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Emerging novel targets for nonalcoholic fatty liver disease treatment: Evidence from recent basic studies

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Abstract

Nonalcoholic fatty liver disease (NAFLD), a leading chronic disease worldwide, affects approximately a quarter of the global population. Nonalcoholic steatohepatitis (NASH) is an advanced form of NAFLD and is more likely to progress to liver fibrosis than simple steatosis. NASH is also identified as the most rapidly growing cause of hepatocellular carcinoma. Although in the past decade, several phase II/III clinical trials have shown promising results in the use of novel drugs targeting lipid synthase, farnesoid X receptor signaling, peroxisome proliferator-activated receptor signaling, hepatocellular injury, and inflammatory signaling, proven pharmaceutical agents to treat NASH are still lacking. Thus, continuous exploration of the mechanism underlying the pathogenesis of NAFLD and the identification of novel therapeutic targets remain urgent tasks in the field. In the current review, we summarize studies reported in recent years that not only

provide new insights into the mechanisms of NAFLD development but also explore the possibility of treating NAFLD by targeting newly identified signaling pathways. We also discuss evidence focusing on the intrahepatic targets involved in the pathogenesis of NAFLD as well as extrahepatic targets affecting liver metabolism and function.

Key Words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Pharmaceutical strategies; Liver microenvironment; Gut-liver axis; Adipose tissue-liver axis

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Core Tip: Because of the urgent need to develop therapeutic approaches to treat nonalcoholic fatty liver disease (NAFLD), a large body of basic research has focused on the mechanisms of NAFLD to explore the possibility of new approaches to treat the disease. The current review summarizes studies reported in recent years that not only provide new insights into the mechanisms of NAFLD development but also explore the possibility of treating NAFLD by targeting newly identified signaling pathways. Evidence focusing on the intrahepatic targets involved in the pathogenesis of NAFLD as well as extrahepatic targets affecting liver metabolism and function are discussed.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has become a leading chronic disease worldwide, affecting approximately a quarter of the global population. Nonalcoholic steatohepatitis (NASH), the advanced form of NAFLD, is closely related to liver fibrosis and even cirrhosis[1]. NASH has also been identified as the most rapidly growing cause of hepatocellular carcinoma (HCC) in liver transplant candidates in the United States[2]. Multiple factors, including disturbed lipid homeostasis, insulin resistance, and inflammation, lead to metabolic stress in hepatocytes and subsequent hepatocyte injury in NAFLD. Hepatocyte injury further triggers the wound-healing response, which involves immune cells, liver sinusoidal endothelial cells (LSECs), hepatic stellate cells (HSCs) and cholangiocytes, eventually leading to liver inflammation and fibrosis[3].

Despite the increasing prevalence of NASH, the United States Food and Drug Administration (FDA) has not yet approved any pharmaceuticals to treat patients with NASH. The mainstay of the current clinical recommendation for patients with NASH is lifestyle modification, with optimization of dietary structure, control of excessive consumption of fructose and fats and increased physical exercise, which may alleviate the progression of NASH to a certain extent[4]. In addition, bariatric surgery may be indicated for some patients with NASH suffering from severe obesity[5]. Regarding the pharmacotherapy for NASH, several biological pathways critical for glycolipid and bile acid metabolism, inflammation, hepatocellular damage (oxidative stress) and liver fibrosis have been explored as drug targets. Pharmaceutical agents, including modulators of farnesoid X receptor, peroxisome proliferator-activated receptors (PPARs), fibroblast growth factor, acetyl-CoA carboxylase (ACC), and apoptosis signal-regulating kinase 1 (ASK1), have been shown to exhibit some positive effects against NAFLD/NASH with various limitations in multiple clinical trials[6]. Thus, there is still an unmet clinical need to identify and validate novel targets for the treatment of NAFLD/NASH.

Recently, numerous novel therapeutic targets for NAFLD have been explored through basic research. These studies have focused on different pathophysiologic processes in NAFLD, including metabolic stress, liver inflammation, liver fibrosis and NASH-associated HCC. Diverse liver cells have been studied, such as hepatocytes, liver immune cells, HSCs and LSECs (Figure 1). As a metabolic disorder, crosstalk between the liver and extrahepatic organs, including the gut, adipose tissue, and skeletal muscle, largely contributes to the pathogenesis of NAFLD[7,8]. Thus, targets outside the liver broaden potential approaches to ameliorate NAFLD (Figure 1). The drugs in phase II/III clinical trials were extensively discussed in a recently published review[6]. In the present review, we summarize recent findings that not only provide new insights into the mechanisms of NAFLD development but also explore the possibility of treating NAFLD by targeting novel signaling pathways.

APPROACHES TARGETING METABOLIC STRESS TO PREVENT NAFLD PROGRESSION

Lipid accumulation in hepatocytes is a major feature of NAFLD. Disturbance of lipid and glucose metabolism causes metabolic stress in the liver. Therapeutic candidates directly regulating fatty acid metabolism that are currently in clinical trials include ACC, fatty acid synthase and stearoyl-CoA desaturase-1 inhibitors[6,9]. In addition to the targets acting on these lipid metabolic enzymes, in-depth basic research has uncovered multiple mechanisms underlying the metabolic disturbance during NAFLD, including but not limited to lipid, glucose, lactate and fructose metabolism, and has provided novel targets for NAFLD treatment.

Sterol regulatory element-binding proteins (SREBPs), including SREBP1a, SREBP1c and SREBP2, are key regulators mediating free fatty acid, triglyceride (TG) and cholesterol synthesis. 25-Hydrox-anoanosterol (25-HL) is a newly identified SREBP inhibitor that induces the SCAP-INSIG interaction, which retains SREBPs in the endoplasmic reticulum (ER). 25-HL reduces hepatic TG and cholesterol levels and improves liver inflammation and fibrosis in western diet-fed mice[10]. Orosomucoid (ORM) 2, a secreted protein, has been shown to inhibit SREBP1c by activating AMP-activated protein kinase (AMPK). Recombinant ORM2 protein or stabilized ORM2-FC fusion protein inhibits lipogenesis and improves steatohepatitis[11].

Citrate regulates lipid metabolism as the substrate for lipogenesis. In the cytoplasm, citrate is catabolized by ATP-citrate lyase (ACLY) to generate acetyl-CoA and oxaloacetate. Acetyl-CoA is then converted to malonyl-CoA by ACC to fuel lipogenesis. The mitochondrial citrate carrier Slc25a1 plays an important role in regulating cytoplasmic and mitochondrial citrate pools. Tan and colleagues revealed that an inhibitor of Slc25a1, CTPI-2, inhibits the lipogenic pathway and prevents hepatic lipid accumulation in high-fat diet (HFD)-fed mice. Additionally, CTPI-2 also showed beneficial effects on liver inflammation[12]. ACLY, the enzyme mediating the production of acetyl-CoA from citrate, has been identified to be upregulated in the transition from simple steatosis to NASH[13]. Hepatocyte-specific deletion of ACLY reduces liver fatty acid and sterol synthesis, increases fatty acid oxidation, and attenuates glucose intolerance, liver steatosis, and ballooning[14]. Consistent with the observations following genetic inhibition, bempedoic acid, a pharmacological inhibitor of ACLY, also reduces fibrosis[14]. During the de novo lipogenesis process, nicotinamide adenine dinucleotide phosphate (NADPH), as an electron donor, aids in the reduction of acetyl-CoA. Thus, fine-tuning the NADPH pool can regulate lipogenesis. One-carbon units come largely from serine catabolism by the enzyme serine hydroxymethyltransferase (SHMT)[15]. Zhang *et al*[16] demonstrated that SHMT1-driven serine catabolism is a substantial NADPH source in the liver. They further found that inhibition of serine catabolism by Shmt1 gene knockout or pharmacological inhibition of SHMT1/2 enzymes significantly decreased hepatic lipogenesis[16]. Moreover, in sucrose-induced fatty liver, lipogenesis also requires NADPH from serine catabolism, which can be inhibited by the SHMT1/2 inhibitor SHIN2 IV. Therefore, SHMT1/2 inhibition has the potential to treat NAFLD by decreasing de novo lipogenesis.

As an energy source and an important glycolysis product, lactate is increased in the plasma and liver of NAFLD individuals. A recent study showed that the acetylation of lactate dehydrogenase B (LDHB) is markedly increased in the livers of mice with NAFLD, which leads to decreased LDHB activity and increased hepatic lactate levels. The authors further found that P300/CBP-associated factor (PCAF)-mediated LDHB acetylation at K82 exacerbates lipid accumulation and inflammatory responses in HFD-fed mice. Consistently, embelin, an inhibitor of PCAF, significantly improves hepatic steatosis and inflammation in NASH mice[17]. In addition, increasing evidence has demonstrated that overconsumption of fructose is associated with NAFLD. Fructose is metabolized to fructose-1-phosphate by ketohexokinase. PF-06835919 is a ketohexokinase inhibitor that showed protective effects against fructose-induced liver steatosis. Moreover, the safety of PF-06835919 has been verified in a phase I clinical trial[18].

Mitochondrial and ER functions are crucial in lipid and glucose metabolism, and mitochondrial dysfunction and ER stress are closely related to NAFLD[19]. Methylation-controlled J (MCJ) protein is located at the inner mitochondrial membrane and restrains mitochondrial respiration. Its expression level is found to be increased in NAFLD patients. MCJ deficiency reduces hepatic steatosis and improves liver fibrosis in methionine- and choline-deficient (MCD) diet-fed mice. In a recent study, lipid-nanoparticle-encapsulated (LNP) siRNA was employed to target MCJ *in vivo*. LNP-siMCJ increased the β -oxidation of fatty acids and ameliorated lipid accumulation and liver fibrosis in MCD diet- or high-fat/high-fructose diet-induced NASH mice. To further specifically target MCJ in hepatocytes, N-acetylgalactosamine (GalNAc)-modified siMCJ was used to treat NASH mice. Consistent with LNP-siMCJ, GalNAc-siMCJ also reduced liver steatosis and fibrosis[20]. In addition, low-dose sorafenib, the first small-molecule multi-kinase inhibitor, was reported to induce mitochondrial uncoupling and subsequently suppress free fatty acid-induced lipid accumulation and inflammation by activating AMPK in hepatocytes. Low-dose sorafenib protects high-fat/high-cholesterol diet-fed mice against liver steatosis, inflammation and fibrosis and prevents the onset of NASH-associated HCC in mice. Notably, the beneficial effects of low-dose sorafenib were also confirmed in NASH monkeys[21]. Moreover, cyclophilin D is located in the mitochondrial matrix and mediates mitochondrial permeability transition pore opening. Cyclophilin D is upregulated in HFD-fed mice, which induces mitochondrial stress and hepatic steatosis. Cyclosporine A, an inhibitor of

cyclophilin D, decreased liver TG levels in HFD-fed mice by decreasing SREBP1c expression[22]. ER stress also plays important roles in NAFLD. The expression of forkhead box A3 (FOXA3) is induced by ER stress, and FOXA3 mediates ER stress-induced liver steatosis. As expected, targeting FOXA3 *via* a siRNA-based approach attenuates liver steatosis in HFD-fed mice[23].

It has been previously reported that the expression of DEAD-box protein 5 (DDX5), an ATP-dependent RNA helicase, is reduced in the livers of patients and mouse models with NASH, as well as in rodent models with NASH-HCC[24]. Hepatic DDX5 improves lipid metabolism by inhibiting mammalian target of rapamycin complex 1 (mTORC1) activation *via* recruitment of the tuberous sclerosis complex (TSC)1/2 complex to mTOR[24]. Through screening a natural compound library, hyperforinol K was found to upregulate DDX5 expression by blocking tripartite motif protein 5-mediated ubiquitinated degradation of DDX5. In an animal study, hyperforinol K was found to be effective in attenuating lipid accumulation in the livers of NASH mice[24].

Sterile 20-type kinase serine/threonine kinase 25 (STK25) has been demonstrated to play important roles in liver lipid partitioning[25,26] and systemic glucose and insulin homeostasis[27]. The level of STK25 protein is positively correlated with the development of NASH in patients[28]. Moreover, STK25 deficiency can protect against liver steatosis, inflammation, and fibrosis in mouse models of NASH-HCC[29]. STK25 antisense oligonucleotides (ASOs) significantly improved the NASH phenotype, and this preclinical validation of the effective metabolic efficacy of pharmacological inhibition of STK25 merits recognition[28].

Many nuclear receptors play critical roles in metabolic regulation. In current phase II and III trials, PPARs, farnesoid X receptor, and thyroid hormone receptor- β are promising candidate targets for NASH treatment[6]. Based on recent basic studies, modulation of retinoic acid receptor-related orphan receptor alpha (RORa) provides a novel target to treat NASH. RS-2982, a newly identified agonist of RORa, exhibited beneficial effects on reducing body weight and hepatic steatosis in HFD-fed mice. Furthermore, RS-2982 decreased alanine aminotransferase (ALT) and aspartate aminotransferase levels and reduced liver inflammation and fibrosis in mice fed an atherogenic diet. Mechanistically, an increase in miR-122 expression may account for these beneficial effects of RS-2982 on obesity and NAFLD/NASH[30].

Arachidonic acid (ARA) is an ω -6 long-chain polyunsaturated fatty acid (PUFA) that can be catalyzed into a series of bioactive eicosanoids *via* cyclooxygenases (COX-1 and COX-2) and microsomal prostaglandin E synthases (mPGES-1 and mPGES-2). It has been recently reported that mPGES-2 deficiency exhibits significant protective effects against diet-induced NASH-associated phenotypes, including hepatic steatosis, inflammation and fibrosis. However, the beneficial effect of mPGES-2 deficiency against NAFLD is dependent on decreased cytochrome P450 4A14 (CYP4A14) and increased acyl-CoA thioesterase 4 levels but not PGE2[31]. Mechanistically, mPGES-2 binds with heme, which is released after mPGES2 inhibition and in turn activates the heme receptor nuclear receptor subfamily 1 group D member 1 (NR1D1) to upregulate CYP4A14 and acyl-CoA thioesterase 4 expression[31]. CYP4A14 catalyzes omega-hydroxylation of medium-chain fatty acids and ARA in mice. Its expression was previously found to be significantly increased in the livers of patients and mice with NAFLD. Loss of CYP4A14 function also markedly attenuated liver damage, inflammation, and fibrosis in MCD diet-induced NASH[32]. Moreover, both the mPGES-2 inhibitor SZ0232 and the CYP4A inhibitor TS-011 are capable of ameliorating the NASH phenotype in MCD diet-fed mice[31-33]. Taken together, these findings demonstrate that ARA metabolic enzymes play critical roles in liver lipid homeostasis and represent attractive targets for developing therapeutic drugs for NAFLD/NASH.

Emerging evidence suggests that novel therapeutic targets can be developed based on the discovery of genetic variants related to liver lipid metabolism, such as *PNPLA3*, *TM6SF2*, *MBOAT7* and *HSD17B13* [34-37]. It has been reported that phosphorylation of HSD17B13 at serine 33 by PKA promotes lipolysis. Reproterol, a β 2 agonist used for treating asthma, protects against the NASH phenotype *via* PKA-mediated Ser33 phosphorylation of 17 β -HSD13[38]. Most recently, a variant in the *pleckstrin and Sec7 domain-containing 3* (*PSD3*) gene, rs71519934, was reported to reduce susceptibility to fatty liver disease, consistent with the finding that the expression level of *PSD3* is increased in patients with NAFLD and that knockdown of *PSD3* by siRNA decreases TG synthesis in hepatocytes. Furthermore, specific downregulation of *PSD3* in hepatocytes by GalNAc-conjugated ASOs resulted in decreased hepatic lipid content and plasma ALT levels and improved liver fibrosis in NASH mice[39], suggesting that *PSD3* may be a potential therapeutic target for the treatment of NAFLD/NASH.

STRATEGIES PROTECTING HEPATOCYTES FROM INJURY DURING NASH DEVELOPMENT

Lipid accumulation in hepatocytes can cause cytotoxicity (lipotoxicity) in NAFLD[40,41]. Hepatocyte injury is a key event during the development of NASH, and ballooned hepatocytes are an essential feature to diagnose NASH. In phase II/III clinical trials, pancaspase inhibitors and ASK1 inhibitors are currently under evaluation as therapeutic agents directly targeting apoptosis[6]. Studies focused on developing targets to prevent hepatocyte injury have also shown therapeutic effects in NASH.

Mitochondrial stress is a major factor driving hepatocyte injury and promotes the progression from simple steatosis to NASH. Mitochondrial matrix caseinolytic protease P (ClpP) is a protease component of the caseinolytic protease complex that maintains protein homeostasis in mitochondria. Its expression level is frequently downregulated in NASH, which induces mitochondrial stress and inflammation in hepatocytes. The ClpP activator A54556A is capable of greatly ameliorating the NASH phenotype in high-fat/high-fructose diet-fed mice[42]. SH3 homology-associated BTK binding protein (SAB) was originally identified as a phosphorylated c-Jun N-terminal kinase (p-JNK) docking protein and a substrate of JNK in the mitochondrial outer membrane. The interaction of JNK with SAB leads to increased mitochondrial reactive oxygen species (ROS) production and promotes liver injury. In established NASH, hepatocyte-targeted GalNAc-Sab-ASO treatment can reverse steatohepatitis and fibrosis by abrogating the adverse effects of the JNK-SAB-ROS activation loop[43]. Sirtuin activation plays an important role in maintaining mitochondrial homeostasis and shows protective effects on NAFLD[44]. Increased NAD⁺ levels can activate sirtuin. The enzyme α -amino- β -carboxymuconate- ϵ -semialdehyde decarboxylase controls NAD⁺ levels, and its inhibitor TES-991 boosts de novo NAD⁺ synthesis and protects mice against liver injury and steatosis by improving mitochondrial function[45]. In addition, the serine/threonine protein phosphatase 2A inhibitors LB100[46], allyl isothiocyanate[47], celastrol[48] and the heme oxygenase inducer cobalt protoporphyrin[49] have all been found to significantly ameliorate NASH *via* the Sirt1 pathway. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a well-known important transcription factor involved in the expression of antioxidant genes during oxidative stress. Targeted deletion of Nrf2 results in enhanced susceptibility to a variety of oxidative stress-induced liver injuries, including NASH. In contrast, pharmacological or genetic activation of hepatic Nrf2 leads to hepatic protection against oxidative damage. Studies have shown beneficial effects of hepatocyte Nrf2 activation in NASH[50]. Pharmacological activation of Nrf2 by the acetylenic tricyclic bis (cyano enone) compounds TBE-31[51], NK-252[52], and dimethyl fumarate[53] suppresses NASH. These findings demonstrate that strategies that increase Nrf2 expression and activity may be attractive strategies to limit the development of NAFLD/NASH by attenuating hepatocyte lipotoxicity and injury.

As mentioned above, apoptosis plays an important role in hepatocyte injury or loss during the development of NAFLD/NASH. BCL-2 belongs to the BCL-2 family, which is antiapoptotic. Through screening a small molecule library, acridone derivative A22 was found to increase BCL-2 expression by stabilizing the BCL-2 promoter i-motif. As expected, A22 can attenuate HFD-induced hepatocyte injury, hepatic steatosis and liver fibrosis[54]. In addition, necroptosis, another form of programmed cell death, was found to be increased in NASH mouse models and the livers of NAFLD patients. Receptor-interacting protein 3 (RIP3) and receptor-interacting protein kinase (RIPK) 1 are key mediators of necroptosis. Liver RIP3 deficiency can attenuate MCD diet-induced liver injury, steatosis, inflammation and fibrosis[55]. Similarly, the RIPK1 inhibitor RIPA-56 can reduce liver inflammation and fibrosis in HFD-fed mice by abrogating necroptosis. In addition, RIPA-56 is able to ameliorate hepatic steatosis by suppressing mixed lineage kinase domain-like protein levels[56].

Iron overload leads to hepatic oxidative stress and hepatocellular ballooning injury and plays a multifactorial role in the pathogenesis of NASH[57]. Approximately one-third of patients with NAFLD show interrupted iron homeostasis[58]. Ferroptosis is a nonapoptotic programmed cell death process characterized by iron-dependent and lipid peroxidation-associated cell death[59]. The ferroptosis inhibitors Trolox and deferiprone can protect hepatocytes from cell death and suppress the subsequent initiation of inflammation in fatty liver[60].

In contrast to hepatocytes, agents that induce HSC apoptosis show beneficial effects against NASH-related liver fibrosis[61]. Thus, when using pharmacological agents to prevent hepatocyte injury, strategies more accurately targeting hepatocytes may strengthen the therapeutic effects of these agents against NASH with limited side effects.

APPROACHES TARGETING THE INFLAMMATORY PATHWAY TO TREAT NAFLD/NASH

Inflammatory responses mediated by various immune cells and hepatocytes promote the onset of NASH and liver fibrosis. Infiltration of neutrophils and macrophages is the main pathological feature of NASH. Neutrophil depletion attenuates diet-induced NASH[62]. CXC chemokine receptor 2 (CXCR2) signaling is considered to play a pivotal role in the entry of neutrophils into peripheral tissues. Leslie and colleagues demonstrated that human and mouse livers with NASH-HCC have more CXCR2⁺ neutrophils[63]. The expression of CXCR2 in neutrophils is induced in NASH in an autocrine manner involving the upregulation of neutrophil-derived lipocalin 2[64]. AZD5069 is a small-molecule inhibitor of CXCR2. AZD5069 can significantly improve liver pathology in NAFLD, with reduced lipid content and hepatic neutrophil accumulation and improved insulin sensitivity[65]. In addition, AZD5069-mediated CXCR2 inhibition induces reprogramming of the tumor immune microenvironment, which promotes immune checkpoint inhibition in NASH-HCC[63], suggesting that blocking infiltrating neutrophil CXCR2 can restore sensitivity to immunotherapy in the NASH liver[66].

It is well known that the expression of macrophage scavenger receptor 1 (MSR1) mediates lipid uptake in macrophages and subsequently induces inflammatory activation *via* the JNK pathway. MSR1 was found to be correlated with liver inflammation in NAFLD patients[67]. Notably, therapeutic inhibition of MSR1 with an anti-MSR1 antibody improved hepatic steatosis in a mouse model of NASH. The number of F4/80-positive cells and the expression level of tumor necrosis factor alpha (TNF- α) were also found to be reduced by the anti-MSR1 antibody therapy[67].

It has long been recognized that the NOD-like receptor protein 3 (NLRP3) inflammasome is activated in NASH livers, which leads to increased inflammation and programmed cell death. MCC950, an NLRP3 inhibitor, can improve NAFLD pathology and fibrosis in obese diabetic mice[68]. X-box binding protein-1 (XBP1) is a key factor regulating the unfolded protein response. Macrophage XBP1 is upregulated in NASH livers, which activates macrophage NLRP3 signaling and promotes hepatocyte steatosis and HSC activation. As expected, the XBP1 inhibitor toyocamycin exhibits protective effects against NASH[69].

Nuclear factor-kappaB (NF- κ B) is an essential transcription factor that mediates the inflammatory response and proinflammatory cytokine production in NASH[70]. miR-378 markedly facilitates the NF- κ B-TNF- α axis in NASH development by directly targeting the *Prkag2* gene, which encodes AMPK- γ 2. Similarly, downregulation of miR-378 by ASO is also capable of alleviating NASH development[71].

In addition to neutrophils and macrophages, other immune cells, including dendritic cells (DCs) and lymphocytes, play pivotal roles in NASH[8]. DC recruitment to the liver promotes the inflammatory response in NAFLD progression. Reportedly, delivery of liposomal curcumin or calcitriol to lipid-rich inflammatory DCs shifted their inflammatory profile toward a regulatory phenotype and improved hepatic steatosis, inflammation and fibrosis in a NASH mouse model[72]. Inflammatory CX₃CR1⁺ monocyte-derived inflammatory DCs (moDCs) are found to contribute to sustained inflammation and liver injury during NASH. Treating MCD-fed mice with the hydrogen sulfide donor *i.e.*, sodium hydrosulphide, prevented the accumulation of CX₃CR1⁺ moDCs and ameliorated parenchymal injury [73]. Moreover, Toll-like receptor 7 (TLR7) signaling can induce proinflammatory cytokine production in Kupffer cells and DCs, subsequently suppressing regulatory T cells (Tregs) and leading to steatohepatitis. Notably, treatment with IRS-661, a TLR7 antagonist, could ameliorate NASH development[74]. It has been reported that α 4 β 7-mediated homing of CD4 T cells to the intestine and liver facilitates NASH development, and α 4 β 7 blockade by neutralizing monoclonal antibody can attenuate hepatic inflammation and fibrosis and improve metabolic dysfunction associated with NASH[75]. In addition, a high level of Tregs reportedly promotes the initiation and progression of cancer in NASH livers. In a NASH-HCC model, anti-CD25 antibodies, capable of alternatively depleting Tregs, decreases the tumor burden and increased survival time[76]. The interaction of B2 Lymphocytes with T cells contributes to NASH progression, B-cell activating factor-neutralizing monoclonal antibody Sandy-2 prevented hepatic B2 cell response and ameliorated the evolution of NASH in mice[77].

Bioactive lipids are important nodes in lipid metabolism and tissue homeostasis networks[78]. An imbalance between protective and deteriorative bioactive lipids contributes to NASH progression[79]. Pharmacological targeting of the synthesizing enzymes or receptors of these bioactive lipids has shown beneficial effects in NASH. Leukotriene B4 (LTB4), a proinflammatory metabolite derived from the ω -6 PUFA ARA, is significantly increased in patients with NAFLD[80]. Both *in vivo* and *in vitro* experiments have shown that LTB4 can promote hepatocyte lipogenesis, which is dependent on the RNase activity of IRE1 α through leukotriene B4 receptor 1 (Ltb4r1). Furthermore, LTB4/Ltb4r1 stimulation increases intracellular cAMP and then promotes IRE1 α Ser724 phosphorylation by PKA[80]. The Ltb4r1 inhibitor CP-105696 significantly alleviated ER stress and dyslipidemia in NAFLD mice[80]. Unlike ω -6 PUFAs, ω -3 PUFAs and their metabolites show anti-inflammatory effects. Fat-1 mice, a transgenic animal model in which tissues are endogenously enriched with ω -3 PUFAs[81], are protected from diet-induced metabolic dysfunction and fibrosis[82]. However, they are vulnerable to lipid peroxidation, which limits their clinical applications[83]. Fraser *et al*[84] developed a structurally modified ω -3 fatty acid, icosabutate, which was designed to resist oxidation and incorporation into hepatocytes and possesses the potential to activate free fatty acid receptor 4. They found that icosabutate, but not the ω -3 PUFA eicosapentaenoic acid, can ameliorate liver inflammation and fibrosis in NASH rats. Moreover, icosabutate treatment decreases liver injury in patients at high risk of NASH and cardiovascular disease [84].

APPROACHES TARGETING HSC ACTIVATION TO PREVENT NASH-RELATED LIVER FIBROSIS

In clinical trials for NASH drug development, improvement of liver fibrosis has been frequently employed as a primary or secondary endpoint. Given the central role of HSCs in liver fibrosis, targeting HSC activation has long been proposed as a therapeutic strategy to prevent NASH-related fibrosis progression.

The Notch, Hedgehog, Hippo and WNT/ β -catenin signaling pathways in hepatocytes play important roles in NASH-related liver fibrosis by modulating the hepatic microenvironment. The production of osteopontin (OPN), as a paracrine factor, from hepatocytes or cholangiocytes increases in NASH, which leads to the activation of HSCs[85-87]. Increased Notch signaling activity has been found to be responsible for the induction of OPN[85]. Thus, several studies have targeted Notch signaling to treat NASH, including studies on Nicastrin ASO and nanoparticle-mediated delivery systems targeting Notch antagonism[85,88]. In addition, nuclear factor of activated T-cell 4 (NFATc4) was also reported to induce OPN expression by negatively regulating the transcriptional activity of PPAR α . As expected, inhibition of NFATc4 decreased lipid content and improved inflammation and fibrosis in NASH mice [89]. Hepatocyte transcriptional co-activator with PDZ-binding motif (TAZ) was found to promote NASH-related liver fibrosis by increasing Indian hedgehog, which activates HSCs[90]. A recent study reported that stabilized GalNAc-siRNAs targeting hepatocyte TAZ can significantly ameliorate liver inflammation and fibrosis in mice with established NASH[91]. Furthermore, WNT1-inducible signaling pathway protein 1 (WISP1), a member of the cellular communication network family, has recently been identified as an extracellular activator of the myocardin-related transcription factor-cytoskeleton pathway in HSCs. Activation of the WISP1-MRIF signaling pathway induces HSC migration and promotes liver fibrosis progression. Notably, an anti-WISP1 antibody significantly ameliorated liver fibrosis in NASH mice[92].

Interleukin-11 (IL-11) has been demonstrated to activate HSCs. Deletion of IL-11 receptor subunit alpha (IL-11RA) protects mice from NASH diet-induced hepatocyte death, liver inflammation and fibrosis. Widjaja *et al*[93] developed a neutralizing anti-IL-11 antibody and neutralizing anti-IL-11RA antibody and found that both of them greatly decreased ALT levels and significantly improved hepatic steatosis and liver fibrosis in mouse models of NASH[93].

Activation of the JAK/signal transducer and activator of transcription (STAT) pathway in HSCs promotes liver fibrosis. Ruxolitinib, an effective small-molecule JAK1/2 selective inhibitor, has been approved by the FDA for myelofibrosis treatment. Recently, it has been reported that ruxolitinib can block HSC activation and attenuate liver fibrosis progression[94]. In addition, the JAK2 inhibitor pacritinib affords protection against NAFLD-related liver fibrosis by inhibiting HSC activation[95]. Rilpivirine, a nonnucleoside reverse transcriptase inhibitor, is widely used to treat HIV infection. Rilpivirine can also ameliorate liver fibrosis, possibly through selective STAT1-dependent induction of apoptosis in HSCs, and suppress HFD- and CCl₄-induced liver fibrosis. In addition, rilpivirine enhances STAT3-dependent proliferation in hepatocytes as an effect secondary to its pro-apoptotic effect in HSCs [96].

Protease-activated receptor-2 (PAR2) is an emerging new target for NASH that regulates liver injury, inflammation and fibrosis and plays a critical role in regulating hepatic cholesterol and glucolipid metabolism[97-99]. Pharmacological inhibition of PAR2 with pepducin PZ-235, a full antagonist of PAR2, not only protects against the activation of HSCs and fibrosis but also promotes hepatocellular viability by inhibiting mitochondrial ROS production induced by PAR2 stimulation[97].

APPROACHES TARGETING LSECS AND CHOLANGIOCYTES TO TREAT NAFLD

LSECs are highly specialized endothelial cells with fenestrae and lack a basement membrane. LSECs interact with hepatocytes, liver immune cells and HSCs and play important roles in regulating liver function. LSEC dysfunction, including LSEC capillarization, disturbed nitric oxide release from LSECs, and increased expression of adhesion molecules, all contribute to NAFLD pathogenesis[100]. Vascular cell adhesion molecule 1 (VCAM-1) is an adhesion molecule upregulated in LSECs in NASH mouse livers. Anti-VCAM1 antibody attenuates hepatic inflammation in NASH mice[101]. Endothelial nitric oxide synthase (eNOS) expression in LSECs is decreased in NASH mice, which is likely the result of Notch activation. Pharmacological inhibition of Notch signaling using DAPT and LY3039478, as well as the eNOS activator YC-1, improved the NASH phenotype in MCD diet-fed mice[102]. Although the role of LSECs in NAFLD has been increasingly emphasized, the underlying mechanisms and therapeutic approaches targeting LSECs need more exploration.

Cholangiocytes also play an important role in NASH development. In addition to hepatocytes, OPN is strongly expressed in cholangiocytes in NASH livers. Thus, it is highly possible that cholangiocyte-derived OPN can promote liver fibrosis by activating HSCs[87]. Cardiotrophin-like cytokine factor 1 is another cholangiocyte-derived paracrine factor that exerts beneficial effects in NASH. Downregulation of a subunit of its receptor complex leukemia inhibitory factor receptor contributes to the progression of NASH[103]. Compared with other nonparenchymal cells, there are fewer studies addressing the effects of cholangiocytes on NASH, and a related therapeutic approach is still lacking.

POTENTIAL TARGETS OUTSIDE THE LIVER

It is well-established that multiple organs form a network to regulate whole-body energy metabolism.

Extrahepatic organs influence liver function in an endocrine manner by releasing hormones or inflammatory factors or by regulating systemic metabolic homeostasis such as energy expenditure and insulin sensitivity. Thus, targeting these extrahepatic organs provides additional options for treating NAFLD/NASH.

Targets affect systemic energy metabolism

Diets with reduced contents of sugars, refined carbohydrates and saturated fat are recommended to treat NAFLD[104]. Moreover, exercise is considered as an effective strategy for preventing and treating NAFLD *via* metabolic pathways and interorgan crosstalk[105]. Glucagon-like peptide (GLP)-1 receptor agonists, which enhance insulin secretion and reduce food intake, show beneficial effects against NASH in clinical trials[6]. In addition, fibroblast growth factor 21 analogs improved systemic energy metabolism and demonstrated potential in NASH therapy[6]. In a recent basic study, a novel Zn supplement, ulvan oligosaccharide (UO)-Zn, can activate AMPK, leading to improved metabolic pathways in HFD-fed mice[106]. The increased hepatic expression of branched chain ketoacid dehydrogenase kinase (BDK) partly induced high levels of branched-chain amino acids (BCAA) in metabolic diseases[107-109]. Moreover, 3,6-dichlorobrenzo(b)thiophene-2-carboxylic acid, a small-molecule allosteric inhibitor of BDK, lowered levels of circulating BCAAs, reduced hepatic steatosis, and improved glucose tolerance in rodent models[107,108].

The gut-liver axis

The crosstalk between the gut and liver is regarded as an important pathway in regulating hepatic functions. Intestinal inflammation and dysfunction of intestinal lipid and bile acid absorption, epithelial cell permeability and the microbiome affect liver function and contribute to NAFLD progression. The relationship between gut microbiota and potential therapeutic targets has been recently discussed in depth elsewhere[110,111]; thus, we only focus on other aspects of the gut-liver axis.

Serum ceramide levels are positively related to NAFLD, and intestine-derived ceramide has been demonstrated to promote NAFLD[112,113]. Intestinal hypoxia-inducible factor 2 α (HIF-2 α) and myelocytomatosis oncogene (MYC) affect NAFLD by regulating ceramide metabolism. Intestinal HIF-2 α , but not HIF-1 α , is activated in obese patients and mice. Intestine-specific HIF-2 α knockout improves hepatic steatosis by decreasing intestine-derived ceramide levels. Mechanistically, HIF-2 α transcriptionally upregulates the expression of Neu3, a key enzyme in the ceramide salvage pathway. Targeting HIF-2 α with its inhibitor PT2385 significantly attenuated hepatic lipid accumulation and decreased plasma ALT levels in HFD-fed mice[112]. Moreover, oral administration of PT2385 contributes to reduced body weight and improved insulin sensitivity[112]. Intestinal MYC expression is positively related to body mass index and serum ALT levels in humans. Genetic ablation of MYC in the intestine suppressed obesity and hepatic steatosis and led to decreased ceramide levels in HFD-fed mice. Ceramide synthase 4 has been further demonstrated to be a target gene of MYC. In line with this finding, pharmacological inhibition of MYC with 10058-F4 was found to ameliorate the metabolic disorders and liver fibrosis induced by HFD feeding[114]. In addition, increased intestinal ceramide also mediates the acceleration of NASH induced by nicotine[115].

Gut-derived 5-hydroxytryptamine (5-HT) has been reported to promote lipogenesis in the liver. Moreover, liver-specific knockout of the 5-HT receptor 2 α (*Htr2a*) gene significantly lowered liver lipid content in HFD-fed mice and decreased the expression of genes involved in lipogenesis. To evaluate the potential of targeting the gut-5-HT-liver *Htr2a* pathway as a therapeutic strategy for NAFLD, the 5-HT receptor HTR2A antagonist sarpogrelate was used to treat HFD-fed mice. The results showed that sarpogrelate greatly ameliorates hepatic steatosis in NAFLD mice[116].

Yan *et al*[117] recently clarified that gut PPAR α activation promotes NASH development by inducing fatty acid binding protein 1 expression, thereby aggravating fatty acid absorption in the small intestine[117]. GW6471, a PPAR α -specific antagonist, was found to accumulate in the small intestine at much higher levels than in the liver. Intestine-specific PPAR α deficiency and gut PPAR α antagonism by GW6471 both improve NASH phenotypes[117]. The pleiotropic roles of PPAR α in different tissues in modulating NASH are worth discussing. Hepatocyte PPAR α is crucial for whole-body fatty acid homeostasis and is protective against NAFLD[118]. Therapeutic strategies to prevent or treat NAFLD by activating hepatocyte PPAR α and/or inhibiting gut PPAR α may help guide drug delivery. Monoacylglycerol acyltransferase 2 (MGAT2) mediates the conversion of monoacylglycerol to diacylglycerol and is critical for dietary fat absorption. In the liver, MGAT2 regulates TG synthesis. BMS-963272, a potent MGAT2 inhibitor, improves the NAFLD activity score and liver fibrosis in NAFLD/NASH mice[119]. Of note, its safety has been confirmed in phase 1 clinical trials[119].

In addition, a long-acting dual agonist of GLP-1 and GLP-2 receptors, GLP1/2-Fc, has been found to greatly alter the microbiome composition and exhibits positive effects on gastrointestinal volume and the intestinal barrier. More importantly, GLP1/2-Fc can significantly ameliorate NASH phenotypes, including hepatic fat accumulation, inflammation, fibrosis and insulin tolerance[120], and its effects are superior to those of liraglutide, which has minimal efficacy on inflammation or fibrosis[121].

The adipose tissue-liver axis

Recently, several novel adipokines have been identified and verified to play important roles in NASH development and progression by mediating the crosstalk between adipose tissue and the liver. Isthmin-1 (ISM1) was identified as an adipokine that can activate phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)-protein kinase B (Akt) signaling independent of insulin. *ISM1* gene expression is positively correlated with body mass index, and its deficiency leads to glucose intolerance *via* inhibition of PI3K-Akt signaling. In addition, ISM1 suppressed de novo lipogenesis in the liver. Recombinant ISM1 protein exhibited beneficial effects on both glucose tolerance and hepatic steatosis in NAFLD mice[122]. Recently, Liu *et al*[123] demonstrated that secreted protein acidic and rich in cysteine-like protein 1 (Sparcl1), which is a white adipose tissue-secreted protein, is correlated with hepatic pathological features in NASH patients. The authors further found that sparcl1 can induce liver inflammation by increasing C-C motif chemokine ligand 2 expression in the liver. To further determine the role of sparcl1 in the pathogenesis of NASH, the authors developed a neutralizing antibody against sparcl1 and found that the sparcl1-neutralizing antibody markedly ameliorated liver inflammation and liver fibrosis in NASH mice[123]. Gremlin 1, a newly identified adipokine, is positively related to insulin resistance and NAFLD/NASH. Treatment with recombinant Gremlin 1 protein impairs insulin sensitivity in various cell types, including human primary adipocytes, skeletal muscle cells, and liver cells. The insulin-sensitizing effect of the neutralizing anti-Gremlin 1 antibody indicates its beneficial effects on insulin resistance and NAFLD/NASH[124]. Neuregulin 4 (NRG4) is an adipose tissue-derived endocrine factor that has been demonstrated to suppress NASH-associated HCC by restraining the tumor-prone liver immune microenvironment. A recombinant fusion protein comprising amino acids 1–55 of human NRG4 and the Fc domain of immunoglobulin G 1 was found to suppress HCC induced by a NASH diet plus oncogene overexpression[125].

SWELL1/LRRC8a, a leucine-rich repeat-containing transmembrane protein, functionally encodes an ion channel signaling complex on the adipocyte plasma membrane[126]. Adipocyte SWELL1 is dispensable for adipose development[127]. SWELL1 protein is reduced in the adipocytes of type 2 diabetic animals. The small molecule SN-401, which binds at a constriction point within the SWELL hexamer, can increase adipocyte SWELL1 protein expression and SWELL1-dependent insulin signaling. Similarly, SN-401 can normalize glucose tolerance by augmenting tissue glucose uptake, suppressing hepatic glucose production, increasing serum fibroblast growth factor 21 levels, and reducing hepatic steatosis and hepatocyte ballooning in obese type 2 diabetic mice[128]. Taken together, these findings demonstrate that targeting the adipose tissue-liver axis may be an attractive strategy to treat NAFLD/NASH.

The skeletal muscle-liver axis

The crosstalk between skeletal muscle and the liver also impacts NAFLD progression. As one of the energy metabolism organs, skeletal muscle can affect liver lipid and glucose metabolism by regulating systemic metabolic homeostasis. In addition, decreased skeletal muscle mass and altered myokine secretion are associated with exacerbation of NAFLD progression[129,130]. Myostatin signaling negatively regulates muscle mass and is positively related to liver fibrosis[131]. Irisin (encoded by fibronectin type III domain containing 5, *Fndc5*), a myokine induced by exercise, is also expressed in adipose tissue and the liver. Serum irisin levels are inversely associated with TG content in the livers of obese adults[132]. Recombinant *Fndc5*/irisin significantly improved the NASH phenotype in HFD-fed mice[133]. The administration of nicotinamide riboside can alleviate obesity and steatosis by increasing irisin levels in HFD-fed mice[133]. Collectively, therapeutic strategies to improve skeletal muscle quantity and quality or target myokine signaling may provide promising options to treat NASH, but basic studies to collect more evidence are warranted.

CONCLUSION

Because of the urgent need to develop therapeutic approaches to treat NAFLD/NASH and the complexity of the pathophysiologic process of NAFLD, a large body of basic research has focused on the mechanisms of NAFLD to explore the possibility of applying new approaches to treat the disease (Tables 1 and 2). Metabolic stress-induced hepatocyte injury is an initial factor driving NASH development. Thus, in hepatocytes, strategies for treating NASH aim to improve metabolic disturbance and protect hepatocytes from injury. Alteration of the liver microenvironment and the interaction between diverse liver cells promote liver inflammation and fibrosis. Therefore, the inflammatory response of hepatocytes and immune cells in the liver is also an important target for NASH treatment. Strategies targeting HSC activation, proliferation and migration show beneficial effects on liver fibrosis and may become a novel way to attenuate NASH outcomes (Figure 1). As an indispensable part of hepatic metabolic regulation, extrahepatic organs play an essential role in liver lipid homeostasis, and their dysfunction contributes to the development and progression of NAFLD/NASH. The gut, adipose tissue and skeletal muscle can functionally affect liver or whole-body energy metabolic homeostasis *via* various endocrine factors (Figure 1 and Table 2).

Table 1 Novel intrahepatic targets explored by recent basic study

Molecular target	Potential agent	Classification	Function	Effects on NAFLD	Ref.
SREBPs	25-HL	Inhibitor	Decrease TG and cholesterol synthesis	-Hepatic steatosis -Liver inflammation -Liver fibrosis	[10]
ORM2	Recombinant ORM2; ORM2-FC fusion protein	Recombinant protein	Inhibit lipogenesis	-Hepatic steatosis -Liver inflammation -Liver fibrosis	[11]
Slc25a1	CTPI-2	Inhibitor	Regulating cytoplasmic and mitochondrial citrate pool	-Hepatic steatosis -Liver inflammation	[12]
ACLY	Bempedoic acid	Inhibitor	Inhibit ACLY activity	-Hepatic steatosis -Liver injury	[14]
SHMT1/2	SHIN2 IV	Inhibitor	Decrease serine catabolism derived NADPH	-Hepatic lipogenesis	[16]
PCAF	Embelin	Inhibitor	Inhibit acetylation of LDHB	-Hepatic steatosis -Liver inflammation	[17]
Ketohexokinase	PF-06835919	Inhibitor	Regulating fructose metabolism	-Fructose-induced liver steatosis	[18]
Mitochondrial uncoupling	Sorafenib	Small molecule	Induce mitochondrial uncoupling and activate AMPK	-Hepatic steatosis -Liver inflammation -Liver fibrosis -NASH-associated HCC	[21]
MCJ	LNP-siMCJ; GalNAc-siMCJ	Nucleic acid-based therapy	Maintain mitochondrial function	+ β -oxidation -Hepatic steatosis -Liver fibrosis	[20]
Cyclophilin D	CsA	Inhibitor		-Hepatic steatosis	[22]
ClpP	A54556A	Activator		-Hepatic steatosis -Liver inflammation -Liver fibrosis	[42]
SAB	GalNAc-Sab ASO	Nucleic acid-based therapy		-Hepatic steatosis -Liver inflammation -Liver fibrosis	[43]
ACMSD	TES-991	Inhibitor		-Hepatic steatosis -Liver inflammation	[45]
FOXA3	FOXA3 siRNA	Nucleic acid-based therapy	Attenuate ER stress induced liver steatosis	-Hepatic steatosis	[23]
TRIM5-DDX5	Hyperforinol K	N/A	Inhibit ubiquitinated degradation of DDX5	-Hepatic steatosis -Liver inflammation	[24]
STK25	STK25 ASO	Nucleic acid-based therapy	Regulating energy homeostasis	-Hepatic steatosis -Liver inflammation -Liver fibrosis	[28]
RORa	RS-2982	Agonist	Increase miR-122 level	-Hepatic steatosis -Liver inflammation	[30]

HSD17B13	Reproterol	Small molecule	Induce the Ser33 phosphorylation of 17 β -HSD13 protein	-Liver fibrosis -Hepatic steatosis [38] -Liver fibrosis
PSD3	GalNAc-Psd3 ASO	Nucleic acid-based therapy	Decrease TG synthesis	-Hepatic steatosis [39] -Liver injury -Liver fibrosis
Nrf2	TBE-31; NK-252; Dimethyl fumarate	Activator	Reduce oxidative stress	-Hepatic steatosis [51-53] -Liver inflammation -Liver fibrosis
BCL-2	A22	Small molecule	Anti-apoptosis	-Liver injury [54] -Liver fibrosis
RIPK1	RIPA-56	Inhibitor	Abrogating necroptosis	-Hepatic steatosis [56] -Liver inflammation
CXCR2	AZD5069	Inhibitor	Inhibit neutrophil infiltration	-Hepatic steatosis [63,65] -Liver inflammation -Liver fibrosis -NASH-associated HCC
MSR1	Anti-MSR1 antibody	Neutralizing antibody	Inhibit inflammatory response	-Hepatic steatosis [67] -Liver inflammation
NLRP3	MCC950	Inhibitor	Inhibit NLRP3 activation	-Liver inflammation [68] -Liver fibrosis
XBP1	Toyocamycin	Inhibitor		-Hepatic steatosis [69] -Liver inflammation -Liver fibrosis
DCs	Curcumin; calcitriol	Small molecule	Shift hepatic DC inflammatory profile toward a regulatory phenotype	-Hepatic steatosis [72] -Liver inflammation -Liver fibrosis
Hydrogen sulfide	NaHS	Hydrogen sulfide donor	Prevent the accumulation of TNF- α -producing CX ₃ CR1 ⁺ moDCs	-Liver injury [73]
TLR7	IRS-661	Antagonist	Decrease proinflammatory cytokine production in Kupffer cells and DCs	-Hepatic steatosis [74] -Liver inflammation
Integrin	Anti- α 4 β 7 antibody	Neutralizing antibody	Decrease α 4 β 7 ⁺ CD4 T-cell recruitment	-Hepatic steatosis [75] -Liver inflammation -Liver fibrosis
Tregs	Anti-CD25 antibodies	Neutralizing antibody	Deplete Tregs	-NASH-associated HCC [76]
BAFF	Sandy-2	Neutralizing antibody	Prevent hepatic B2-cell responses	-Hepatic steatosis [77] -Liver inflammation -Liver fibrosis
Notch	Nicastrin ASO	Nucleic acid-based therapy	Inhibit Notch signaling	-Liver fibrosis [85]
	NP- dibenzazepine	Inhibitor with target delivery system		-Liver fibrosis [88]
TAZ	GalNAc-TAZ siRNA	Nucleic acid-based	Inhibit TAZ in hepatocyte	-Liver inflammation [91]

WISP1	Anti-WISP1 antibody	therapy	and inhibit HSC activation	-Liver fibrosis	[92]
		Neutralizing antibody	Inhibit HSC migration	-Liver fibrosis	
IL-11	Anti-IL-11 antibody	Neutralizing antibody	Inhibit HSC activation; inhibit hepatocyte injury	-Liver injury	[93]
				-Liver fibrosis	
JAK1/2	Ruxolitinib	Inhibitor	Inhibit HSC activation	-Liver fibrosis	[94]
JAK2	Pacritinib	Inhibitor	Inhibit HSC activation	-Liver fibrosis	[95]
STAT1	Rilpivirine	Inhibitor	Induce HSC apoptosis and promote hepatocyte proliferation	-Liver fibrosis	[96]
PAR2	Pepducin PZ-235	Antagonist	Inhibit HSC activation	-Liver injury	[97]
				-Liver fibrosis	
VCAM-1	Anti-VCAM-1 antibody	Neutralizing antibody	Suppress monocyte adhesion to LSEC	-Liver inflammation	[101]
				-Liver fibrosis	
eNOS	YC-1	Activator	Increase NO production from LSEC	-Hepatic steatosis	[102]
				-Liver inflammation	
				-Liver fibrosis	
Ltb4r1	CP-105696	Inhibitor	Inhibit the effects of LTB4	-Hepatic steatosis	[80]
				-Liver inflammation	
				-Liver fibrosis	
mPGES-2	SZ0232	Inhibitor	Regulating ARA metabolism	-Hepatic steatosis	[31]
CYP4A	TS-011	Inhibitor		-Hepatic steatosis	[32]
				-Liver inflammation	
				-Liver fibrosis	
N/A	Icosabutate	Structurally modified ω -3 fatty acid	Resist oxidation and activate free fatty acid receptor 4	-Liver inflammation	[84]
				-Liver fibrosis	

-: Inhibit; +: Stimulate; SREBPs: Sterol regulatory element-binding proteins; TG: Triglyceride; 25-HL: 25-Hydroxycortisol; HSC: Hepatic stellate cell; LSEC: Liver sinusoidal endothelial cell; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; NO: Nitric oxide; N/A: No application; ORM2: Orosomucoid 2; ACLY: ATP-citrate lyase; SHMT1/2: Serine hydroxymethyltransferase 1/2; NADPH: Nicotinamide adenine dinucleotide phosphate; PCAF: P300/CBP-associated factor; LDHB: Lactate dehydrogenase B; AMPK: AMP-activated protein kinase; HCC: Hepatocellular carcinoma; MCJ: Methylation-controlled J; LNP: Lipid-nanoparticle-encapsulated; GalNAc: N-acetylgalactosamine; ClpP: Caseinolytic protease P; SAB: SH3 homology-associated BTK binding protein; ASO: Antisense oligonucleotides; ACMSD: α -amino- β -carboxymuconate- ϵ -semialdehyde decarboxylase; FOXA3: Forkhead box A3; STK25: Sterile 20-type kinase serine/threonine kinase 25; ROR α : Receptor-related orphan receptor alpha; PSD3: Pleckstrin and Sec7 domain-containing 3; Nrf2: Nuclear factor erythroid 2-related factor 2; RIPK1: Receptor-interacting protein kinase 1; CXCR2: CXC chemokine receptor 2; MSR1: Macrophage scavenger receptor 1; NLRP3: NOD-like receptor protein 3; XBP1: X-box binding protein-1; DC: Dendritic cell; TLR7: Toll-like receptor 7; Tregs: Regulatory T cells; BAFF: B-cell activating factor; NP: Nanoparticle-encapsulated; TAZ: Transcriptional co-activator with PDZ-binding motif; WISP1: WNT1-inducible signaling pathway protein 1; IL-11: Interleukin-11; JAK: Janus kinase; STAT1: Signal transducer and activator of transcription 1; PAR2: Protease-activated receptor-2; VCAM: Vascular cell adhesion molecule; eNOS: Endothelial nitric oxide synthase; LTB4: Leukotriene B4; mPGES: Microsomal prostaglandin E synthases; ARA: Arachidonic acid; CYP4A: Cytochrome P450 4A14; CsA: Cyclosporine A; TRIM5: Tripartite motif protein 5; DDX5: DEAD-box protein 5.

With the rapid development of research techniques, single-cell sequencing and spatial transcriptomics, single-cell proteomics and metabolomics have been widely used and will undoubtedly accelerate the discovery of novel NAFLD/NASH mechanisms and therapeutic targets. Drug libraries enable us to quickly find effective small molecules to target specific pathways identified in the basic research field. Endocrine factors that mediate the crosstalk between the liver and extrahepatic tissues provide an ideal target for developing neutralization antibodies or recombinant proteins for the treatment of NAFLD/NASH. In addition to traditional small molecules, neutralizing antibodies and recombinant proteins, nucleic acid-based therapy has become an attractive approach for the development of drugs for NAFLD/NASH patients. Nucleic acid-based therapeutics include ASOs, siRNAs, miRNAs and mRNAs with modifications to improve their stability, immunogenicity, and diversity[134]. Through nucleic acid-based approaches, therapeutic target genes can be specifically silenced or overexpressed in the liver. As an example, the safety and efficiency of HSD17B13 RNAi[36] and DGAT2 ASOs have been examined in a few clinical trials, which showed a positive impact on liver

Table 2 Novel extrahepatic targets explored by recent basic study

Molecular target	Potential agent	Classification	Function	Effect	Ref.
AMPK	UO-Zn	Small molecule	Improve lipid metabolism	-Lipid accumulation in liver and circulation	[106]
BDK	BT2	Inhibitor	Regulating BCAA metabolism	-Hepatic steatosis -Liver inflammation -Liver fibrosis	[107,108]
HIF-2 α (gut)	PT2385	Inhibitor	Decrease intestine-derived ceramide	-Hepatic steatosis -Liver injury	[112]
MYC (gut)	10058-F4	Inhibitor	Decrease intestine-derived ceramide	-Hepatic steatosis -Liver injury -Liver fibrosis	[114]
5-HT(gut)/HTR2A	Sarpogrelate	Antagonist	Inhibit gut-5-HT-liver Htr2a pathway	-Hepatic steatosis	[116]
PPAR α (gut)	GW6471	Antagonist	Inhibit fatty acid absorption by intestine	-Hepatic steatosis -Liver inflammation -Liver fibrosis	[117]
MGAT2	BMS-963272	Inhibitor	Regulating fat absorption and liver TG synthesis	-Liver inflammation -Liver fibrosis	[119]
ISM1 (AT)	Recombinant Ism1	Recombinant protein	Suppress lipogenesis in liver	-Hepatic steatosis +Glucose tolerance	[122]
Sparcl1 (AT)	Anti-Sparcl1 antibody	Neutralizing antibody	Decrease CCL2 expression in liver	-Liver inflammation -Liver fibrosis	[123]
Gremlin 1 (AT)	Anti-Gremlin 1 antibody	Neutralizing antibody	Increase insulin sensitivity	-Insulin resistance	[124]
NRG4	hNRG4-Fc	Recombinant protein	Restrain the tumor-prone liver immune microenvironment	-NASH-associated HCC	[125]
SWELL1/LRRC8a (AT)	SN-401	Small molecule	Enhance insulin sensitivity and secretion	+Insulin sensitivity -Hepatic steatosis -Hepatocyte damage	[128]

AT: Adipose tissue; -: Inhibit; +: Stimulate; AMPK: AMP-activated protein kinase; BDK: Branched chain ketoacid dehydrogenase kinase; BCAA: Branched-chain amino acids; HIF-2 α : Hypoxia-inducible factor 2 α ; MYC: Myelocytomatosis oncogene; 5-HT: 5-hydroxytryptamine; PPAR: Peroxisome proliferator-activated receptor; MGAT2: Monoacylglycerol acyltransferase 2; TG: Triglyceride; ISM1: Isthmin-1; Sparcl1: Secreted protein acidic and rich in cysteine-like protein 1; CCL2: C-C motif chemokine ligand 2; NRG4: Neuregulin 4; hNRG4-Fc: Human NRG4 and the Fc domain of immunoglobulin G 1; NASH: Nonalcoholic steatohepatitis; HCC: Hepatocellular carcinoma; UO: Ulvan oligosaccharide; BT2: 3,6-dichlorobrenzo(b)thiophene-2-carboxylic acid.

function and stiffness in patients with NASH[135].

To avoid side effects, efforts have been made to better target the liver or more accurately target specific hepatic cell types by exploring novel drug delivery systems. Based on the hepatocyte-specific expression of asialoglycoprotein receptor, conjugation of GalNAc with nucleic acids or nanoparticles can provide better targeting to hepatocytes. To specifically target HSCs, nanoparticles integrated with vitamin A, cyclic peptides, mannose 6-phosphate, and antibodies against synaptophysin have shown high affinity for HSCs[136,137]. By using these approaches, drugs can be more precisely delivered to HSCs to alleviate NASH-related liver fibrosis. For hepatic macrophages, nanoparticles modified with the phospholipid serine to mimic apoptotic cells can enhance uptake of the nanoparticles by hepatic macrophages[137]. However, challenges remain in targeting other cell types.

Finally, novel preclinical and *in vitro* models are required for drug screening for NASH. A 3D human liver model constructed *via* coculture of hepatocytes with non-parenchymal cells in a 3D collagen matrix has been shown to mimic NASH features when treated with free fatty acids and TNF- α [138]. Liver organoids from pluripotent stem cells or induced pluripotent stem cells also provide unique preclinical platforms to fill the gap between animal studies and clinical trials for therapeutic target validation and

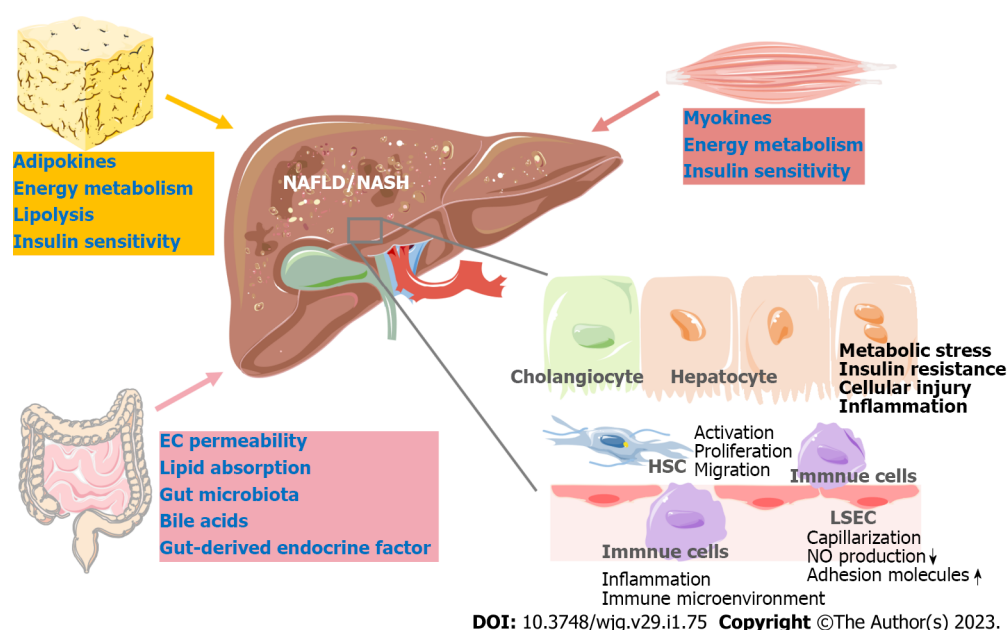


Figure 1 An overview of intrahepatic and extrahepatic targets for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis treatment.

In hepatocytes, strategies for treating nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) aim to improve metabolic disturbance and protect hepatocytes from injury. In the liver, the crosstalk network of nonparenchymal cells, including immune cells, hepatic stellate cells, liver sinusoidal endothelial cells and hepatocytes, is an important target for NAFLD/NASH. Outside the liver, the gut, adipose tissue and skeletal muscle interact with the liver via various endocrine factors or affect whole-body energy metabolic homeostasis, which has been verified to be an extrahepatic target for NAFLD/NASH treatment. EC: Epithelial cell; HSC: Hepatic stellate cell; LSEC: Liver sinusoidal endothelial cell; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; NO: Nitric oxide.

drug development[139].

FOOTNOTES

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