids, organelle dysfunction, cellular damage, and chronic inflammation. In this study, we focused on the relationship between FA toxicity and NAFLD as well as lipotoxicity, which causes direct damage to mitochondria and peroxisomes [44, 45]. Mitochondrial damage results in the loss of membrane polarization, rendering mitochondria incapable of effectively completing β -oxidation and energy metabolism, hence further aggravating FA accumulation. FA exacerbates insulin resistance and promotes inflammation [46–50] and fibrosis [51–53] in progressively worsening liver cells, resulting in liver cell damage. Damaged liver cells release many inflammatory mediators. Inflammasomes, cytokines, chemokines and their receptors, and innate and adaptive immunity cells are all induced by liver inflammation and the direction of NASH treatment [46–49]. Liver inflammation results in the inactivation of tissue repair mechanisms. These mechanisms replace damaged liver cells by activating the staminal compartment, stimulating hepatocyte proliferation, and remodeling the extracellular matrix (ECM) [54, 55]. If inflammation persists for a longer period of time, ECM-forming cells are recruited and activated, leading to excessive deposition of

ECM and eventually liver fibrosis [56]. Briefly, FA accumulation causes mitochondrial damage that further aggravates FA accumulation and results in insulin resistance and, finally, liver inflammation and fibrosis.

4.2. Arachidonic Acid Metabolism and Inflammation. An elevated level of FFA in the liver is recognized as the leading cause of cell damage and death in NASH [57–60]. A recent study found that although the total lipid content increased, the liver FFA content remained unchanged in NAFLD patients. However, the FFA level in circulation may not be associated with that in cells. This may be because polyunsaturated FAs (PUFAs) play a key role, either proinflammatory or anti-inflammatory depending on their structure, in NAFLD progression [61]. Arachidonic acid is one of the long-chain polyunsaturated omega-6 FAs (n-6 PUFAs), which are the precursors of the potent proinflammatory eicosanoids [62, 63]. The progression from simple hepatic steatosis to NASH may be due to escalation of inflammation [64]. Histologically, both isolated steatosis and NASH present with intracellular lipid accumulation and lipid droplet (LD) formation in the cytoplasm of hepatocytes; however, no inflammation is observed in isolated steatosis, and pathological inflammation resulting in cell necrosis is observed in NASH. LDs are thought to be the source of overproduction of proinflammatory eicosanoids, presenting early involvement of arachidonic acid metabolites in NAFLD [65]. In addition, studies with a lipidomics approach on NAFLD patients have consistently demonstrated that a higher n-6:n-3 ratio in the blood and liver is associated with the presence and severity of NAFLD [61]. Another study used this approach to quantify the major lipid species in the liver [66] and provide some novel and interesting insights into the pathophysiology of NAFLD. An increase in the level of arachidonic acid and a decrease in the level of key n-3 FAs cause the ratio of n-6:n-3 FAs to increase. After, arachidonic acid (20:4n-6) is released from membrane phospholipids by phospholipase A2 and from the breakdown of phosphatidylinositol bisphosphate through diacylglycerol (DAG) by phospholipase C; it is promptly transformed into proinflammatory prostaglandins, thromboxanes, and leukotrienes by cyclooxygenase [67]. CYP4A14 is a hydroxylase that catalyzes omega-hydroxylation of medium-chain FAs and arachidonic acid in mice and is highly expressed in the liver. In both NAFLD patients and mouse models, CYP4A14 was reported to be significantly upregulated. In addition, CYP4A14 overexpression resulted in increased hepatic lipid accumulation in wild-type mice, whereas CYP4A14 ablation prevented NASH progression [68]. In conclusion, arachidonic acid induces inflammation and, thus, plays an important role in NAFLD.

4.3. Hepatic Ceramide Overload and Hepatic Injury. Ceramide, composed of an amino group of a sphingoid base, usually sphingosine and saturated or monounsaturated fatty acyl chains, forms the hydrophobic core of all the complex sphingolipids (sphingomyelin, cerebral gangliosides, and gangliosides) [57]. Ceramide is involved in key steps of the pathogenesis of NAFLD, including the disruption of insulin

sensitivity and mitochondrial metabolism, metabolic disturbance, and stimulation of cell death [69–72]. It has been confirmed that the level of hepatic ceramide is elevated in NAFLD and associated with the severity of liver disease [73–75]. Hepatic ceramide overload is caused by an increase in hydrolysis of sphingomyelin through acid sphingomyelinase (ASM). Several studies have reported that elevated levels of sphingolipid in the liver and plasma were consistent with the progress of hepatic insulin resistance, hepatic dysfunction, and steatosis in rodents [76, 77]. Generally, serine palmitoyl transferase (SPT) stimulates the binding of palmitoyl-CoA to serine to form sphingolipids. However, SPT can stimulate the binding of acyl-CoAs to amino acids to produce a group of atypical sphingoid bases such as 1-deoxysphingolipids. Sphingolipids, especially 1-deoxysphingolipids, were regarded as biomarkers of NAFLD progression in a recent omics approach [78]. Myostatin, an SPT inhibitor, reduced ceramide levels in the experimental models of NAFLD [79, 80]. In addition, ASM is associated with the process of simple steatosis to NASH. ASM mRNA levels are three-fold higher in NASH patients than those in healthy controls [81]. Moreover, ASM knockout mice are protected from diet-induced steatosis [82] and NASH [83]. The ASM activity is enhanced in NASH stimulated by proinflammatory substances such as TNF- α , reactive oxygen species (ROS), and death receptor ligands [84] and by increased SFAs, which are the key substrates for the de novo synthesis of ceramides. Mitochondria are the main cellular target of ceramide, which damages FA β -oxidation, promotes ROS production, TG accumulation, and insulin resistance [85, 86]. Inhibitors such as myriocin (SPT inhibitor) and fenretinide (inhibitor of the enzyme catalyzing DES1 synthesis [last step of bioactive ceramide synthesis]) have been found to ameliorate insulin resistance in experimental models of NAFLD [80, 87, 88]. In all these experiments, inhibition of ceramide synthesis was associated with reduction of hepatic steatosis [89]. Other mechanisms of ceramide lipotoxicity in NASH are as follows: imbalance of calcium homeostasis in the endoplasmic reticulum (ER), leading to ER stress-mediated apoptosis; activation of NLRP3 inflammasome, leading to autophagy damage; and increase in hepcidin expression, leading to liver iron overload [83, 90–93]. In addition, ASM activation may promote liver damage by interfering with the metabolism of methionine and phosphatidylcholine and, thus, contribute to permeabilization of the lysosomal membrane [83] and activation of hepatic stellate cells (HSCs) [81]. Moreover, ceramide has been reported to mediate many of the adverse effects of SFAs, especially palmitic acid, which is a substrate in the SPT response [71, 94]. However, weight loss was reported to reduce steatosis and hepatocellular damage and remarkably alter the expression of ceramide-related genes in the liver. Changes in calorie intake and fat consumption, particularly saturated fat, dramatically correlated with changes in the expression of ceramide-related genes [95]. Briefly, ceramide causes disruption of insulin sensitivity and mitochondrial metabolism, imbalance of calcium homeostasis in the ER, and ultimately liver injury.

5. Therapy

5.1. Lifestyle Changes and Medication. A strict diet control seems to be an attractive and safe method for treating NASH. Both the Mediterranean and ketogenic diets advocate a reduced intake of carbohydrates. In addition, more physical exercise routinely can prevent and relieve NAFLD by improving lipid homeostasis. Further, statins (lipid-lowering drugs) present some benefits for the liver.

The Mediterranean diet is characterized by decreased intake of sugars and refined carbohydrates and enhanced intake of monounsaturated and n-3 FAs [96]. Different types of lipids (e.g., n-3 and n-6) may have opposite net influence on inflammation, and therefore, the final biological net effect is determined by their relative proportion [57]. Unlike n-6, n-3 PUFAs have important anti-inflammatory effects; they reduce adipogenesis and increase fatty acid oxidation (FAO), leading to a decrease in hepatic steatosis [97–99]. Fish and n-3 PUFA intake are reported to be lower in NAFLD patients than in nonfatty liver patients. Similarly, a downward trend of n-3 FA, eicosapentaenoic acid (20:5n-3) and docosahexaenoic (22:6n-3), intake is observed in these patients considering multiple lipids [98, 99]. These two n-3 FAs have significant antiproliferative, anti-inflammatory, and modulatory effects on the metabolic and immune systems [57]. The observed decreasing trends in the intake of these key n-3 FAs may promote steatosis, inflammation, dyslipidemia, cell damage, and carcinogenic risk in NASH patients [100, 101]. This reveals the theoretical basis for NASH treatment with n-3 FAs [73]. To date, most studies have used the methods of complementing patients with n-3 PUFAs. In 2012, a meta-analysis of nine studies revealed that n-3 PUFA supplementation has a beneficial influence on the liver fat and liver enzyme level [102]. The Mediterranean diet results in reduced calories, which is acceptable by patients and should be encouraged.

Ketogenic diets (KDs) are very low in carbohydrates and high in fats and/or proteins compared with various diets and, therefore, have gained popularity [103]. Low-calorie, especially low-carbohydrate, KD quickly reduces liver fat content and related metabolic abnormalities [104]. KD has been reported to promote weight loss, reduce intrahepatic triglyceride content, and alleviate metabolic parameters in obese patients. In addition, KD was reported to provoke weight loss in rodents. However, maintaining a long-term KD stimulated the progression of NAFLD and systemic glucose intolerance in mice. Thus, the relationship between KD and systemic insulin resistance in humans and rodents remains to be elucidated [105].

Physical activity (PA) is an integral part of any therapeutic strategy for weight loss, and it may play an important role in preventing NAFLD [106–108]. Multiple cohort studies revealed that change in body weight was correlated with both the development and remission of NAFLD [109, 110]. In men, initiation of an exercise regimen was remarkably associated with NAFLD remission [111]. The role of PA in delaying NAFLD progression has been demonstrated to be beneficial in the presence and absence of one or more

metabolic syndromes [112]. In addition, an increase in PA prevents and/or retards NAFLD-related disease progression independent of weight loss [113, 114]. Dietary counseling and appropriate exercise should be combined and adjusted according to individual circumstances, targeting a gradual weight loss of 7%–10% [115, 116].

Atorvastatin and rosuvastatin [117] are widely used for treating dyslipidemia; however, they have not been well established as specific treatments for NAFLD. The guidelines of the European Association for the Study of the Liver (EASL)/European Association for the Study of Diabetes (EASD)/European Association for the Study of Obesity (EASO) [106] consider that statins have not been thoroughly tested. However, a large number of animal and human studies have demonstrated that the use of statins was safe in NAFLD, without an increase in the risk of hepatotoxicity, and may even significantly reduce aminotransferases. Animal data suggested that statins had certain beneficial effects on liver histology in NASH models [118]. Three post hoc analyses of randomized controlled trials in humans revealed that the use of atorvastatin had a beneficial effect on NAFLD in terms of liver enzyme reduction and ultrasonography improvement [118]. Statins may be the valuable option to be considered in patients with NAFLD/NASH, as it significantly reduces the risk of cardiovascular disease and liver cancer simultaneously [119–148].

5.2. Targeted Therapy. NAFLD is characterized by ectopic toxic lipid accumulation, which is due to an extensive derangement in hepatic lipid metabolism [149–151]. Underlying these abnormalities is a wide range of disorder of nuclear transcription factors that adjust lipid metabolism, inflammation, and fibrogenesis, which consist of CD36; peroxisome proliferator-activated receptor- (PPAR-) α , PPAR- δ , and PPAR- γ ; farnesoid X receptor (FXR); and sterol regulatory element binding protein 1 (SREBP-1), which are ideal targets for NAFLD treatment [152, 153].

CD36 is a FA receptor that plays a significant role in regulating lipid and glucose use, and the upregulation of CD36 expression is associated with NASH [154]. The RNA expression of nuclear factor kappa-B (NF- κ B), a key regulator involved in the inflammation process, can be affected by the manipulation of CD36 expression [155]. Several studies have indicated that abnormal expression of CD36 in the liver was markedly associated with insulin resistance, hyperinsulinemia, and steatosis in NAFLD patients [154]. CD36 expression was reported to be elevated in mouse models with genetic obesity and high-fat diet- (HFD-) induced fatty livers [37]. Hence, treatment strategies designed to reverse this process by restoring normal levels of CD36 may provide a new method for treating NAFLD. A study reported that the absence of CD36 in the liver remarkably retarded the development of hepatic steatosis, although FA level increased. In addition, CD36 deletion affected the blood FA composition and improved the serum markers of hepatic inflammation [156]. Further, hepatocyte-specific loss of CD36 was found to significantly improve whole body insulin sensitivity in HFD-fed mice [156]. Briefly, CD36 not only is a disease marker but also plays an active role in FA uptake and has a

significant influence on insulin sensitivity and hepatic lipid content and composition [157].

PPAR- α , a transcription factor, is mainly expressed in metabolically active tissues and regulates FAO. Lipid accumulation owing to FAO inhibition indirectly accelerates fibrogenesis by promoting inflammation. Agonists of PPAR- α presented beneficial effects of reversing deficiencies in FAO and improving NAFLD progression in animal and cell models [157, 158]. A randomized controlled trial demonstrated that pharmacological modulation of the PPAR- α nuclear receptor leads to substantial histological improvements in NASH patients, including the improvement of steatohepatitis and alleviation of cardiometabolic risk profile, with a sound security profile [157]. Several studies have emphasized on developing dual agonists against PPAR- α and PPAR- δ . The effects of PPAR- α promoted FAO [158], and those of PPAR- δ reduced de novo lipogenesis and inhibited inflammation [159, 160]. One such agent, elafibranor (GFT505), improved diet-induced NASH in rodents [160]. Elafibranor has been reported to improve hepatic and peripheral insulin sensitivity in humans [161]. In addition, improvements in NASH, insulin resistance, and dyslipidemia to some extent have been reported in long-term studies [157]. In summary, PPAR- α is important in reversing deficiencies in FAO and alleviating NAFLD progression.

The most widely studied drugs with potential benefits for NASH are thiazolidinediones (TZDs). TZDs such as pioglitazone and rosiglitazone activate the nuclear receptor, PPAR- γ , allowing preadipocyte differentiation into insulin-sensitive, fat-storing adipocytes [106]. It is noteworthy that the PPAR- γ ligands attenuate liver fibrosis by inhibiting transdifferentiation of liver stellate cells into activated myofibroblasts, suggesting a direct hepatoprotective influence. In addition, they present anti-inflammatory effects and increase circulating adiponectin, which is an adipokine that resists adipogenesis, and insulin sensitization [106]. Similarly, a clinical research study reported that they ameliorate glycemic control and NASH-associated parameters [162–164]. However, rosiglitazone has been withdrawn from the market in most of the countries due to the deficiency and the possible long-term treatment. We hold the opinion that it is necessary to overcome this obstacle [108, 117]. According to the current guidelines, pioglitazone is useful and is advocated for elderly patients with advanced fibrosis, confirmed by biopsy, who are unable to adopt or maintain lifestyle interventions and have persistent metabolic risk factors; however, pioglitazone should be administered to patients with T2DM and/or heart failure with caution [162, 165, 166]. Meta-analyses have revealed that rosiglitazone and pioglitazone were remarkably better than placebo in relieving balloon formation, lobular inflammation, and steatosis [167, 168]. Pharmacological inhibition of PPAR- γ resulted in the amelioration of NAFLD development [169]. For instance, in HFD-fed mice, hepatocyte/macrophage-specific PPAR- γ knockout protected against hepatic steatosis and PPAR- γ knockdown induced by RNA interfering-adenovirus vector injection improved a fatty liver [10, 170, 171]. In summary, TZDs improved hepatic steatosis and alleviated NASH and liver fibrosis by increasing insulin sensitivity in skeletal muscle and adipose

tissue, thus overcoming the direct steatogenic influence on liver cells [171–173].

Bile acids (BAs) and their receptors (e.g., BA nuclear receptor and FXR) play indispensable roles in regulating systemic metabolism and hepatic lipid homeostasis. FXR is a nutrient-sensing nuclear receptor in the gut and liver that regulates glucose and fat metabolism [174]. These functions of FXR were assessed through a quantitative proteomic analysis of mouse liver tissue [175]. Studies had found that FXR regulates amino acid catabolism and detoxification of ammonium in the livers of mice through ureagenesis and glutamine synthesis. Further, the synthesis of ceramide pools throughout the body was reported to be regulated by the BA/FXR axis in the ileum and cecum [176]. Intestinal specific genetic or pharmacological inhibition of FXR led to a decrease in circulating ceramide levels, increase in browning of adipose tissue, and amelioration of liver insulin resistance and liver injury in HFD-induced obese mice [177]. Activation of hepatic FXR has been shown to reduce liver glucose, adipogenesis, and steatosis in animal models [178]. FXR is important for liver inflammation and has been proven to be a potential therapeutic target for NASH [179, 180]. FXR activation reprograms arachidonate metabolism in mice [181] and stimulates 1-deoxysphingolipid catabolism and thereby attenuates the cytotoxic effects [182]. A phase 2 randomized double-blind placebo control trial in Japan showed that compared with placebo, high doses of obeticholic acid (OCA) intake remarkably resolved NASH [178]. In the FXR Ligand OCA in NASH Treatment (FLINT) trial, OCA induced NASH remission in 22% of patients, whereas placebo induced NASH remission in 13% of patients [157]. In summary, FXR regulates circulating ceramide levels and improves hepatic insulin resistance and liver damage in NAFLD/NASH patients.

Hepatic de novo lipogenesis is stimulated by activation of the nutrient-sensing mTORc1 pathway, a substrate of insulin-Akt signaling under physiological conditions [179]. For example, treatment of hepatocytes with rapamycin, an allosteric inhibitor of mTORc1, inhibited insulin activation of the lipogenic transcription factor SREBP-1c [183, 184]. In addition, specific knockout of the mTORc1-defining component, raptor, in the liver alleviated HFD-induced hepatic steatosis, which may be due to reduced lipogenesis [185]. It has been demonstrated that Notch antagonism uncouples Akt from mTor activation, implying that NAFLD can be treated by Notch antagonists [186].

6. Conclusion

This article documented recent advances in lipid abnormalities in NAFLD. We proposed that an abnormality in lipid metabolic pathways eventually leads to NAFLD. This viewpoint was theoretically and experimentally validated by elaborately elucidating the role of FA, arachidonic acid metabolic disorders, and ceramide overload in the pathogenesis of NAFLD. In addition, we offered some treatment options for NAFLD. All these observations and experimental findings provide the scientific basis for the prevention and treatment of NAFLD.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

K.P., T.G., Z.G., Q.Z., W.D., D.K., and H.F. contributed in writing the manuscript. Z.G., J.W., and Y. Y. conceived the idea. Y.L. did the funding acquisition. Ke Pei and Ting Gui contributed equally to this work.

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References

- [1] R. Loomba and A. J. Sanyal, "The global NAFLD epidemic," *Nature Reviews Gastroenterology & Hepatology*, vol. 10, no. 11, pp. 686–690, 2013.
- [2] A. Lonardo, C. D. Byrne, S. H. Caldwell, H. Cortez-Pinto, and G. Targher, "Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes," *Hepatology*, vol. 64, no. 4, pp. 1388–1389, 2016.
- [3] Z. M. Younossi, A. B. Koenig, D. Abdelatif, Y. Fazel, L. Henry, and M. Wymer, "Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes," *Hepatology*, vol. 64, no. 1, pp. 73–84, 2016.
- [4] F. Bessone, M. V. Razori, and M. G. Roma, "Molecular pathways of nonalcoholic fatty liver disease development and progression," *Cellular and Molecular Life Sciences*, vol. 76, no. 1, pp. 99–128, 2019.
- [5] N. Magee, A. Zou, and Y. Zhang, "Pathogenesis of nonalcoholic steatohepatitis: interactions between liver parenchymal and nonparenchymal cells," *BioMed Research International*, vol. 2016, Article ID 5170402, 11 pages, 2016.
- [6] H. Wobser, C. Dorn, T. S. Weiss et al., "Lipid accumulation in hepatocytes induces fibrogenic activation of hepatic stellate cells," *Cell Research*, vol. 19, no. 8, pp. 996–1005, 2009.
- [7] L. A. Adams, J. F. Lymp, J. St Sauver et al., "The natural history of nonalcoholic fatty liver disease: a population-based cohort study," *Gastroenterology*, vol. 129, no. 1, pp. 113–121, 2005.
- [8] J. Ertle, A. Dechêne, J. P. Sowa et al., "Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis," *International Journal of Cancer*, vol. 128, no. 10, pp. 2436–2443, 2011.
- [9] D. Goldberg, I. C. Ditah, K. Saeian et al., "Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation," *Gastroenterology*, vol. 152, no. 5, pp. 1090–1099.e1, 2017.
- [10] X. Palomer, L. Salvadó, E. Barroso, and M. Vázquez-Carrera, "An overview of the crosstalk between inflammatory processes and metabolic dysregulation during diabetic

- cardiomyopathy,” *International Journal of Cardiology*, vol. 168, no. 4, pp. 3160–3172, 2013.
- [11] Y. Chu, L. G. Rosso, P. Huang et al., “Liver Med23 ablation improves glucose and lipid metabolism through modulating FOXO1 activity,” *Cell Research*, vol. 24, no. 10, pp. 1250–1265, 2014.
- [12] Y. Li, Z. Ma, S. Jiang et al., “A global perspective on FOXO1 in lipid metabolism and lipid-related diseases,” *Progress in Lipid Research*, vol. 66, pp. 42–49, 2017.
- [13] M. S. Strable and J. M. Ntambi, “Genetic control of *de novo* lipogenesis: role in diet-induced obesity,” *Critical Reviews in Biochemistry and Molecular Biology*, vol. 45, no. 3, pp. 199–214, 2010.
- [14] D. R. Snow, R. E. Ward, A. Olsen, R. Jimenez-Flores, and K. J. Hintze, “Membrane-rich milk fat diet provides protection against gastrointestinal leakiness in mice treated with lipopolysaccharide,” *Journal of Dairy Science*, vol. 94, no. 5, pp. 2201–2212, 2011.
- [15] S. J. Ten Bruggencate, P. D. Frederiksen, S. M. Pedersen et al., “Dietary milk-fat-globule membrane affects resistance to diarrheagenic *Escherichia coli* in healthy adults in a randomized, placebo-controlled, double-blind study,” *The Journal of Nutrition*, vol. 146, no. 2, pp. 249–255, 2016.
- [16] S. Watanabe, T. Takahashi, L. Tanaka et al., “The effect of milk polar lipids separated from butter serum on the lipid levels in the liver and the plasma of obese-model mouse (KK-A^y),” *Journal of Functional Foods*, vol. 3, no. 4, pp. 313–320, 2011.
- [17] J.-G. Fan, S.-U. Kim, and V. W.-S. Wong, “New trends on obesity and NAFLD in Asia,” *Journal of Hepatology*, vol. 67, no. 4, pp. 862–873, 2017.
- [18] S. Milić, D. Lulić, and D. Štimac, “Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations,” *World Journal of Gastroenterology*, vol. 20, no. 28, pp. 9330–9337, 2014.
- [19] M. Ciupińska-Kajor, M. Hartleb, M. Kajor et al., “Hepatic angiogenesis and fibrosis are common features in morbidly obese patients,” *Hepatology International*, vol. 7, no. 1, pp. 233–240, 2013.
- [20] S. Hafeez and M. H. Ahmed, “Bariatric surgery as potential treatment for nonalcoholic fatty liver disease: a future treatment by choice or by chance?,” *Journal of Obesity*, vol. 2013, Article ID 839275, 11 pages, 2013.
- [21] A. Abid, O. Taha, W. Nseir, R. Farah, M. Grosovski, and N. Assy, “Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome,” *Journal of Hepatology*, vol. 51, no. 5, pp. 918–924, 2009.
- [22] Sugar and Sweeteners Team, Market and Trade Economics, Economic Research Service, US Department of Agriculture, “US per capitaloric sweeteners estimated deliveries for domestic food and beverage use, by calendar year,” <http://www.ers.usda.gov/data-products/sugar-and-sweeteners-yearbook-tables.aspx>.
- [23] R. J. Johnson, T. Nakagawa, L. G. Sanchez-Lozada et al., “Sugar, uric acid, and the etiology of diabetes and obesity,” *Diabetes*, vol. 62, no. 10, pp. 3307–3315, 2013.
- [24] H. Sobrecases, K. A. Lê, M. Bortolotti et al., “Effects of short-term overfeeding with fructose, fat and fructose plus fat on plasma and hepatic lipids in healthy men,” *Diabetes & Metabolism*, vol. 36, no. 3, pp. 244–246, 2010.
- [25] M. Maersk, A. Belza, H. Stødkilde-Jørgensen et al., “Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study,” *The American Journal of Clinical Nutrition*, vol. 95, no. 2, pp. 283–289, 2012.
- [26] M. F.-F. Chong, B. A. Fielding, and K. N. Frayn, “Mechanisms for the acute effect of fructose on postprandial lipemia,” *The American Journal of Clinical Nutrition*, vol. 85, no. 6, pp. 1511–1520, 2007.
- [27] A. E. Feldstein, A. Canbay, M. E. Guicciardi, H. Higuchi, S. F. Bronk, and G. J. Gores, “Diet associated hepatic steatosis sensitizes to Fas mediated liver injury in mice,” *Journal of Hepatology*, vol. 39, no. 6, pp. 978–983, 2003.
- [28] World Health Organization, *Guidelines: Sugar Intake for Adults and Children*, World Health Organization, Geneva, Switzerland, 2015.
- [29] US Department of Health and Human Services and US Department of Agriculture, *2015-2020 Dietary Guidelines for Americans*, 8th Editin, 2015, <https://health.gov/dietaryguidelines/2015/guidelines/>.
- [30] J. P. Gorvel, P. Chavrier, M. Zerial, and J. Gruenberg, “rab5 controls early endosome fusion in vitro,” *Cell*, vol. 64, no. 5, pp. 915–925, 1991.
- [31] R. L. Silverstein and M. Febbraio, “CD36, a scavenger receptor involved in immunity, metabolism, angiogenesis, and behavior,” *Science Signaling*, vol. 2, no. 72, p. re3, 2009.
- [32] A. L. C. McLay, R. Jackson, F. Meyboom, and J. M. B. Jones, “Glomerular basement membrane thinning in adults: clinicopathological correlations of a new diagnostic approach,” *Nephrology, Dialysis, Transplantation*, vol. 7, no. 3, pp. 191–199, 1992.
- [33] A. Demers, S. Samami, B. Lauzier et al., “PCSK9 induces CD36 degradation and affects long-chain fatty acid uptake and triglyceride metabolism in adipocytes and in mouse LiverSignificance,” *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 35, no. 12, pp. 2517–2525, 2015.
- [34] X. Su and N. A. Abumrad, “Cellular fatty acid uptake: a pathway under construction,” *Trends in Endocrinology and Metabolism*, vol. 20, no. 2, pp. 72–77, 2009.
- [35] W. Stremmel, J. Pohl, A. Ring, and T. Herrmann, “A new concept of cellular uptake and intracellular trafficking of long-chain fatty acids,” *Lipids*, vol. 36, no. 9, pp. 981–989, 2001.
- [36] Y. Li, P. Yang, L. Zhao et al., “CD36 plays a negative role in the regulation of lipophagy in hepatocytes through an AMPK-dependent pathway,” *Journal of Lipid Research*, vol. 60, no. 4, pp. 844–855, 2019.
- [37] D. Greco, A. Kotronen, J. Westerbacka et al., “Gene expression in human NAFLD,” *American Journal of Physiology. Gastrointestinal and Liver Physiology*, vol. 294, no. 5, pp. G1281–G1287, 2008.
- [38] D. P. Y. Koonen, R. L. Jacobs, M. Febbraio et al., “Increased hepatic CD36 expression contributes to dyslipidemia associated with diet-induced obesity,” *Diabetes*, vol. 56, no. 12, pp. 2863–2871, 2007.
- [39] L. Zhao, C. Zhang, X. Luo et al., “CD36 palmitoylation disrupts free fatty acid metabolism and promotes tissue inflammation in non-alcoholic steatohepatitis,” *Journal of Hepatology*, vol. 69, no. 3, pp. 705–717, 2018.
- [40] A. V. Hertzler and D. A. Bernlohr, “The mammalian fatty acid-binding protein multigene family: molecular and genetic

- insights into function,” *Trends in Endocrinology and Metabolism*, vol. 11, no. 5, pp. 175–180, 2000.
- [41] Y. L. Wu, Y. B. Zhu, R. D. Huang, X. E. Peng, and X. Lin, “Multiple microRNAs ameliorate hepatocyte steatosis and injury by suppressing FABP1 expression,” *Cellular Physiology and Biochemistry*, vol. 44, no. 6, pp. 2243–2255, 2018.
- [42] G. G. Martin, A. L. McIntosh, H. Huang et al., “The human liver fatty acid binding protein T94A variant alters the structure, stability, and interaction with fibrates,” *Biochemistry*, vol. 52, no. 51, pp. 9347–9357, 2013.
- [43] G. G. Martin, B. P. Atshaves, K. K. Landrock, D. Landrock, F. Schroeder, and A. B. Kier, “Loss of L-FABP, SCP-2/SCP-x, or both induces hepatic lipid accumulation in female mice,” *Archives of Biochemistry and Biophysics*, vol. 580, pp. 41–49, 2015.
- [44] F. Marra and G. Svegliati-Baroni, “Lipotoxicity and the gut-liver axis in NASH pathogenesis,” *Journal of Hepatology*, vol. 68, no. 2, pp. 280–295, 2018.
- [45] A. Suzuki and A. M. Diehl, “Nonalcoholic steatohepatitis,” *Annual Review of Medicine*, vol. 68, no. 1, pp. 85–98, 2017.
- [46] B. Gao and H. Tsukamoto, “Inflammation in alcoholic and nonalcoholic fatty liver disease: friend or foe?,” *Gastroenterology*, vol. 150, no. 8, pp. 1704–1709, 2016.
- [47] F. Heymann and F. Tacke, “Immunology in the liver – from homeostasis to disease,” *Nature Reviews Gastroenterology & Hepatology*, vol. 13, no. 2, pp. 88–110, 2016.
- [48] N. Pejnovic, I. Jeftic, N. Jovicic, N. Arsenijevic, and M. L. Lukic, “Galectin-3 and IL-33/ST2 axis roles and interplay in diet-induced steatohepatitis,” *World Journal of Gastroenterology*, vol. 22, no. 44, pp. 9706–9717, 2016.
- [49] M. L. Berres, A. Nellen, and H. E. Wasmuth, “Chemokines as immune mediators of liver diseases related to the metabolic syndrome,” *Digestive Diseases*, vol. 28, no. 1, pp. 192–196, 2010.
- [50] K. Brandl and B. Schnabl, “Intestinal microbiota and nonalcoholic steatohepatitis,” *Current Opinion in Gastroenterology*, vol. 33, no. 3, pp. 128–133, 2017.
- [51] D. Schuppan, R. Surabattula, and X. Y. Wang, “Determinants of fibrosis progression and regression in NASH,” *Journal of Hepatology*, vol. 68, no. 2, pp. 238–250, 2018.
- [52] T. Tsuchida and S. L. Friedman, “Mechanisms of hepatic stellate cell activation,” *Nature Reviews Gastroenterology & Hepatology*, vol. 14, no. 7, pp. 397–411, 2017.
- [53] Z. M. Younossi, R. Loomba, Q. M. Anstee et al., “Diagnostic modalities for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and associated fibrosis,” *Hepatology*, vol. 68, no. 1, pp. 349–360, 2018.
- [54] V. J. Barbero-Becerra, P. J. Giraudi, N. C. Chávez-Tapia, M. Uribe, C. Tiribelli, and N. Rosso, “The interplay between hepatic stellate cells and hepatocytes in an *in vitro* model of NASH,” *Toxicology In Vitro*, vol. 29, no. 7, pp. 1753–1758, 2015.
- [55] P. Dongiovanni, M. Meroni, G. A. Baselli et al., “Insulin resistance promotes lysyl oxidase like 2 induction and fibrosis accumulation in non-alcoholic fatty liver disease,” *Clinical Science (London, England)*, vol. 131, no. 12, pp. 1301–1315, 2017.
- [56] A. Saeed, R. Dullaart, T. Schreuder, H. Blokzijl, and K. Faber, “Disturbed Vitamin A Metabolism in non-alcoholic fatty liver disease (NAFLD),” *Nutrients*, vol. 10, no. 1, pp. 29, 2018.
- [57] P. C. Calder, “N-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic,” *Lipids*, vol. 38, no. 4, pp. 343–352, 2003.
- [58] T. A. Mori, R. J. Woodman, V. Burke, I. B. Puddey, K. D. Croft, and L. J. Beilin, “Effect of eicosapentaenoic acid and docosahexaenoic acid on oxidative stress and inflammatory markers in treated-hypertensive type 2 diabetic subjects,” *Free Radical Biology & Medicine*, vol. 35, no. 7, pp. 772–781, 2003.
- [59] A. E. Feldstein, N. W. Werneburg, A. Canbay et al., “Free fatty acids promote hepatic lipotoxicity by stimulating TNF-alpha expression via a lysosomal pathway,” *Hepatology*, vol. 40, no. 1, pp. 185–194, 2004.
- [60] B. A. Neuschwander-Tetri and S. H. Caldwell, “Nonalcoholic steatohepatitis:summary of an AASLD single topic conference,” *Hepatology*, vol. 37, no. 5, pp. 1202–1219, 2003.
- [61] A. Wree, L. Broderick, A. Canbay, H. M. Hoffman, and A. E. Feldstein, “From NAFLD to NASH to cirrhosis—new insights into disease mechanisms,” *Nature Reviews Gastroenterology & Hepatology*, vol. 10, no. 11, pp. 627–636, 2013.
- [62] P. C. Calder, “Omega-3 fatty acids and inflammatory processes,” *Nutrients*, vol. 2, no. 3, pp. 355–374, 2010.
- [63] J. Z. Nowak, “Anti-inflammatory pro-resolving derivatives of omega-3 and omega-6 polyunsaturated fatty acids,” *Postępy Higieny i Medycyny Doświadczalnej*, vol. 64, pp. 115–132, 2010.
- [64] S. Chitturi and G. C. Farrell, “Etiopathogenesis of Nonalcoholic Steatohepatitis,” *Seminars in Liver Disease*, vol. 21, no. 1, pp. 027–042, 2001.
- [65] P. T. Bozza, I. Bakker-Abreu, R. A. Navarro-Xavier, and C. Bandeira-Melo, “Lipid body function in eicosanoid synthesis: an update,” *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, vol. 85, no. 5, pp. 205–213, 2011.
- [66] J. Xu, M. Teran-Garcia, J. H. Y. Park, M. T. Nakamura, and S. D. Clarke, “Polyunsaturated fatty acids suppress Hepatic-Sterol regulatory element-binding Protein-1Expression by accelerating transcript decay,” *The Journal of Biological Chemistry*, vol. 276, no. 13, pp. 9800–9807, 2001.
- [67] V. Di Marzo, “Arachidonic acid and eicosanoids as targets and effectors in second messenger interactions,” *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, vol. 53, no. 4, pp. 239–254, 1995.
- [68] X. Zhang, S. Li, Y. Zhou et al., “Ablation of cytochrome P450 omega-hydroxylase 4A14 gene attenuates hepatic steatosis and fibrosis,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 114, no. 12, pp. 3181–3185, 2017.
- [69] M. Shimabukuro, Y. T. Zhou, M. Levi, and R. H. Unger, “Fatty acid-induced beta cell apoptosis: a link between obesity and diabetes,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 5, pp. 2498–2502, 1998.
- [70] T. S. Park, Y. Hu, H. L. Noh et al., “Ceramide is a cardiotoxin in lipotoxic cardiomyopathy,” *Journal of Lipid Research*, vol. 49, no. 10, pp. 2101–2112, 2008.
- [71] S. A. Summers, “Ceramides in insulin resistance and lipotoxicity,” *Progress in Lipid Research*, vol. 45, no. 1, pp. 42–72, 2006.
- [72] L. P. Bharath, T. Ruan, Y. Li et al., “Ceramide-Initiated Protein phosphatase 2A activation contributes to arterial

- dysfunction in vivo,” *Diabetes*, vol. 64, no. 11, pp. 3914–3926, 2015.
- [73] P. Puri, R. A. Baillie, M. M. Wiest et al., “A lipidomic analysis of nonalcoholic fatty liver disease,” *Hepatology*, vol. 46, no. 4, pp. 1081–1090, 2007.
- [74] P. Puri, M. M. Wiest, O. Cheung et al., “The plasma lipidomic signature of nonalcoholic steatohepatitis,” *Hepatology*, vol. 50, no. 6, pp. 1827–1838, 2009.
- [75] Y. Zhou, M. Orešič, M. Leivonen et al., “Noninvasive detection of nonalcoholic steatohepatitis using clinical markers and circulating levels of lipids and metabolites,” *Clinical Gastroenterology and Hepatology*, vol. 14, no. 10, pp. 1463–1472.e6, 2016.
- [76] I. Ichi, K. Nakahara, K. Fujii, C. Iida, Y. Miyashita, and S. Kojima, “Increase of ceramide in the liver and plasma after carbon tetrachloride intoxication in the rat,” *Journal of Nutritional Science and Vitaminology (Tokyo)*, vol. 53, no. 1, pp. 53–56, 2007.
- [77] J. Y. Xia, T. S. Morley, and P. E. Scherer, “The adipokine/ceramide axis: key aspects of insulin sensitization,” *Biochimie*, vol. 96, pp. 130–139, 2014.
- [78] D. L. Gorden, D. S. Myers, P. T. Ivanova et al., “Biomarkers of NAFLD progression: a lipidomics approach to an epidemic,” *Journal of Lipid Research*, vol. 56, no. 3, pp. 722–736, 2015.
- [79] K. Kurek, D. M. Piotrowska, P. Wiesiołek-Kurek et al., “Inhibition of ceramide de novo synthesis reduces liver lipid accumulation in rats with nonalcoholic fatty liver disease,” *Liver International*, vol. 34, no. 7, pp. 1074–1083, 2014.
- [80] G. Yang, L. Badeanlou, J. Bielawski, A. J. Roberts, Y. A. Hannun, and F. Samad, “Central role of ceramide biosynthesis in body weight regulation, energy metabolism, and the metabolic syndrome,” *American Journal of Physiology. Endocrinology and Metabolism*, vol. 297, no. 1, pp. E211–E224, 2009.
- [81] A. Moles, N. Tarrats, A. Morales et al., “Acidic Sphingomyelinase Controls Hepatic Stellate Cell Activation and *in Vivo* Liver Fibrogenesis,” *The American Journal of Pathology*, vol. 177, no. 3, pp. 1214–1224, 2010.
- [82] G. M. Deevska, K. A. Rozenova, N. V. Giltiy et al., “Acid sphingomyelinase deficiency prevents diet-induced hepatic triacylglycerol accumulation and hyperglycemia in mice,” *The Journal of Biological Chemistry*, vol. 284, no. 13, pp. 8359–8368, 2009.
- [83] R. Fucho, L. Martínez, A. Baulies et al., “ASMase regulates autophagy and lysosomal membrane permeabilization and its inhibition prevents early stage non-alcoholic steatohepatitis,” *Journal of Hepatology*, vol. 61, no. 5, pp. 1126–1134, 2014.
- [84] N. Beckmann, D. Sharma, E. Gulbins, K. A. Becker, and B. Å. Edelman, “Inhibition of acid sphingomyelinase by tricyclic antidepressants and analogs,” *Frontiers in Physiology*, vol. 5, p. 331, 2014.
- [85] S. Raichur, S. T. Wang, P. W. Chan et al., “CerS2 haploinsufficiency inhibits β -oxidation and confers susceptibility to diet-induced steatohepatitis and insulin resistance,” *Cell Metabolism*, vol. 20, no. 5, p. 919, 2014.
- [86] S. M. Turpin, H. T. Nicholls, D. M. Willmes et al., “Obesity-induced CerS6-dependent C_{16:0} ceramide production promotes weight gain and glucose intolerance,” *Cell Metabolism*, vol. 20, no. 4, pp. 678–686, 2014.
- [87] J. R. Ussher, T. R. Koves, V. J. J. Cadete et al., “Inhibition of de novo ceramide synthesis reverses diet-induced insulin resistance and enhances whole-body oxygen consumption,” *Diabetes*, vol. 59, no. 10, pp. 2453–2464, 2010.
- [88] W. L. Holland, J. T. Brozinick, L. P. Wang et al., “Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance,” *Cell Metabolism*, vol. 5, no. 3, pp. 167–179, 2007.
- [89] M. Nikolova-Karakashian, “Alcoholic and non-alcoholic fatty liver disease: focus on ceramide,” *Advances in Biological Regulation*, vol. 70, pp. 40–50, 2018.
- [90] Z. Liu, Y. Xia, B. Li et al., “Induction of ER stress-mediated apoptosis by ceramide via disruption of ER Ca²⁺ homeostasis in human adenoid cystic carcinoma cells,” *Cell & Bioscience*, vol. 4, no. 1, p. 71, 2014.
- [91] R. Cinar, G. Godlewski, J. Liu et al., “Hepatic cannabinoid-1 receptors mediate diet-induced insulin resistance by increasing de novo synthesis of long-chain ceramides,” *Hepatology*, vol. 59, no. 1, pp. 143–153, 2014.
- [92] E. B. Harvald, A. S. B. Olsen, and N. J. Fægeman, “Autophagy in the light of sphingolipid metabolism,” *Apoptosis*, vol. 20, no. 5, pp. 658–670, 2015.
- [93] S. Lu, S. K. Natarajan, J. L. Mott, K. K. Kharbanda, and D. D. Harrison-Findik, “Ceramide induces human hepcidin gene transcription through JAK/STAT3 pathway,” *PLoS One*, vol. 11, no. 1, article e0147474, 2016.
- [94] N. Alkhoury, L. J. Dixon, and A. E. Feldstein, “Lipotoxicity in nonalcoholic fatty liver disease: not all lipids are created equal,” *Expert Review of Gastroenterology & Hepatology*, vol. 3, no. 4, pp. 445–451, 2014.
- [95] K. Promrat, L. Longato, J. R. Wands, and S. M. de la Monte, “Weight loss amelioration of non-alcoholic steatohepatitis linked to shifts in hepatic ceramide expression and serum ceramide levels,” *Hepatology Research*, vol. 41, no. 8, pp. 754–762, 2011.
- [96] M. Romero-Gómez, S. Zelber-Sagi, and M. Trenell, “Treatment of NAFLD with diet, physical activity and exercise,” *Journal of Hepatology*, vol. 67, no. 4, pp. 829–846, 2017.
- [97] H. Seki, Y. Tani, and M. Arita, “Omega-3 PUFA derived anti-inflammatory lipid mediator resolvin E1,” *Prostaglandins & Other Lipid Mediators*, vol. 89, no. 3-4, pp. 126–130, 2009.
- [98] R. Dentin, F. Benhamed, J. P. Pégrier et al., “Polyunsaturated fatty acids suppress glycolytic and lipogenic genes through the inhibition of ChREBP nuclear protein translocation,” *The Journal of Clinical Investigation*, vol. 115, no. 10, pp. 2843–2854, 2005.
- [99] M. Sekiya, N. Yahagi, T. Matsuzaka et al., “Polyunsaturated fatty acids ameliorate hepatic steatosis in obese mice by SREBP-1 suppression,” *Hepatology*, vol. 38, no. 6, pp. 1529–1539, 2003.
- [100] R. S. Chapkin, L. A. Davidson, L. Ly, B. R. Weeks, J. R. Lupton, and D. N. McMurray, “Immunomodulatory effects of (n-3) fatty acids: putative link to inflammation and colon cancer,” *The Journal of Nutrition*, vol. 137, no. 1, pp. 200S–204S, 2007.
- [101] Y. Yonezawa, T. Hada, K. Uryu et al., “Inhibitory effect of conjugated eicosapentaenoic acid on mammalian DNA polymerase and topoisomerase activities and human cancer cell proliferation,” *Biochemical Pharmacology*, vol. 70, no. 3, pp. 453–460, 2005.
- [102] H. M. Parker, N. A. Johnson, C. A. Burdon, J. S. Cohn, H. T. O’Connor, and J. George, “Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and

- meta-analysis," *Journal of Hepatology*, vol. 56, no. 4, pp. 944–951, 2012.
- [103] C. Kosinski and F. R. Jornayvaz, "Effects of Ketogenic diets on cardiovascular risk factors: evidence from animal and human studies," *Nutrients*, vol. 9, no. 5, p. 517, 2017.
- [104] H. Yki-Järvinen, "Nutritional modulation of non-alcoholic fatty liver disease and insulin resistance," *Nutrients*, vol. 7, no. 11, pp. 9127–9138, 2015.
- [105] R. C. Schugar and P. A. Crawford, "Low-carbohydrate ketogenic diets, glucose homeostasis, and nonalcoholic fatty liver disease," *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 15, no. 4, pp. 374–380, 2012.
- [106] A. L. Sberna, B. Bouillet, A. Rouland et al., "European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with type 2 diabetes," *Diabetic Medicine*, vol. 35, no. 3, pp. 368–375, 2018.
- [107] L. Abenavoli, N. Milic, V. Peta, F. Alfieri, A. de Lorenzo, and S. Bellentani, "Alimentary regimen in non-alcoholic fatty liver disease: Mediterranean diet," *World Journal of Gastroenterology*, vol. 20, no. 45, pp. 16831–16840, 2014.
- [108] N. Chalasani, Z. Younossi, J. E. Lavine et al., "The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association," *Hepatology*, vol. 55, no. 6, pp. 2005–2023, 2012.
- [109] M. Hamaguchi, T. Kojima, N. Takeda et al., "The metabolic syndrome as a predictor of nonalcoholic fatty liver disease," *Annals of Internal Medicine*, vol. 143, no. 10, pp. 722–728, 2005.
- [110] S. Zelber-Sagi, R. Lotan, A. Shlomai et al., "Predictors for incidence and remission of NAFLD in the general population during a seven-year prospective follow-up," *Journal of Hepatology*, vol. 56, no. 5, pp. 1145–1151, 2012.
- [111] N. Yoshioka, M. Ishigami, Y. Watanabe et al., "Effect of weight change and lifestyle modifications on the development or remission of nonalcoholic fatty liver disease: sex-specific analysis," *Scientific Reports*, vol. 10, no. 1, p. 481, 2020.
- [112] G. Pagano, G. Pacini, G. Musso et al., "Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association," *Hepatology*, vol. 35, no. 2, pp. 367–372, 2002.
- [113] M. E. Rinella, "Nonalcoholic fatty liver disease: a systematic review," *JAMA*, vol. 313, no. 22, pp. 2263–2273, 2015.
- [114] S. Golbidi, A. Mesdaghinia, and I. Laher, "Exercise in the metabolic syndrome," *Oxidative Medicine and Cellular Longevity*, vol. 2012, Article ID 349710, 13 pages, 2012.
- [115] European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO), "EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease," *Journal of Hepatology*, vol. 64, no. 6, pp. 1388–1402, 2016.
- [116] S. A. Polyzos, J. Kountouras, and C. S. Mantzoros, "Adipokines in nonalcoholic fatty liver disease," *Metabolism*, vol. 65, no. 8, pp. 1062–1079, 2016.
- [117] T. Bader, "Yes! Statins can be given to liver patients," *Journal of Hepatology*, vol. 56, no. 2, pp. 305–307, 2012.
- [118] V. G. Athyros, C. Boutari, K. Stavropoulos et al., "Statins: an under-appreciated asset for the prevention and the treatment of NAFLD or NASH and the related cardiovascular risk," *Current Vascular Pharmacology*, vol. 16, no. 3, pp. 246–253, 2018.
- [119] Y. Okada, K. Yamaguchi, T. Nakajima et al., "Rosuvastatin ameliorates high-fat and high-cholesterol diet-induced non-alcoholic steatohepatitis in rats," *Liver International*, vol. 33, no. 2, pp. 301–311, 2013.
- [120] G. Ji, X. Zhao, L. Leng, P. Liu, and Z. Jiang, "Comparison of dietary control and atorvastatin on high fat diet induced hepatic steatosis and hyperlipidemia in rats," *Lipids in Health and Disease*, vol. 10, no. 1, pp. 23–32, 2011.
- [121] S. H. Seif el-Din, N. M. el-Lakkany, A. A. el-Naggar et al., "Effects of rosuvastatin and/or β -carotene on non-alcoholic fatty liver in rats," *Research in Pharmaceutical Sciences*, vol. 10, no. 4, pp. 275–287, 2015.
- [122] A. M. Kabel, M. A. Abd Elmaaboud, and A. A. Albarraq, "Ameliorative potential of omega 3 fatty acids and HMG-CoA reductase inhibitors on experimentally-induced non-alcoholic steatohepatitis," *Prostaglandins, Leukotrienes and Essential Fatty Acids*, vol. 96, pp. 1–9, 2015.
- [123] P. Matafome, T. Louro, L. Rodrigues et al., "Metformin and atorvastatin combination further protect the liver in type 2 diabetes with hyperlipidaemia," *Diabetes/Metabolism Research and Reviews*, vol. 27, no. 1, pp. 54–62, 2011.
- [124] L. Vilà, A. Rebollo, G. S. Adalsteisson et al., "Reduction of liver fructokinase expression and improved hepatic inflammation and metabolism in liquid fructose-fed rats after atorvastatin treatment," *Toxicology and Applied Pharmacology*, vol. 251, no. 1, pp. 32–40, 2011.
- [125] L. W. Chong, Y. C. Hsu, T. F. Lee et al., "Fluvastatin attenuates hepatic steatosis-induced fibrogenesis in rats through inhibiting paracrine effect of hepatocyte on hepatic stellate cells," *BMC Gastroenterology*, vol. 15, no. 1, p. 22, 2015.
- [126] T. Miyaki, S. Nojiri, N. Shinkai et al., "Pitavastatin inhibits hepatic steatosis and fibrosis in non-alcoholic steatohepatitis model rats," *Hepatology Research*, vol. 41, no. 4, pp. 375–385, 2011.
- [127] V. G. Athyros, K. Tziomalos, T. D. Gossios et al., "Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study: a post-hoc analysis," *The Lancet*, vol. 376, no. 9756, pp. 1916–1922, 2010.
- [128] M. J. Tikkanen, R. Fayyad, O. Faergeman et al., "Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels," *International Journal of Cardiology*, vol. 168, no. 4, pp. 3846–3852, 2013.
- [129] V. G. Athyros, N. Katsiki, and D. P. Mikhailidis, "Statins and non-alcoholic steatohepatitis," *Metabolism*, vol. 66, pp. e1–e2, 2017.
- [130] V. G. Athyros, N. Katsiki, A. Karagiannis, and D. P. Mikhailidis, "Are statins 'IDEAL' for non-alcoholic fatty liver disease?," *Current Medical Research and Opinion*, vol. 30, no. 2, pp. 229–231, 2014.

- [131] K. Tziomalos, V. G. Athyros, and A. Karagiannis, "Non-alcoholic fatty liver disease in type 2 diabetes: pathogenesis and treatment options," *Current Vascular Pharmacology*, vol. 10, no. 2, pp. 162–172, 2012.
- [132] C. Vlachopoulos, E. Manesis, K. Baou et al., "Increased arterial stiffness and impaired endothelial function in nonalcoholic fatty liver disease: a pilot study," *American Journal of Hypertension*, vol. 23, no. 11, pp. 1183–1189, 2010.
- [133] V. G. Athyros, E. Ganotakis, G. D. Kolovou et al., "Assessing the Treatment Effect in metabolic syndrome without perceptible Diabetes (ATTEMPT): a prospective-randomized study in middle aged men and women," *Current Vascular Pharmacology*, vol. 9, no. 6, pp. 647–657, 2011.
- [134] V. G. Athyros, D. P. Mikhailidis, T. P. Didangelos et al., "Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study," *Current Medical Research and Opinion*, vol. 22, no. 5, pp. 873–883, 2006.
- [135] P. Angulo, D. E. Kleiner, S. Dam-Larsen et al., "Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease," *Gastroenterology*, vol. 149, no. 2, pp. 389–397.e10, 2015.
- [136] A. Lonardo, S. Sookoian, C. J. Pirola, and G. Targher, "Non-alcoholic fatty liver disease and risk of cardiovascular disease," *Metabolism*, vol. 65, no. 8, pp. 1136–1150, 2016.
- [137] L. S. Rallidis, C. K. Drakoulis, and A. S. Parasi, "Pravastatin in patients with nonalcoholic steatohepatitis: results of a pilot study," *Atherosclerosis*, vol. 174, no. 1, pp. 193–196, 2004.
- [138] H. Hyogo, S. Tazuma, K. Arihiro et al., "Efficacy of atorvastatin for the treatment of nonalcoholic steatohepatitis with dyslipidemia," *Metabolism*, vol. 57, no. 12, pp. 1711–1718, 2008.
- [139] K. Kargiotis, N. Katsiki, V. Athyros et al., "Effect of rosuvastatin on non-alcoholic steatohepatitis in patients with metabolic syndrome and hypercholesterolaemia: a preliminary report," *Current Vascular Pharmacology*, vol. 12, no. 3, pp. 505–511, 2014.
- [140] K. Kargiotis, V. G. Athyros, O. Giouleme et al., "Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome," *World Journal of Gastroenterology*, vol. 21, no. 25, pp. 7860–7868, 2015.
- [141] P. Dongiovanni, S. Petta, V. Mannisto et al., "Statin use and non-alcoholic steatohepatitis in at risk individuals," *Journal of Hepatology*, vol. 63, no. 3, pp. 705–712, 2015.
- [142] G. Mintziari and S. A. Polyzos, "Emerging and future therapies for nonalcoholic steatohepatitis in adults," *Expert Opinion on Pharmacotherapy*, vol. 17, no. 14, pp. 1937–1946, 2016.
- [143] S. Sookoian and C. J. Pirola, "Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease," *Hepatology*, vol. 53, no. 6, pp. 1883–1894, 2011.
- [144] F. Nascimbeni, J. Aron-Wisniewsky, R. Pais et al., "Statins, antidiabetic medications and liver histology in patients with diabetes with non-alcoholic fatty liver disease," *BMJ Open Gastroenterology*, vol. 3, no. 1, article e000075, 2016.
- [145] L. Eslami, S. Merat, R. Malekzadeh, S. Nasseri-Moghaddam, and H. Aramin, "Statins for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis," *Cochrane Database of Systematic Reviews*, vol. 12, 2013.
- [146] S. Singh, P. P. Singh, A. G. Singh, M. H. Murad, and W. Sanchez, "Statins Are Associated With a Reduced Risk of Hepatocellular Cancer: A Systematic Review and Meta-analysis," *Gastroenterology*, vol. 144, no. 2, pp. 323–332, 2013.
- [147] T. G. Simon, H. Bonilla, P. Yan, R. T. Chung, and A. A. Butt, "Atorvastatin and fluvastatin are associated with dose-dependent reductions in cirrhosis and hepatocellular carcinoma, among patients with hepatitis C virus: results from ERCHIVES," *Hepatology*, vol. 64, no. 1, pp. 47–57, 2016.
- [148] G. Kim, S. Y. Jang, E. Han et al., "Effect of statin on hepatocellular carcinoma in patients with type 2 diabetes: A nationwide nested case-control study," *International Journal of Cancer*, vol. 140, no. 4, pp. 798–806, 2017.
- [149] Y. Xu, J. Huang, W. Xin et al., "Lipid accumulation is ahead of epithelial-to-mesenchymal transition and therapeutic intervention by acetyl-CoA carboxylase 2 silencing in diabetic nephropathy," *Metabolism*, vol. 63, no. 5, pp. 716–726, 2014.
- [150] W. Xin, X. Zhao, L. Liu et al., "Acetyl-CoA carboxylase 2 suppression rescues human proximal tubular cells from palmitic acid induced lipotoxicity via autophagy," *Biochemical and Biophysical Research Communications*, vol. 463, no. 3, pp. 364–369, 2015.
- [151] M. Herman-Edelstein, P. Scherzer, A. Tobar, M. Levi, and U. Gafter, "Altered renal lipid metabolism and renal lipid accumulation in human diabetic nephropathy," *Journal of Lipid Research*, vol. 55, no. 3, pp. 561–572, 2014.
- [152] V. Souza-Mello, "Peroxisome proliferator-activated receptors as targets to treat non-alcoholic fatty liver disease," *World Journal of Hepatology*, vol. 7, no. 8, pp. 1012–1019, 2015.
- [153] M. Pawlak, E. Baugé, W. Bourguet et al., "The transrepressive activity of peroxisome proliferator-activated receptor alpha is necessary and sufficient to prevent liver fibrosis in mice," *Hepatology*, vol. 60, no. 5, pp. 1593–1606, 2014.
- [154] M. E. Miquilena-Colina, E. Lima-Cabello, S. Sanchez-Campos et al., "Hepatic fatty acid translocase CD36 upregulation is associated with insulin resistance, hyperinsulinaemia and increased steatosis in non-alcoholic steatohepatitis and chronic hepatitis C," *Gut*, vol. 60, no. 10, pp. 1394–1402, 2011.
- [155] D. Cao, J. Luo, D. Chen et al., "CD36 regulates lipopolysaccharide-induced signaling pathways and mediates the internalization of *Escherichia coli* in cooperation with TLR4 in goat mammary gland epithelial cells," *Scientific Reports*, vol. 6, no. 1, article 23132, 2016.
- [156] C. G. Wilson, J. L. Tran, D. M. Erion, N. B. Vera, M. Febbraio, and E. J. Weiss, "Hepatocyte-specific disruption of CD36 attenuates fatty liver and improves insulin sensitivity in HFD-fed mice," *Endocrinology*, vol. 157, no. 2, pp. 570–585, 2016.
- [157] V. Ratziu, S. A. Harrison, S. Francque et al., "Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor α and δ , Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening," *Gastroenterology*, vol. 150, no. 5, pp. 1147–1159.e5, 2016.
- [158] M. Pawlak, P. Lefebvre, and B. Staels, "Molecular mechanism of PPAR α action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease," *Journal of Hepatology*, vol. 62, no. 3, pp. 720–733, 2015.
- [159] L. A. Bojic and M. W. Huff, "Peroxisome proliferator-activated receptor δ ," *Current Opinion in Lipidology*, vol. 24, no. 2, pp. 171–177, 2013.

- [160] B. Staels, A. Rubenstrunk, B. Noel et al., "Hepatoprotective effects of the dual peroxisome proliferator-activated receptor alpha/delta agonist, GFT505, in rodent models of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis," *Hepatology*, vol. 58, no. 6, pp. 1941–1952, 2013.
- [161] B. Cariou, R. Hanf, S. Lambert-Porcheron et al., "Dual Peroxisome Proliferator-Activated Receptor α/δ Agonist GFT505 Improves Hepatic and Peripheral Insulin Sensitivity in Abdominally Obese Subjects," *Diabetes Care*, vol. 36, no. 10, pp. 2923–2930, 2013.
- [162] T. Hardy, Q. M. Anstee, and C. P. Day, "Nonalcoholic fatty liver disease: new treatments," *Current Opinion in Gastroenterology*, vol. 31, no. 3, pp. 175–183, 2015.
- [163] L. He, X. Liu, L. Wang, and Z. Yang, "Thiazolidinediones for nonalcoholic steatohepatitis: a meta-analysis of randomized clinical trials," *Medicine (Baltimore)*, vol. 95, no. 42, article e4947, 2016.
- [164] V. Ratziu, S. Bellentani, H. Cortez-Pinto, C. Day, and G. Marchesini, "A position statement on NAFLD/NASH based on the EASL 2009 special conference," *Journal of Hepatology*, vol. 53, no. 2, pp. 372–384, 2010.
- [165] M. Del Ben, F. Baratta, L. Polimeni et al., "Under-prescription of statins in patients with non-alcoholic fatty liver disease," *Nutrition, Metabolism, and Cardiovascular Diseases*, vol. 27, no. 2, pp. 161–167, 2017.
- [166] H. W. Liao, J. L. Saver, Y. L. Wu, T. H. Chen, M. Lee, and B. Ovbiagele, "Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: a systematic review and meta-analysis," *BMJ Open*, vol. 7, no. 1, article e013927, 2017.
- [167] V. G. Athyros, T. K. Alexandrides, H. Bilianou et al., "The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and related cardiovascular risk. An Expert Panel Statement," *Metabolism*, vol. 71, pp. 17–32, 2017.
- [168] E. Boettcher, G. Csako, F. Pucino, R. Wesley, and R. Loomba, "Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis," *Alimentary Pharmacology & Therapeutics*, vol. 35, no. 1, pp. 66–75, 2012.
- [169] T. Yamauchi, H. Waki, J. Kamon et al., "Inhibition of RXR and PPAR γ ameliorates diet-induced obesity and type 2 diabetes," *The Journal of Clinical Investigation*, vol. 108, no. 7, pp. 1001–1013, 2001.
- [170] L. Shen, Z. Liu, J. Gong et al., "Prenatal ethanol exposure programs an increased susceptibility of non-alcoholic fatty liver disease in female adult offspring rats," *Toxicology and Applied Pharmacology*, vol. 274, no. 2, pp. 263–273, 2014.
- [171] X. Feng, W. Yu, X. Li et al., "Apigenin, a modulator of PPAR γ , attenuates HFD-induced NAFLD by regulating hepatocyte lipid metabolism and oxidative stress via Nrf2 activation," *Biochemical Pharmacology*, vol. 136, pp. 136–149, 2017.
- [172] R. Rueda, J. L. Sabatel, J. Maldonado, J. A. Molina-Font, and A. Gil, "Addition of gangliosides to an adapted milk formula modifies levels of fecal *Escherichia coli* in preterm newborn infants," *The Journal of Pediatrics*, vol. 133, no. 1, pp. 90–94, 1998.
- [173] V. R. Gupta, H. K. Patel, S. S. Kostolansky, R. A. Ballivian, J. Eichberg, and S. R. Blanke, "Sphingomyelin functions as a novel receptor for *Helicobacter pylori* VacA," *PLoS Pathogens*, vol. 4, no. 5, article e1000073, 2008.
- [174] J. S. Teodoro, A. P. Rolo, and C. M. Palmeira, "Hepatic FXR: key regulator of whole-body energy metabolism," *Trends in Endocrinology and Metabolism*, vol. 22, no. 11, pp. 458–466, 2011.
- [175] V. Massafra, A. Milona, H. R. Vos et al., "Farnesoid X receptor activation promotes hepatic amino acid catabolism and ammonium clearance in mice," *Gastroenterology*, vol. 152, no. 6, pp. 1462–1476.e10, 2017.
- [176] C. Jiang, C. Xie, Y. Lv et al., "Intestine-selective farnesoid X receptor inhibition improves obesity-related metabolic dysfunction," *Nature Communications*, vol. 6, no. 1, article 10166, 2015.
- [177] G. Musso, M. Cassader, E. Paschetta, and R. Gambino, "Bioactive lipid species and metabolic pathways in progression and resolution of nonalcoholic steatohepatitis," *Gastroenterology*, vol. 155, no. 2, pp. 282–302.e8, 2018.
- [178] Y. Sumida and M. Yoneda, "Current and future pharmacological therapies for NAFLD/NASH," *Journal of Gastroenterology*, vol. 53, no. 3, pp. 362–376, 2018.
- [179] S. G. Kim, B. K. Kim, K. Kim, and S. Fang, "Bile acid nuclear receptor farnesoid X receptor: therapeutic target for nonalcoholic fatty liver disease," *Endocrinology and Metabolism*, vol. 31, no. 4, pp. 500–504, 2016.
- [180] J. Zhou, S. Cui, Q. He et al., "SUMOylation inhibitors synergize with FXR agonists in combating liver fibrosis," *Nature Communications*, vol. 11, no. 1, p. 240, 2020.
- [181] Z. Gai, M. Visentin, T. Gui et al., "Effects of farnesoid X receptor activation on arachidonic acid metabolism, NF- κ B signaling, and hepatic inflammation," *Molecular Pharmacology*, vol. 94, no. 2, pp. 802–811, 2018.
- [182] Z. Gai, T. Gui, I. Alecu et al., "Farnesoid X receptor activation induces the degradation of hepatotoxic 1-deoxysphingolipids in non-alcoholic fatty liver disease," *Liver International*, vol. 40, no. 4, pp. 844–859, 2020.
- [183] S. Li, M. S. Brown, and J. L. Goldstein, "Bifurcation of insulin signaling pathway in rat liver: mTORC1 required for stimulation of lipogenesis, but not inhibition of gluconeogenesis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 8, pp. 3441–3446, 2010.
- [184] D. M. Sabatini, "mTOR and cancer: insights into a complex relationship," *Nature Reviews Cancer*, vol. 6, no. 9, pp. 729–734, 2006.
- [185] T. R. Peterson, S. S. Sengupta, T. E. Harris et al., "mTOR complex 1 regulates lipin 1 localization to control the SREBP pathway," *Cell*, vol. 146, no. 3, pp. 408–420, 2011.
- [186] U. B. Pajvani, L. Qiang, T. Kangsamaksin, J. Kitajewski, H. N. Ginsberg, and D. Accili, "Inhibition of Notch uncouples Akt activation from hepatic lipid accumulation by decreasing mTORC1 stability," *Nature Medicine*, vol. 19, no. 8, pp. 1054–1060, 2013.