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REVIEW ARTICLE

Li et al: RNA-binding proteins in NAFLD therapy

Review of roles of RNA-binding proteins on NAFLD and the related pharmaceutical measures

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide and poses a serious threat to public health. NAFLD is considered a risk factor for metabolic syndrome (MS) and is closely associated with type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, and cardiovascular disease. Recently, increasing attention has been paid to the role of RNA-binding proteins (RBPs) in the pathogenesis of NAFLD. A growing body of research has linked RBPs—such as human antigen R (HuR), sequestosome 1 (p62), polypyrimidine tract-binding protein 1 (PTBP1), and heterogeneous nuclear ribonucleoproteins (hnRNPs)—to lipogenesis and inflammation, both of

which contribute to NAFLD through mechanisms involving transcriptional regulation, alternative splicing, RNA stability, polyadenylation, and subcellular localization. However, these findings are often fragmented and lack a comprehensive synthesis. The interactions and mechanisms between RBPs and NAFLD have not yet been thoroughly reviewed. This article provides an overview of the roles and mechanisms of various RBPs in NAFLD, summarizing current knowledge with the aid of figures and tables. In particular, it highlights the influence of HuR on NAFLD through multiple pathways, categorizing its effects based on increased or decreased expression. Furthermore, it reviews drugs that alleviate NAFLD by modulating RBPs, aiming to offer valuable insights for drug-targeted therapies based on RBP regulatory networks.

Keywords: RNA binding proteins; nonalcoholic fatty liver disease; NAFLD; therapy; mechanism

INTRODUCTION

NAFLD stands as one of the most prevalent liver disorders globally, afflicting over 25% of the adult population, which imposes significant social and economic burdens [1]. Accumulation of lipids in hepatocytes and increased levels of liver-related enzymes is characteristics of NAFLD. Diagnosis of steatosis occurs when at least 5% of liver cells exhibit excessive fat deposition, notably in individuals who abstain from alcohol or restrict their consumption to 20 g (women)/30 g (men) per day [2, 3]. NAFLD spans from simple intrahepatic fat build up (steatosis) to nonalcoholic steatohepatitis (NASH), marked by hepatocyte inflammation and death, potentially progressing to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [4, 5]. NASH is pivotal in NAFLD progression, with hepatic fibrosis emerging as the principal determinant of liver-related mortality [6]. A recent model predicts a 178% increase in liver-related deaths linked to NASH by 2030 [7]. Recently, researchers in fatty liver disease have proposed "MAFLD" (metabolic associated fatty liver disease) as a more fitting overarching term, acknowledging the evolving understanding of the metabolic dysfunctions associated with the condition. Like NAFLD, MAFLD embodies the hepatic manifestation of a multisystem disorder [8]. Despite this, we'll continue using the term NAFLD in this review, reflecting its prevalent usage in the literature we've reviewed.

The dominant explanation for the etiology and pathophysiology of NAFLD is the "multiple factors" hypothesis, which encompasses fat accumulation, insulin resistance (IR), oxidative stress,

mitochondrial dysfunction, endoplasmic reticulum stress (ERS), disruptions in metabolism of hepatic lipid and bile acid, alterations in gut microbiota, and genetic predispositions [9]. NAFLD is a multifactorial disease closely associated with MS, T2DM, and obesity, with IR identified as a central component in its pathogenesis [10]. IR exacerbates with disease advances, activating lipogenic enzymes via sterol receptor-binding protein 1c (SREBP-1c), thereby increasing lipogenesis [11, 12]. IR impairs insulin's ability to restrain fat breakdown in adipose tissue, resulting in higher levels of free fatty acids transported to the liver [13, 14].

RBPs are pivotal in coordinating RNA processing, post-transcriptional gene regulation (PTGR), as well as maturation, localization, stabilization, and translation of both coding and non-coding RNAs [15]. RBPs interact with RNA at RNA-binding domains (RBDs), predominantly located within the 5' and 3' untranslated regions (UTRs) of RNA. Typically, RBPs possess multiple repeat RBPs that enhance affinity and specificity for the target mRNAs. One RBP can control the expression of several mRNAs, whereas multiple RBPs might engage with the same mRNA, either cooperating or competing [16, 17]. RBPs function lose or functional mutation can disrupt homeostasis, contributing to metabolic disorder such as NAFLD [18, 19].

Despite existing literature reporting on the role of RBPs in NAFLD, these studies are often limited due to the vast diversity of RBPs. The primary highlight of this work is to conduct a comprehensive review of as many RBPs as possible that have a relevant effect on NAFLD, and try to thoroughly elaborate and summarize the roles and mechanisms of RBPs in NAFLD. Also, the drugs development derived from RBP regulatory pathways has garnered significant attention, and several RBP-based drugs for treating NAFLDs are described considering the critical role of RBPs and their interactions with RNA in NAFLD progression.

RBPs in NAFLD

Hu proteins

The embryonic lethal abnormal vision (ELAV)/Hu proteins constitute a vital family of RBPs, including four mammalian variants encoded by distinct genes: human antigen B, C, D, and R (HuB, HuC, HuD, and HuR). These proteins are crucial for post-transcriptionally enhancing gene expression [20]. HuR, widely distributed in tissues, stabilize and/or enhance mRNA translation of pro-inflammatory agents within the cytoplasm, thus acting as a key regulator of inflammatory and

immune responses [21]. On the other hand, HuB, HuC, and HuD are specifically expressed in neurons and contribute to neuronal differentiation, axonal outgrowth, and the maintenance of neuronal integrity [22].

Human antigen R

HuR, encoded by the embryonic lethal abnormal vision like 1 (Elavl1) gene, is situated on human chromosome 19p13.2 [23]. Its mRNA spans 6 kb and encodes a translation production with a molecular weight 36 kD. Functionally, HuR controls post-transcriptional gene expression by regulating the levels and activity of RNAs it interacts with. Structurally, HuR consists of three RNA recognition motifs (RRMs): a tandem RRM1 and RRM2, linked by a flexible segment, and a C-terminal RRM3 [24]. Although predominantly localized in the nucleus, HuR moves to the cytoplasm when triggered, facilitated by a shuttling sequence located between RRM2 and RRM3 [20]. In the cytoplasm, HuR engages with its mRNAs, exerting diverse effects such as promoting mRNA stability, enhancing mRNA translation, or suppressing these functions in specific tissues [25, 26]. Recently, the pivotal roles of HuR in cell signaling, inflammation, fibrosis, and HCC development have garnered significant attention [27]. Several studies have highlighted the role of hepatic HuR in NAFLD by modulating lipid and glucose metabolism, regulating lipid transport, and suppressing adipogenesis [28-30].

Recently, a study observed a notable decrease in HuR expression in the livers of mice exposed to a high-fat diet (HFD). However, contrary to this finding, a separate study by Zhang et al. reported that hepatic HuR deficiency exacerbated HFD-induced NAFLD [31]. The differing outcomes may stem from variations in HFD conditions used in another study with HuR-deficient mice. This study observed upregulation triglyceride (TG) and cholesterol ester (CE) species, and depressed expression of genes involved in cholesterol biosynthesis and the bile acid (BA)-activated farnesoid X receptor (FXR)/retinoid X receptor (RXR) pathway. Consequently, these mice showed increased inflammation and fibrosis, ultimately leading to HCC-like tumor development [28]. In livers of HuR-deficient mice, Serum taurocholic acid (TCA), macrophage markers, innate immune response markers, various chemokines, and LINC01018 activation significantly increased, while tauroursodeoxycholic acid (TUDCA), known for inhibiting ERS, depressed [28,32]. These livers also exhibited elevated expression of genes involved in fatty acid biosynthesis, including acetyl CoA

carboxylase *(*Acc1), fatty acid synthase (Fas), elongation of very-long-chain fatty acids member 6 (Elovl6), and fatty acid desaturases (Fads1&2) [32]. As summarized in Figure 1, HuR affects NAFLD by regulating ERS and fatty acid metabolism.

The long noncoding RNA (lncRNA) H19, a 2.3 kb RNA molecule, emerged as a vital regulator of hepatic lipid metabolism and ERS [33, 34]. H19 is pivotal in promoting steatosis and increasing lipid accumulation by modulating miR-130a/proliferator-activated receptor gamma (PPARγ) axis, MLX-interacting protein like (MLXIPL) expression, and mTOR complex 1 (mTORC1) signaling pathways [35, 36]. Mechanistically, HuR deficiency boosts H19 and sphingosine-1 phosphate receptor 2 (S1PR2), while diminishing sphingosine kinase 2 (SphK2) expression, fostering inflammation and hepatic lipid accumulation (as summarized in Figure 1). In summary, HuR serves as a critical regulator in metabolism of hepatic lipid, homeostasis of enterohepatic bile acid, inflammation, and fibrosis. Deletion of HuR in hepatocytes exacerbates the above changes, implying HuR as a promising therapy for NAFLD [32].

The phosphatase and tensin homolog deleted on chromosome 10 (PTEN) functions as a phosphatase capable of dephosphorylating phosphatidylinositol-3,4,5-trisphosphate (PIP3). This action halts signaling downstream of phosphatidylinositol 3-kinase (PI3K), leading to a decline in AKT activity [37]. In liver, PTEN is in charge of regulating lipogenesis, glucose metabolism, and hepatocyte homeostasis. Liver-specific deficiency of PTEN promotes NAFLD and tumorigenesis and improves glucose tolerance [38]. Conversely, Mice overexpressing PTEN are protected from steatosis [39] (Figure 1). HuR binds to the 3′UTR of PTEN mRNA, enhancing its stability and translation. In HuR-deficient mice, PTEN overexpression mitigates -induced liver fat accumulation [30].

HuR interacts with intron 24 of Apob pre-mRNA, 3′UTR of UQCRB, and 5′UTR of NDUFB6 mRNA, thus modulating Apob mRNA splicing and translation of UQCRB and NDUFB6. Deletion of HuR specifically in hepatocytes reduces expression of Apob, UQCRB, and NDUFB6 in mice, leading to impaired ATP synthesis and liver lipid transport, exacerbating HFD-induced NAFLD [31], as shown in Figure1, deletion of HuR exacerbate HFD-induced-NAFLD. Given HuR's dual effects on insulin sensitivity, combining HuR with insulin sensitizers such as thiazolidinediones, glucagon-like peptide-1 receptor agonists, biguanides, and dipeptidyl peptidase IV inhibitors might offer a more effective therapy for NAFLD [40]. The increase in HuR, NDUFB6, CYCS, Apob-100,

UQCRB, and Apob-48 levels following oral metformin intake may represent a side effect of metformin.

LINC01018, a non-conserved intergenic long non-coding RNA (lncRNA) on Chromosome 5, is highly expressed in liver. In NAFLD patients, LINC01018 is significantly lowered compared to healthy controls. Dietary intervention with low carbohydrate intake in NAFLD patients upregulates LINC01018 expression in liver, along with the induction of LINC01018 related genes. LINC01018 modulates fatty acid metabolism by interacting with HuR[41]. Reducing HuR expression by more than 60% in the livers of humanized mice leads to a notable reduction of three genes regulated by LINC01018: ADH1C, CYP4A11, and ALDH5A1. Reduced HuR leads to reduction of genes regulated by LINC01018: ADH1C, CYP4A11, and ALDH5A1, leading to NAFLD(Figure1).

As a plasma lipoprotein, apolipoprotein A-IV (APOA4) is primarily synthesized by the liver and small intestine [1]. In mice, APOA4 enhances hepatic TG secretion, thereby increasing plasma TG levels [42]. APOA4-AS acts as a coordinated regulator of APOA4 expression, mirroring the expression pattern of the APOA4 gene. Elevated APOA4-AS and APOA4 are detected in the livers of individuals with NAFLD. Knockdown of APOA4-AS has been shown to decline APOA4 expression in vitro and in vivo, leading to lowered plasma TG and total cholesterol (TC) in mice. Mechanistically, APOA4-AS achieves this by directly binding and interacting with HuR, thereby stabilizing APOA4 mRNA. Deleting HuR reduces both APOA4-AS and APOA4 transcripts [43]. As in Figure1 HuR decrease TG and TC by reduced APOA4-AS and APOA4.

CCAAT enhancer-binding protein beta (C/EBPβ), a member of the C/EBP family, can initiate adipogenesis and contribute to diabetes pathogenesis by regulating key enzymes like PEPCK in adipose tissue and liver. In models of NASH induced by a methionine choline deficient (MCD) diet, C/EBPβ expression obviously increases. Deleting C/EBPβ in the liver protects against excessive TG accumulation, inflammation, ERS, and oxidative stress. Conversely, overexpression of C/EBPβ exacerbates PPARγ activation and nuclear factor kappa B (NF-κB) activity [44]. Previous research highlights HuR's action of facilitating the nucleocytoplasmic transport and stability of C/EBPβ mRNA during early adipogenesis stages [45, 46] (Figure1). While direct evidence is still needed, these findings suggest HuR might influence C/EBPβ expression, consequently impact the development of NAFLD.

HAMP, the sole human hepcidin gene, is primarily expressed in the liver and regulates iron

absorption from duodenum and iron release from macrophages [47]. Research indicates that in NAFLD, increased saturated fatty acids in the liver enhances the movement of HuR between the nucleus and cytoplasm, promoting HuR's binding to the 3'UTR of HAMP mRNA, leading to elevated HAMP mRNA in hepatocytes [48]. Modulating HuR-mediated HAMP expression could provide benefits in preventing NAFLD progression. As shown in Figure 1, Modulating HuR-mediated HAMP expression could provide benefits in preventing NAFLD progression.

Treatment with obeticholic acid (OCA) increases low-density lipoprotein receptor (LDLR) expression in the liver, resulting in lower levels of low-density lipoprotein cholesterol (LDLC) in plasma of mice. This effect occurs through the activation of FXR, which induces the expression of HuR, a factor that stabilizes LDLR mRNA [49]. Deleting HuR prevents OCA from enhancing LDLR expression and impairs the clearance of plasma cholesterol via LDLR (Figure1).

ABCB1 reverse cholesterol transport by facilitating cholesterol efflux and the biogenesis of high-density lipoprotein (HDL). HuR enhances the expression of ABCA1 by stabilizing its mRNA through binding to the 3'UTR. Silencing HuR diminishes ABCA1 expression and reduces cholesterol efflux to APOA1 in both hepatocytes and macrophages [50]. HuR enhances the expression of ABCA1, reversing cholesterol transport and biogenesis of HDL (Figure 1).

In a recent study, mice lacking HuR specifically in adipose tissue exhibited higher susceptibility to HFD, characterized by increased IR and inflammation. HuR reduces lipid accumulation and lowers serum TC and high-density lipoprotein cholesterol (HDLC) by enhancing the stability and translation of adipose triglyceride lipase (ATGL) mRNA [29] (Figure1).

HuR safeguards liver cells against oxidative damage caused by excessive fat accumulation by regulating the stability of manganese-dependent superoxide dismutase (MnSOD) and heme oxygenase-1 (HO-1) mRNA. Researchers identified ten HuR binding sites in the 3' UTR region of MnSOD mRNA, and Knockdown of HuR led to decreased levels of MnSOD mRNA and protein [51]. In mice, lowered MnSOD levels intensified oxidative stress, exacerbating symptoms of NASH [52]. Lower MnSOD levels have also been observed in NASH patients, with genetic variations impacting MnSOD function correlating with increased NASH risk in human [53, 54]. Recent studies have shown that administering the HO-1 inducer hemin distinctly alleviates steatosis, inflammation, and fibrosis severity in mice fed a MCD diet, while reducing serum ALT and AST levels by inhibiting

both canonical and non-canonical Wnt signaling pathways [55]. In an MCD model of NASH, HuR governs the stability of MnSOD and HO-1 mRNA. Reduced HuR levels correlate with depressed MnSOD and HO-1 expression, suggesting that impaired HuR-mediated modulation of antioxidant enzymes may contribute to the progression from simple fatty liver to NASH [56] (Figure1).

Angiotensin II (Ang II) and its type 1 receptor (AT1R) have been identified as promoters of NAFLD, with AT1R blockers showing potential in ameliorating fatty liver and being considered for NAFLD therapy [57, 58]. The AT1R-associated protein (ATRAP, also known as AGTRAP) acts to reduce the activation of AT1R, thereby counteracting the effects of Ang II through direct binding [59]. S-adenosylmethionine (SAM), a methyl supplement, influences genetic and protein modifications [60]. ATRAP mRNA interacts with HuR. SAM maintains ATRAP mRNA nucleocytoplasmic shuttling by preserving HuR methylation, which enhances ATRAP protein production, potentially reducing NAFLD (Figure1). This highlights HuR's role in mRNA transport, essential for NAFLD regulation. Further research into HuR's function could offer valuable insights in this area [61]. Additionally, compounds like berberine, quercetin, and apigenin, among others, inhibit HuR, thereby lowering the expression of HuR-regulated genes, particularly those involved in inflammation (Figure 1). This property may helpful for NAFLD treatment [62].

Circular RNA poly (A) binding protein nuclear 1 (circPABPN1) can recruit HuR to suppress its interaction with PABPN1 mRNA, leading to reduced PABPN1 translation [63]. But the potential role of PABPN1 in NAFLD onset and progression remains underexplored [64, 65].

Based on the above analysis and description, we clearly summarize the main interactions between HuR and NAFLD (Figure 1).

Human antigen D

HuD is essential for regulating TG levels in pancreatic β-cells. Research shows that lowering HuD levels increases intracellular TG in βTC6 cells by reducing the post-transcriptional expression of insulin-induced gene 1 (INSIG1), which normally inhibits lipid synthesis. This reduction in HuD also enhances the nuclear localization of SREBP1c, promoting the activation of genes involved in lipogenesis [66]. However, similar changes have not been observed in the liver, warranting further investigation in this area.

LncRNAs

lncRNAs are single-stranded nucleotide sequences, varying from approximately 200 bp to 10 kb in length, and represent the most common non-coding RNAs in the human genome, more than microRNAs [67, 68]. LncRNAs exert control over almost every aspect of post-transcriptional processing of their RNA. This includes pre-mRNA splicing, cleavage and polyadenylation, translational control, nuclear export, RNA stability, RNA localization, and RNA editing [17]. RBPs can recognize and interact with specific RNA to form heterogeneous nuclear ribonucleoprotein (hnRNP) complexes. In mammalian cells, the hnRNP family comprises at least 20 RNA-binding nuclear proteins [69, 70]. Several hnRNPs related to lncRNAs have been confirmed to be involved in NAFLD, such as hnRNI, hnRNPU, hnRNPA1, and others. However, there remains a significant gap in our understanding regarding the roles, underlying molecular mechanisms, and levels of expression of these hnRNPs in NAFLD.

hnRNPI/ Polypyrimidine tract-binding protein 1

Polypyrimidine tract-binding protein 1 (PTBP1), also recognized as PTB or hnRNP I, belong to the PTBP family, alongside PTBP2 and PTBP3, each comprising four RRMs [71]. PTBP1 is widely expressed in various non-neural systems and nerve generating cells. PTBP2 (also known as nPTB) is predominantly found in nerve cells, spermatocytes, and myoblasts, while PTBP3 (alternatively known as ROD1) exhibits high distribution in hemopoiesis and hepatic cells. PTBP3, a splicing factor, promotes HCC [72]. It's down-regulation can inhibit PI3K/AKT signaling pathway activation, thereby impeding HCC growth, migration, and invasion [73]. However, there are no reports linking PTBP3 to NAFLD thus far. PTBP1, a hnRNP histones in HeLa cells, crosslinks with hnRNA, hence its alternative name hnRNP I [74,75]. PTBP1 participate in mRNA stabilization, alternative splicing and nucleocytoplasmic transport by binding to the polypyrimidine-rich tract in pre-mRNAs [75].

H19 shares multiple binding sites with PTBP1 [76]. By synergizing with PTBP1, H19 regulates hepatic metabolism and exacerbates the progression of fatty liver [77]. Research by Schmidt et al. reported that overexpression of H19 protects against obesity and improves insulin sensitivity [78].

Further inhibition of H19 enhances the differentiation of human adipose-derived stem cells and promotes lipid accumulation by targeting PTBP1 [76]. Disruption of hepatic lipid balance induces the expression of H19 and PTBP1, enhancing their interaction. This facilitates PTBP1 binding to Srebp1c mRNA and protein, leading to greater stability, increased cleavage, nuclear translocation,

and enhanced transcriptional activity, further stimulating the lipogenisis. The study unveils a H19/PTBP1/SREBP1 feedforward loop that amplifies signaling, contributing to the progression of NAFLD [77]. Human lncRNA metabolic regulator 1 (hLMR1) enhances the binding of PTBP1 on the promoters of Sc5d, Lss, Fdps, and Hmgcs1, thereby positively regulating transcription of genes involved in cholesterol metabolism [79]. Circular RNA circMBOAT2, located on the chromosome 2p25 amplicon, promotes lipid metabolism reprogramming of intrahepatic cholangiocarcinoma (ICC) by the circMBOAT2/PTBP1/FASN axis [80]. CircMBOAT2 binds to PTBP1, protecting it from degradation in a ubiquitin-dependent mechanism. The altered lipid profile affects cell membrane composition, energy metabolism, and redox balance, potentially influencing the progression of NAFLD. Additionally, hyperglycemia and elevated levels of free fatty acids (FFAs) stimulate the expression of the pancreatic and duodenal homeobox 1 (PDX1). This upregulation subsequently boosts the transcription of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), potentially inducing β-cell dysfunction through the PDX1/MALAT1/PTBP1 pathway [81], which may be associated with NAFLD. Moreover, PTBP1 influences the invasion and metastasis of hepatocarcinoma by regulating the splicing of Axl exon 10 [82].

hnRNPU

A recent investigation introduced lncRNA regulator of hyperlipidemia (lncRHL), which suppresses hepatic VLDL secretion. The study revealed that lncRHL binds hnRNPU, enhancing its stability. hnRNPU, in turn, activates Bmal1 transcriptionally, leading to reduced VLDL secretion. When lncRHL is deficient, hnRNPU degradation accelerates, suppressing Bmal1 transcription and increasing VLDL secretion in liver cells. The lncRHL/hnRNPU/Bmal1/microsomal triglyceride transfer protein (MTTP) axis could be a potential approach to maintain liver and plasma lipid homeostasis [83]. Inactivation of hnRNPU in liver cells exacerbates HFD-induced NASH by inducing a truncated form of the Tyrosine Kinase receptor B (TrkB). This aberration promotes liver inflammation and cell death, contributing to liver injury, inflammation, and fibrosis [84]. The family with sequence similarity 3D (FAM3D) - formyl peptide receptor 1 (FPR1) axis upregulates the expression of hnRNP U, which boost its transcription to enhance lipid oxidation and mitigate fat accumulation in obese mice by recruiting the glucocorticoid receptor (GR) to the promoter region of the short-chain acyl-CoA dehydrogenase (SCAD) gene [85].

Brown fat lncRNA1 (Blnc1) and lnc-BATE1 are both noteworthy regulators in the realm of brown

adipocyte differentiation [86]. Lnc-BATE1 binds hnRNPU in trans, guiding lncRNAs to specific subnuclear domains for functional activity [87]. This interaction forms a complex crucial for brown adipogenesis [86]. The transcription factor zinc finger and BTB domain-containing 7b (Zbtb7b) is essential for the development of brown and beige fat by facilitating the assembly of the Blnc1/hnRNPU ribonucleoprotein complex [88].

Lnc-RAP-1, also known as Firre, is another lncRNA capable of binding to hnRNPU [87]. Inhibition of lnc-RAP-1 impedes lipid accumulation and the expression of adipocyte markers during white preadipocyte differentiation [89]. Furthermore, hnRNPU recruits Blnc1 to EBF2, forming the Blnc1/hnRNPU/EBF2 ribonucleoprotein complex, which subsequently promotes the expression of genes involved in thermogenesis [90]. While these mechanisms are undoubtedly involved in fat metabolism, remainning unexplored.

hnRNPA1

HnRNPA1, a highly enriched hnRNP, stabilizes mRNA and regulates its expression [70]. Recent findings by Zhao et al. revealed visibly elevated levels of TG and TC in liver tissues and serum of hnRNPA1-knockout mice. Loss of hnRNPA1 in murine skeletal muscle exacerbates IR and hepatic steatosis induced by a HFD [91]. This exacerbation is attributed to hnRNPA1's interaction with glycogen synthase 1 (gys1) mRNA, which promotes glycogen synthesis and maintains insulin sensitivity [91]. Gui et al. demonstrated that hnRNPA1 regulates lipid metabolism by binding to H19 and increasing the translation of genes crucial for fatty acid oxidation like carnitine almitoyl transferase 1B (CPT1b) and peroxisome proliferators-activated receptor γ coactivator 1 alpha (PGC1α), thereby improving IR [92]. In a steatosis model of HepG2 cells [93], upon supplementation with free fatty acids (FFA), hnRNPA1's binding to the SREBP-1a 5′-UTR increases via the p38 MAPK signal pathway. This increment leads to cap-independent translation of SREBP-1a, which activates SREBP-responsive genes, including those involved in fatty metabolism. The lncRNA SHGL suppresses lipogenesis and gluconeogenesis in the liver, which occurs through lnc-SHGL's recruitment of hnRNPA1 to increase calmodulin translation, thereby activating the PI3K/Akt pathway while inhibiting the mTOR/SREBP1c pathway [94]. These mechanisms independently suppress gluconeogenesis and lipogenesis in hepatocytes, offering a promising approach for treating steatosis by the LncSHGL/hnRNPA1 axis (Figure 2) [95].

lncSHGL recruits hnRNPA1 to boost CALM1-3 mRNA translation, raising cellular CaM protein levels. This

activates Akt and suppresses mTOR/SREBP-1C pathways, curbing gluconeogenesis and lipogenesis in hepatocytes.

hnRNPA2B1

Lnc-HC binds hnRNPA2B1 to form a ribonucleoprotein complex that acts on transcripts of CYP7A1 and ABCA1, critical in lipid and cholesterol metabolism [96]. In vitro studies reveal this interaction causes nuclear retention and subsequent degradation of CYP7A1 and ABCA1 transcripts, leading to cholesterol accumulation in hepatocytes [97].

hnRNPC

Umbilical cord-derived mesenchymal stem cells-derived extracellular vesicles (UCMSCs-EVs) deliver circ-Tulp4 into hepatocytes, where circ-Tulp4 inhibits the HNRNPC/ABHD6 axis, thereby reducing apoptosis and alleviating DM-NAFLD, providing a novel therapeutic avenue for targeting DM-NAFLD through modulation of cell apoptosis [98].

p62/ insulin like growth factor 2 (IGF2) mRNA binding protein 2

The human insulin-like growth factor 2 (IGF2) mRNA binding proteins (IMP1-3 or IGF2BP1–3) were identified in 1999 for their interaction with IGF2 leader 3 mRNA [99]. These proteins are pivotal in modulating RNA dynamics in a transcript-specific manner across the genome [100]. While the expression of Imp1 and Imp3 diminishes clearly after birth, Imp2 remains widely expressed postnatally [101]. p62 is a splice variant of IGF2BP2 that lacks exon 10, but this deletion doesn't affect the six characteristic RNA binding motifs [102].

Studies have demonstrated that liver-specific overexpression of p62 can induce histologically steatotic features in approximately 60% of animals without causing liver damage [103]. Transgenic animals with elevated p62 levels on a regular diet develop fatty liver conditions [103] and can also contribute to the development of NASH [104]. When animals with liver-specific p62 overexpression are fed a MCD diet, they show increased expression levels of Ccl2 [104]. On the other hand, IMP2-deficient mice highly resist HFD-induced fatty liver conditions [105]. These mice show reduced fat mass, particularly evident during HFD consumption, along with lower circulating lipids, reduced liver TG accumulation, and improved glucose tolerance and insulin sensitivity [105]. Notably, most lipid species are elevated in p62-induced steatosis, with TG showing the most significant increase [106]. When p62 liver-specific transgenic mice are fed an MCD diet, they experience earlier and more severe fibrosis [104, 107], suggesting that IMP2 accelerate NAFLD

progression. Following treatment with diethylnitrosamine (DEN), livers of p62-transgenic mice show increased inflammation and an elevated ductular reaction (DR) marked by dedifferentiated cells, leading to the progression of steatohepatitis-associated cirrhosis [108].

Overexpressing IMP2 in hepatocytes may disrupt miRNA regulation, affecting the translation efficiency of its RNAs and causing aberrant fatty acid metabolism, contributing to steatosis [109]. Animal studies suggest that p62 drives NASH progression by iron deposition in liver and hepatic free cholesterol production, leading to lipid peroxidation and inflammation via NF-κB activation [110]. Stephan Laggai's research on p62 transgenic mice reveals elevated C18:C16 ratio and incremental fatty acid elongase 6 (ELOVL6), accompanied by liver inflammation [111]. ELOVL6 expression specifically characterizes steatotic events being linked to inflammation [112]. Mechanistically, p62 induces hepatic C18 fatty acid production via SREBP1-dependent ELOVL6 induction, promoting NASH in mice and humans [113]. ELOVL6 overexpression has been associated with NASH development. In mice fed a HFD, miR-130b expression increases [114], while activated AKT pathway inhibits hepatic adipogenesis and gluconeogenesis in NAFLD mice [115]. Recent findings show that in NAFLD mice, downregulated miR-130b-5p reduces lipid accumulation by upregulating IGFBP2, while miR-130b-5p upregulation increases lipid accumulation by inhibiting IGFBP2. In HFD-fed mice, downregulation of miR-130b-5p or overexpression of IGFBP2 enhances IGFBP2 expression and AKT/AKT phosphorylation, leading to suppression of lipid synthesis genes (SREBP-1, SCD1, LXRα, ChREBP, ACC1, and Fas). This inhibits lipid accumulation and IR in NAFLD. In conclusion, miR-130b-5p exacerbates lipid accumulation and IR in NAFLD mice by inhibiting the AKT pathway through IGFBP2 [116]. Hepatocyte-specific IMP2 deletion modestly induces diet-induced fatty liver by impairing fatty acid oxidation through increased degradation of IMP2 client mRNAs, including carnitine palmitoyltransferase 1A (CPT1A) and PPARα, while not affecting lipogenic gene expression [117]. IGFBP-2 repression is common in NAFLD and NASH patients due to methylation, and its expression varies in NAFLD [118]. Notably, hypermethylation of IGFBP2 precedes hepatic steatosis development in dietary NAFLD models when mice are metabolically stable, indicating its potential as a liver disease risk indicator. Additionally, IGFBP2 expression varies with age, decreasing in young mice prone to obesity induced by a HFD [119].

Tristetraprolin

Tristetraprolin (TTP) contains two zinc finger motifs that facilitate RNA binding. Despite limited and inconsistent understanding of its exact function of liver physiology, studies suggest hepatic TTP contributes to the progression of steatosis, inflammation, and fibrosis. Deleting TTP prevents steatosis in mice on an MCD diet, possibly by enhancing VLDL secretion [120]. Bone marrow-specific TTP deletion reduces serum levels of TG, TC, and VLDL/LDL, promotes hepatic steatosis, and influences the expression of lipid metabolism and inflammation-related genes like SREBP1, SAA1, and CCR2 [121]. TTP shares common targets with HuR, another protein implicated in hepatic steatosis; thus, downregulation of TTP might indirectly promote steatosis by reducing competition with HuR for shared targets [122].

Carbon monoxide (CO) promotes the sequestration of plasminogen activator inhibitor 1 (PAI-1) in stress granules (SGs), and CO-induced TTP activation enhances PAI-1 degradation in SG assembly. This CO-dependent TTP activation reduces PAI-1 levels in SGs, potentially alleviating age-dependent NAFLD, suggesting TTP as a novel direction in age-related NAFLD [123]. Inhibition of linc-SCRG1 leads to a reduction in fibrosis-related genes by inhibiting TTP expression [124]. Linc-SCRG1 exerts an inhibitory effect on TTP, leading to the inactivation of hepatic stellate cell (HSC) phenotypes [124]. Studies have shown that Metformin-induced TTP activation declines TNF-α production in Kupffer cells (KCs), preventing hepatocyte necroptosis. TTP-mediated destabilization of Ras homolog enriched in the brain (Rheb) increases lipophagy in primary hepatocytes and liver of mice. Consequently, TTP is promising for reducing hepatosteatosis [125]. TTP modulates TNF-α levels by binding to the AU-rich element (ARE) in TNF-α mRNA [126]. TNF-α treatment can upregulate TTP expression [127], suggesting a reciprocal regulation between TTP and TNF-α, which may react on NAFLD. Recent findings indicate a potential novel function for TTP in metabolism regulation, particularly in hepatic glucose and lipid metabolism [128]. Sawicki et al. highlighted that TTP post-transcriptionally represses a hormone in liver named fibroblast growth factor 21 (FGF21), which further modulates insulin response. Loss of TTP leads to increased FGF21. Thus, hepatic TTP and their impact on liver and systemic insulin sensitivity could be a promising approach for treating NAFLD. Here, we outline the main mechanisms by which RNA-TTP influences IR and hepatic fat deposition (Figure3) [129].

Cytoplasmic polyadenylation element-binding protein 1

Cytoplasmic polyadenylation element-binding protein 1 (CPEB1) is an mRNA-binding protein involved in regulating translation through cytoplasmic polyadenylation. It interacts with the 3'UTR's cytoplasmic polyadenylation element (CPE) along with three regulatory proteins: Gld2, PARN, and Maskin [130]. Increased CPEB1 levels have been implicated in inducing pathological angiogenesis in chronic liver disease [131] and mediating HCC stemness and chemoresistance [132]. Additionally, its homolog, CPEB4, has been found to counter hepatic steatosis under ERS [133]. A previous study indirectly linked circRNA-002581 to CPEB1 regulation via microRNA 122 (miR-122) sequestration [134]. A recent study has highlighted the active role of the CircRNA-002581-miR-122-CPEB1 axis in NASH pathogenesis through the PTEN-AMPK-mTOR pathway and suppressing autophagy. Knockdown of CircRNA-002581 in NASH models reduced lipid accumulation, ALT, AST, H2O2, pro-inflammatory cytokines, and apoptosis while increasing ATP levels, suggesting circRNA-002581 is a remedy for NASH (Figure 4) [135]. A microarray analysis of mRNAs regulated by CPEB1 demonstrated that CPEB1 deficiency results in widespread impairment of insulin signaling. CPEB1 knockout mice exhibit IR, as CPEB represses the translation of Stat3 and PTEN mRNAs. Thus, CPEB1 may be implicated in NAFLD through its effects on glucose homeostasis [136].

Tat-activating regulatory DNA-binding protein-43

Tat-activating regulatory DNA-binding protein-43 (TDP-43) contains two RRM domains flanked by N-terminal and glycine-rich C-terminal, structurally similar to the hnRNP family, participating in RNA processing [137]. Mutations in TDP-43 can aggregate and mislocalize from the nucleus to the cytoplasm [138]. Overexpression of TDP-43 boosts IL-6 levels in pre-adipocytes, macrophages and adipocytes [139]. Steatosis triggers increased NF-κβ signaling through upstream activation of IKKβ, leading to the produce of TNF-α, IL-6, and IL-1β, which recruit and activate KCs, mediating inflammation in NASH [139]. A study found a positive correlation between IL-6 and BMI, increasing sIL-6Ra and gp130/sIL-6Rb alleviate NAFLD in obesity [140]. Dampening IL-6/signal transducer and activator of transcription 3 (STAT3) activity was demonstrated to alleviate I148M-mediated susceptibility to NAFLD [141]. The liver-specific triglyceride regulator (lncLSTR) collaborates with TDP-43 to regulate Cyp8b1 expression, a key enzyme in bile acid synthesis. This complex enhances bile pool that promotes apoC2 expression via FXR, leading to activation of lipoprotein lipase and increased plasma TG clearance [142].

Yes-associated protein 1

Yes-associated protein 1 (YAP1 or YAP) participates in repair, cell fate determination, and tumorigenesis of liver. LncARSR prevents YAP phosphorylation, leading to the activation of insulin receptor substrate 2 (IRS2) and expression of SREBP-1c gene. IRS2, in turn, activates the PI3K/AKT pathway, thereby inducing lipogenic gene expression programs and accelerating NAFLD progression [143]. Another study has demonstrated that LATS2 modulates the phosphorylation of YAP, thereby regulating its activity in NAFLD [144]. The STING-YAP axis in macrophages regulates steatosis by reprogramming lipid metabolism through a pathway involving transmembrane protein 205 (TMEM205), mitofusin 2 (MFN2), and protein disulfide isomerase (PDI). The YAP target gene TMEM205 activates AMPKα, which interacts with hepatocyte MFN2, promoting PDI-hypoxia-inducible factor-1α (HIF-1α) signaling, and degrading perilipin 2 (PLIN2) on lipid droplets (LD). Macrophage STING deficiency boosts nuclear YAP activity, reducing lipid accumulation and PLIN2 expression under HFD-induced oxidative stress [145]. Studies have highlighted the Wnt/β-catenin signaling pathway in regulating lipid metabolism in the liver [146, 147]. Ma et al. observed elevated YB-1 and β-catenin in mouse NAFLD livers. They further elucidated that the effect of YB-1 on lipid synthesis and β-oxidation in mouse NAFLD livers is mediated by the Wnt/β-catenin pathway [148]. The lncRNA MST1/2-Antagonizing for YAP Activation (MAYA) promotes liver cell senescence by downregulating YAP expression [149], and hepatocyte senescence contributes to NAFLD pathogenesis [150].

In monkeys with hepatic steatosis, there is increased nuclear YAP in hepatocytes [151]. Studies have demonstrated that Si-Ni-San reduces YAP expression and mitigates lipid droplet deposition in NAFLD liver cells [152]. Rosmarinic acid (RA) downregulates YAP protein expression, ameliorating NAFLD by modulating the YAP/TAZ-PPARγ/proliferator-activated receptor γ coactivator-1α (PGC-1α) signaling pathway [153]. Curcumol inhibits hepatocyte senescence through YAP/nuclear receptor coactivator 4 (NCOA4)-mediated regulation of ferritinophagy in NAFLD. Supplementation with curcumol improves liver damage and hepatic steatosis in HFD-fed golden hamsters [154]. SRD5A3-AS1 inhibits miR-1205, boosting NF2 expression. NF2, in response, suppresses YAP, reducing cell proliferation and dampening IL-6, TGF-β1, and α-SMA levels in NAFLD [155]. Lian-Mei-Yin (LMY), a long-standing traditional Chinese medicine for liver disorders, reduces hepatic steatosis in zebrafish and mouse models of NAFLD in a time- and dose-dependent manner. It works by inhibiting Yap1-mediated Foxm1 activation, a key factor in NAFLD [156].

YAP expression in HSC and KCs is crucial for fibrosis and the development of NASH [157]. In mice with diet-induced NAFLD, liver CYR61 expression rises in a YAP-dependent manner, which is linked to the development of fibrosis [158]. The Hippo pathway effector YAP plays an early and key role in the HSC activation process [159], promoting scarring during NASH [160]. Inhibition of the Hippo/YAP signaling pathway is necessary for magnesium isoglycyrrhizinate to ameliorate HSC inflammation and activation [161]. New research demonstrates that CSN6 (gene name), which stabilizes hydroxymethylglutaryl-CoA synthase 1 (HMGCS1), activates YAP via mevalonate metabolism. Focusing on the CSN6-HMGCS1-YAP1 axis unveils a potential vulnerability in NAFLD-associated cancer [162]. In NASH, YAP activation may be related to ductular reaction (DR). During NASH development, YAP activation precedes DR. YAP activation in hepatocytes may contribute to DR by promoting hepatocyte dedifferentiation [163].

Y-box binding protein 1

The Y-box binding protein 1 (YB-1 or YBX1) is a multifunctional DNA- and RNA-binding protein, characterized by a conserved cold shock domain (CSD) [164]. Its diverse functions arise from its interactions with nucleic acids and its capability to form homomultimers and complexes with other proteins. YBX1 orchestrates many DNA/RNA-dependent processes including transcription, splicing, translation, DNA repair and mRNA stability [157, 165].

In the pathogenesis of NAFLD, adipocyte autophagy plays a significant role. Autophagy is heightened in the white adipose tissues of mice fed an HFD. Suppression of autophagy in white adipose tissue alleviates liver steatosis, inflammation, and fibrosis [166]. Studies have shown that YB1 facilitates adipogenesis by enhancing Unc-51–like kinases 1 and 2 (ULK1 and ULK2)-mediated autophagy. Further investigation revealed that YB1 specifically binds to m5C-containing Ulk1 transcript, stabilizing its mRNA. YB1 acts as a DNA-binding protein, promoting Ulk2 transcription, thereby increasing ULK1 and ULK2, and consequently enhancing autophagy and adipogenesis. Increasing YB1 levels in white adipose tissue (WAT) augments autophagy and stimulates the expansion of adipose tissue in mice. YB1 could be a promising remedy for combating obesity and associated metabolic disorders due to its regulation in autophagy and adipogenesis [167]. The well-characterized lncRNA HOX Transcript Antisense RNA (HOTAIR) was shown to interact with YBX1 to drive proliferation through YBX1 target genes [168]. But the impact

on NAFLD still requires further research.

Eukaryotic initiation factor 4E

Eukaryotic initiation factor 4E (EIF4E), an mRNA cap-binding protein, is essential for mRNA-ribosome interplay and capture-dependent translation by interacting to eukaryotic initiation factor 4G [169]. Yan et al. found that higher levels of EIF4E in plasma may causally contribute to the occurrence of NAFLD in the European population [170]. Wang et al. shew that inflammatory stress enhances the phosphorylation of mammalian of rapamycin (mTOR) and EIF4E, which in turn stimulates the translation of Recombinant Cluster of Differentiation 36 (CD36) [171]. CD36 promotes the uptake of long-chain fatty acids, inducing steatosis and resulting in NAFLD [172]. Rapamycin decreases CD36 expression by blocking the mTOR pathway and phosphorylation of downstream, thereby alleviating NAFLD [173]. Moreover, a clinical trial conducted by Kubrusly et al. [174] demonstrated that EIF4E levels are increased in NASH-related cirrhosis.

Astrocyte elevated gene-1

Astrocyte elevated gene-1 (AEG-1), also named metadherin (MTDH), is a 582 amino acid protein anchored to the endoplasmic reticulum membrane [175]. Increased AEG-1 has been observed in NASH who developed steatosis after consuming an HFD. Molecular analysis revealed that AEG-1 regulates fatty acid β-oxidation (FAO) by inhibiting the activation of peroxisome proliferator-activated receptor alpha (PPARα) while promoting de novo lipogenesis (DNL) and TG accumulation by enhancing the translation of mRNAs encoding enzymes involved in fatty acid synthesis. AEG-1 can activate the NF-κB pathway, driving inflammation and fibrosis of liver. In hepatocyte-specific AEG-1 transgenic mice (Alb/AEG-1), inhibition of PPARα activation and FAO leads to spontaneous NASH, a condition reversed in AEG-1ΔHEP mice, suggesting a protective effect against diet-induced NASH [176]. AEG-1 contains an LXXLL motif at amino acids 2125 [177], which, promoting its steatotic activity, also regulate inflammatory and tumorigenesis, keeping a balance in AEG-1's activity [175]. Research has shown that AEG-1 is S-palmitoylated on Cys75 by the palmitoyltransferase ZDHHC6. S-palmitoylation regulates AEG-1 negatively, keeping its inflammatory and oncogenic functions in check. Depalmitoylase inhibition would increase AEG-1 palmitoylation, potentially suppressing NASH and HCC [178]. PPARα, a key regulator of FAO, is inhibited in Alb/AEG-1 mice, resulting in reduced fatty acid β-oxidation, increased translation of fatty acid synthase, leading to DNL, and enhanced NF-κB-mediated inflammation, collectively

contributing to NASH. Therapeutically, nanoparticle-delivered AEG-1 siRNA specifically applied to hepatocytes offered significant protection against NASH induced by HFD in wild-type mice. Strategies aimed at inhibiting AEG-1 could be promising interventions for NASH patients [176].

Quaking 5

Sirtuins (SIRT1-7) exert diverse functions by regulating post-translational protein modifications. SIRT1, closely linked to cellular metabolism, deacetylates cellular proteins, a process implicated in NAFLD development [179]. Downregulation of SIRT1 in mice treated with small hairpin RNA induces hepatic steatosis. PPARγ, highly expressed in adipose tissue, exhibits upregulated expression in NAFLD patients. Increased PPARγ activity in the liver promotes lipid storage [180]. Quaking (QKI), a member of the Signal Transduction and Activators of RNA (STAR) family of RBPs, is expressed in the liver, with QKI 5 being the predominant isoform. Weiyan demonstrated that SIRT1 deacetylates QKI 5, influencing TG synthesis in NAFLD mouse models. It activates the transcription factor Forkhead box protein O1 (FoxO1) through post-transcriptional regulation of PPARα, inhibiting TG synthesis and impeding NAFLD progression [181].

Endothelial differentiation-related factor 1

Endothelial differentiation-related factor 1 (EDF1), also named hMBF-1, is a highly conserved intracellular protein consisting of 148 amino acids. EDF1 functions as a coactivator for several nuclear receptors involved in lipid metabolism, including LXRα, steroidogenic factor 1, liver receptor homologue 1 and PPARγ [182, 183]. It facilitates the recruitment of Blnc1, leading to formation of the LXR ribonucleoprotein transcriptional complex [184]. EDF1, in collaboration with LXRα/retinoid X receptor β (RXRβ), enhances SREBP1c promoter activity, with Blnc1 further augmenting the complex's transcriptional activity. Overexpression of EDF1 in hepatocytes stimulates the expression of lipogenic genes, and co-expression of Blnc1 intensifies this effect. EDF-1 is essential for PPARγ transcriptional activation during 3T3-L1 differentiation [183], suggesting its potential significance in NAFLD.

DEAD-box family

DEAD-box protein 1

DEAD-box protein 1 (DDX1) is a member of the DEAD-box RNA helicase family and participates in mRNA translation, microRNA maturation, rRNA processing, tRNA splicing, and repair of DNA double-strand breaks

[185-187]. Studies show DDX1 directly binds insulin mRNA, and upon FFA stimulation, DDX1 is phosphorylated and dissociates from insulin mRNA, reducing insulin translation [188]. DDX1 also influences insulin translation by interacting with EIF3a and EIF4b [188]. Deficiency of DDX1 impairs calcium influx and insulin secretion in pancreatic β cells [189]. We hypothesized that DDX1 might influence NAFLD by acting on insulin metabolism. However, there is no direct report of DDX1 on NAFLD.

p 68 and p72

p68 and p72, members of the DEAD-box family, are RBPs function in RNA helicase activity and RNA-protein complex remodeling. They interact with noncoding RNA Steroid Receptors RNA Activator (SRA), which acts as a transcriptional coactivator for PPARγ, promoting adipocyte differentiation in vitro. SRA-deficient mice resist HFD-induced obesity, displaying reductive fat mass and increased lean content. Their livers exhibit fewer lipid droplets and depressed expression of lipogenesis genes and reduced hepatic steatosis [190]. Knockdown of SRA inhibits adipocyte differentiation in cell models [191], and SRA promotes hepatic steatosis by repressing adipose TG lipase expression [192].

LIN28

LIN28 was originally discovered as a regulator of developmental timing in Caenorhabditis elegans [193]. LIN28 regulates the degradation of let-7 miRNAs and acts in various human cancers [194, 195]. There are two isoforms of LIN28: LIN28A (in cytoplasm), and LIN28B (in cytoplasm and the nucleus). Unlike LIN28A, LIN28B functions exclusively in the nucleus by sequestering primary let-7 transcripts and inhibiting its processing [196]. LIN28B was first identified as overexpressed in HCC [197].

C1632 inhibits Lin28, promoting lipid catabolism and ketogenesis, and reducing SREBP1-mediated fat synthesis, collectively curbing intracellular lipid accumulation in HepG2 and AML12 cells. In genetic and dietary mouse models of NAFLD, C1632 activates an anti-steatotic response, suggesting inhibition of Lin28 could be beneficial for NAFLD prevention or treatment [198].

Zhu et al. discovered that LIN28A and LIN28B transgenic mice are resistant to obesity and show improved glucose tolerance. Conversely, muscle-specific Lin28a knockout and let-7 overexpression in mice led to glucose intolerance. The way LIN28A/B and let-7 influence glucose metabolism is the

insulin-PI3K-mTOR pathway [199]. Moreover, in osteosarcoma cells with high LIN28B, aerobic glycolysis was enhanced but mitochondrial function was impaired [200]. These findings highlight the importance of LIN28 isoforms as essential regulators of glucose homeostasis, which may impact NAFLD through glucose metabolism.

RPL 8

RCRIN, a conserved read circRNA that inhibits MASLD, was downregulated in patients with MASLD. In normal hepatocytes, RCRIN binds to the RPL 8 protein to recruit RNF2 for its degradation, reducing the number of ribosomes containing RPL 8 to inhibit lipid accumulation and ERS. In MASLD hepatocytes, the lower level of RCRIN leads to the release of RPL 8 protein to form RPL 8-containing ribosomes, thereby enhancing lipid accumulation and ERS in the liver. It is notable that RCRIN overexpression and RPL 8 silencing significantly inhibit the development and progression of MASLD. RCRIN and RPL8 might be ideal biomarkers for MASLD and related diseases.Whether RCRIN contents in serum could act as a diagnostic marker of MASLD warrants further investigation [201].

Sarcopenia-related RBPs

Rosenberg first coined the term "sarcopenia" to describe the age-related decline in skeletal muscle mass and volume in 1989 [202]. Sarcopenia is considered an extrahepatic manifestation of NAFLD [203]. NAFLD and sarcopenia may share common mechanisms such as IR, vitamin D deficiency, inflammation, and lessened physical activity. Sarcopenia is recognized as a novel risk factor for NAFLD development [204]. In a prospective observational cohort study, individuals with low muscle mass have a higher risk of NAFLD [205]. Those with sarcopenia is facing a 2.3 to 3.34 folds increased odds of NAFLD [206] and a 24-fold increased risk of fibrosis [204]. Sarcopenia in biopsy-proven NAFLD is linked to NASH and significant fibrosis, irrespective of obesity, inflammation, and IR [207]. Among young and middle-aged populations, both the prevalence and severity of MAFLD are notably associated with sarcopenia [208]. Evaluating sarcopenia has proven valuable for risk assessment in MAFLD patients [209]. In a prospective study of 225 Caucasian individuals, sarcopenia prevalence increased linearly with liver fibrosis severity. Even after adjusting for confounders, sarcopenia remained correlated with hepatic steatosis severity [210]. Due to overlapping pathophysiology between NAFLD and sarcopenia, it's unclear whether sarcopenia precedes or follows NAFLD progression [211].

In response to LPS, TNFα mRNA can be stabilized via the phosphorylation of TTP, inducing TTP binds to the TNFα mRNA 3'UTR [212]. IL-6 mRNA interacts with HuR, TTP, and ARE-binding protein 1 (AUF1, also called

hnRNP D), suggesting a role in accelerating muscle wasting in the elderly [213-215]. Quaking protein (QK) levels increase during myogenesis [216] and regulate alternative splicing by binding to ACUAA-motifs. RNA binding Fox homolog proteins 1 and 2 (RBFOX1 and 2) depletion in mice leads to severe muscle mass loss and alteration of splicing of numerous transcripts [217]. Masuda et al. [218] showed that AUF1 increases, TIA-1 and TTP declines, HuR no change in skeletal muscle with aging. PABPN1 has emerged as a candidate RBP, reduced in aged muscle [219], and genetic reduction of PABPN1 in a mouse model triggered muscle atrophy [220]. HNRNPH1 controls alternative splicing of RBFOX2 [221] and muscle PABPN1 decreases during aging [222]. In summary, These RBPs likely contribute to RNA processing in skeletal muscle and could impact NAFLD via sarcopenia.

Interplay across multiple RBPs in NAFLD

Thousands of overlapping binding sites of TTP and HuR were found in more than 1300 genes. TTP decaies but HuR stabilizes and promotes translation of target mRNAs. RNA-IP experiments indicated that TTP can bind directly to and destabilize HuR mRNA. High-expression or aberrant nuclear/cytoplasmic distribution of HuR and decreased TTP have been found in many types of cancers [223、224]. The lncRNA NEAT1 with its two most abundant transcripts NEAT1_v1 and NEAT1_v2 has been shown to play a role in NAFLD. A study by Ahne showed that NEAT1 is regulated by TTP and HuR conversely in NAFLD [225]. Some RBPs can bind to many mRNA targets, potentially generating competitive or synergistic effects, which have been studied in some diseases or pathophysiological processes [226-228]. However, there are still few related studies on the influence of the joint regulation of multiple RBPs and specific RNAs on the progression or treatment strategies of NAFLD, which awaits further research in the future.

Based on the introduction of the above content, some common and relatively well-studied RBPs implicated in NAFLD are listed in Table 1. And, several drugs that can alter the corresponding indicators of RBPs to further treat or alleviate fatty liver disease have also been listed in Table 2.

CONCLUSION

Despite a wealth of literature on RBPs and their implications in NAFLD, existing research is often fragmented and lacks systematic reviews. Given the prevalence and severity of NAFLD, a comprehensive understanding of RBPs' post-transcriptional regulatory roles is imperative for developing novel RNA-based therapies. This review seeks to elucidate the pathogenesis of NAFLD by discussing recent advances in understanding different RBPs' involvement in its development.

Ultimately, we anticipate a thorough understanding of the dynamic RBPs-mediated regulatory network in NAFLD. Correcting gene expression abnormalities via RBPs in NAFLD holds promise as an effective therapeutic approach through RNA-based therapies, which mimic or antagonize specific RNA processes either by mimicking protective RBPs or inhibiting pathogenic RBPs. However, improving target specificity remains a challenging problem that needs to be addressed. Furthermore, while a direct link between RBPs and NAFLD has yet to be identified, the majority of results are from in vivo and in vitro models, necessitating studies in patients to validate the utility through the generation and implementation of panels of the RBPs described here. Despite many unresolved issues and connections related to RBPs, existing knowledge and growing evidence suggest an opportunity to usher in a new era in NAFLD therapy.

Future research could develop in multiple technological directions, including genomics, high-throughput screening (HTS), and gene editing, to deeply understand and applicate this field. The widespread use of HTS, such as RNA-Seq, will help identify new RBPs and potential therapeutic targets, enabling the rapid identification of therapeutic molecules for NAFLD, thus shortening the drug development cycle. Gene editing, especially CRISPR-Cas9, will help create NAFLD animal models, providing new breakthroughs for precision medicine. With the advancement of these technologies, drug development costs are expected to decrease significantly, while RBPs-targeted drugs may have more precise mechanisms of action, reducing side effects and adverse reactions, further improving curative effect and reducing economic burden on patients.

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TABLES AND FIGURES WITH LEGENDS

Table 1. A comprehensive summary between the RBPs and RBPs -RNA in NAFLD

RBPs	Expression	Related RNA	Expression	Mechanism	Results	NAFLD	Reference
HuR	↓	Acc1, Fas , Elovl6,Fads1&2-related genes	↑	fatty acid biosynthesis	fatty acid biosynthesis	↑	[32]
	↓	H19	↑	miR-130a/ PPARγ axis, MLXIPL expression, mTORC1 signaling	steatosis and lipid accumulation	↑	[35、36]
	↑	PTEN mRNA	↑	increases stability and translation of PTEN	lipid deposition in hepatocytes↓	↓	[30]
	↓	Apob pre-mRNA, UQCRB, NDUFB6 mRNA	↓	regulate splicing of Apob mRNA and translation of UQCRB and NDUFB6	liver lipid transport and ATP synthesis↓	↑	[31、40]
	↓	ADH1C, CYP4A11, ALDH5A1	↓	LINC01018 binds to HuR and regulate its activity	regulates hepatic fatty acid metabolism	↑	[41]
	↑	APOA4 mRNA	↑	HuR–APOA4-AS complex stabilizes APOA4 mRNA	Increases TGs and TC	↑	[42、43]
	↑	C/EBPβ mRNA	↑	binds to 3'UTR of C/EBP βmRNA and increases its stability and translation	aggravates hepatic PPARγ activation, NF-κB activation	↑	[44-46]
	↑	HAMP mRNA	↑	binds to the 3'UTR of HAMP mRNA, up-regulate HAMP mRNA in hepatocytes	lipid content↑	↑	[48]
	↑	LDLR mRNA	↑	stabilizes LDLR mRNA, increase LDLR in the liver	LDLC in the plasma↓	↓	[49]
	↑	ABCA1 mRNA	↑	promotes ABCA1 through 3'UTR binding-mediated mRNA stabilization	cholesterol efflux, HDLC biogenesis	↓	[50]
	↑	ATGL mRNA	↑	increases its stability and protein level of ATGL mRNA	TC and HDLC↓	↓	[29]
	↓	MnSOD and HO-1 mRNA	↓	protective role of HuR against oxidative stress↓	oxidative stress↑	↑	[56]
HnRNPI (PTBP1)	↑	H19, SREBP1	↑	H19/PTBP1/SREBP1 forward amplifying pathway	lipogenic program	↑	[77]

RBPs	Expression	Related RNA	Expression	Mechanism	Results	NAFLD	Reference
		Sc5d, Lss, Fdps, and Hmgcs1	↑	hLMR1 enhances the binding of PTBP1 on the promoters of Sc5d, Lss, Fdps, and Hmgcs1	cholesterol synthesis, adipogenic differentiation	↑	[79]
hnRNPU	↑	lncRHL	↑	lncRHL/hnRNPU/BMAL1/MTTP axis	VLDL secretion in hepatocytes	↓	[83]
hnRNPA1	↓	gys1 mRNA	↓	gys1 mRNA stability↓	glycogen storage ↓ IR↑	↑	[91]
	↑	lncRNA SHGL	↑	activates PI3K/Akt pathway activate CaM/Akt pathway represse mTOR/SREBP-1C pathway	hyperglycemia and steatosis↓	↓	[92,95]
		H19	↑	increases translation of PGC1a and CPT1b	lipid ectopic deposition and IR↓	↓	[93]
hnRNPC	↓	circ-Tulp4	↑	inhibits the HNRNPC/ABHD6 axis	reduces apoptosis	↓	[98]
p62	↑	miR-130b-5p	↓	AKT pathway	expression of lipid synthesis genes↓	↓	[116]
TTP	↓	FGF21 mRNA	↑	FGF21↑	improves glucose tolerance and insulin sensitivity	↓	[129]
CPEB1	↓	miR-122	↓	CircRNA-002581-miR-122-CPEB1 axis PTEN-AMPK-mTOR pathway	autophagy ↑	↓	[134-136]
TDP-43	↑	lncLSTR	↑	TDP-43/FXR/apoC2 pathway	TG↓	↓	[142]
YAP	↑	lncARSR	↑	LncARSR activates IRS2/AKT pathway by reducing YAP1 phosphorylation	lipid accumulation	↑	[143]
		MAYA	↓	regulates iron overload in hepatocytes	cellular senescence↓	↓	[149、150]
	↓	SRD5A3-AS1	↑	SRD5A3-AS1 inhibite miR-1205, upregulating NF2, upregulate NF2 negatively regulate YAP1	NAFLD cell proliferation↓, IL-6, TGF-β1, α-SMA ↓	↓	[155]
YBX1	↑	Ulk1 mRNA	↑	YBX1 enhances ULK1- and ULK2-mediated autophagy	adipogenesis	↑	[167]
AEG-1	↑	fatty acid synthesis related mRNA	↑	fatty acid synthesis↑	DNL and TG↑	↑	[176]
EDF1	↑	Blnc1 RNA	↑	facilitates formation of LXR ribonucleoprotein transcriptional complex	Stimulates lipogenic gene expression	↑	[183、184]
p68 and p72	↑	SRA	↑	adipocyte differentiation repress adipose triglyceride lipase	Lipogenesis	↑	[190-192]
RPL 8	↑	RCRIN	↓	form of RPL 8-containing ribosomes	lipid accumulation and ERS	↑	[201]

Expression: The increase or decrease in the expression levels of RBPs and related RNAs.

Results: The impact of RBPs on NAFLD and its metabolism through relevant mechanisms.

Table 2. Potential Drugs Targeting RBPs and RBPs-RNA in NAFLD

RBPs	Drugs	Diseases	Function	Stage	Reference
HuR	TUDCA	NAFLD	inhibites ERS	animal experiment	[28]
HuR	Insulin sensitizers	NAFLD	ameliorates insulin resistance	speculation	[40]
HuR	OCA	NAFLD	inducts hepatic HuR expression	animal experiment	[49]
HuR	SAM	NAFLD	maintains HuR methylation	animal experiment	[61]
HuR	Flavonoids	NAFLD	inhibites HuR and reduce expression of HuR target genes	speculation	[62]
TTP	Metformin	NASH	decreases TNF-α production in KCs	animal experiment	[125]
YAP	Si-Ni-San	NAFLD	reduces YAP expression	cell and animal experiment	[152]
YAP	RA	NAFLD	down-regulates the expression of YAP	cell and animal experiment	[153]
YAP	Curcumol	NAFLD	inhibites hepatocyte senescence	cell and animal experiment	[154]
YAP	SRD5A3-AS1	NAFLD	negatively regulates YAP	animal experiment	[155]
YAP	LMY	NAFLD	suppresses YAP1-mediated Foxm1 activation	animal experiment	[156]
YAP	Magnesium isoglycyrrhizinate	HSC	inhibites Hippo/YAP signaling pathway	cell and animal experiment	[161]
YAP	HMGCS1	NAFLD related cancer	activates YAP	cell and animal experiment	[162]
EIF4E	Rapamycin	NAFLD	inhibites phosphorylation of EIF4E	cell and animal experiment	[171-173]
AEG-1	ZDHHC6	NASH	increases AEG-1 palmitoylation	animal experiment	[178]
Lin28	C1632	NAFLD	inhibites Lin28	cell and animal experiment	[198]

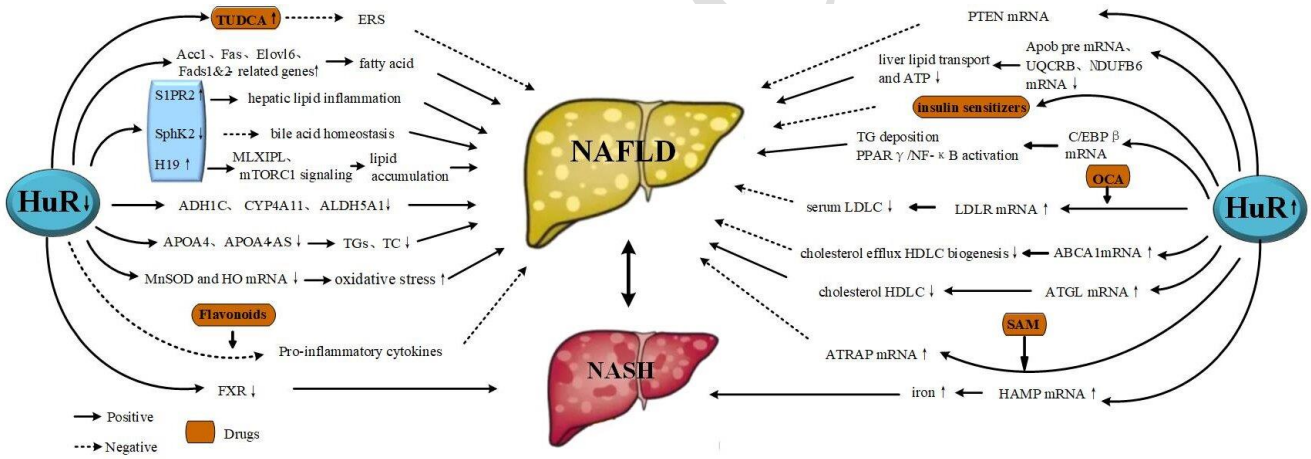

Figure 1. Interactions between HuR and according RNAs in NAFLD.

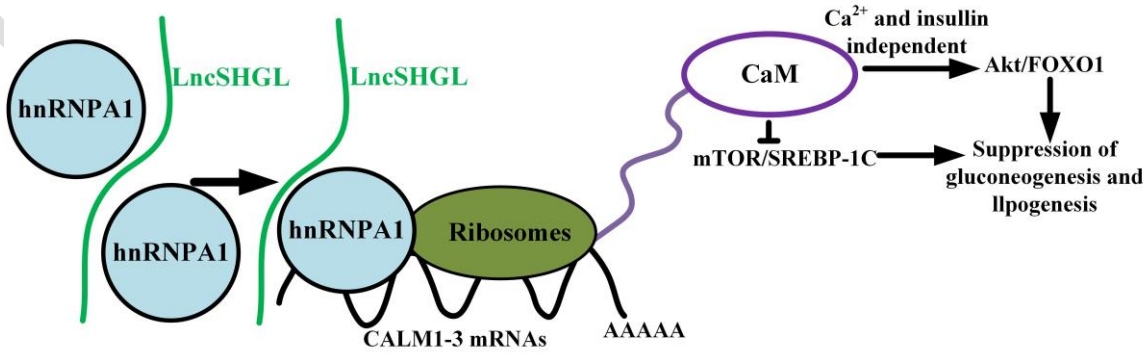

Figure 2. Proposed mechanism of lncSHGL in inhibiting liver gluconeogenesis and lipogenesis. Adapted from Wang et al. (2018), Diabetes, with permission from the publisher [95].

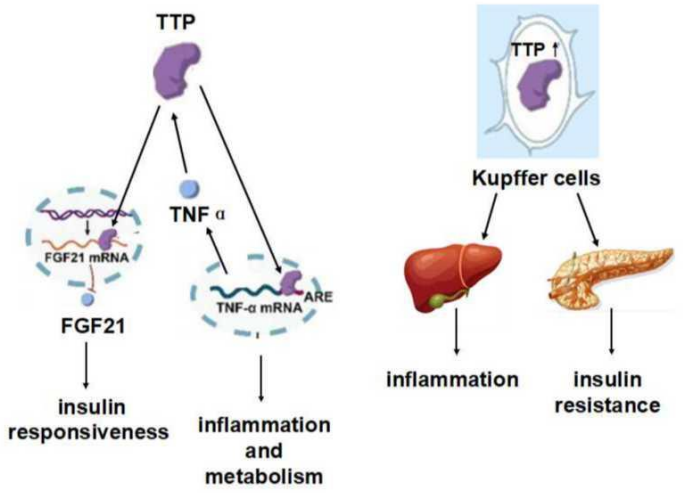

Figure 3. RNA-TTP interaction in IR and hepatic fat deposition

TTP controls TNF-α levels by binding to its mRNA's ARE region, influenced by TNF-α, affecting inflammation and metabolism. It also suppresses FGF21 mRNA, impacting insulin sensitivity. Elevated TTP in KCs worsens liver inflammation and IR.

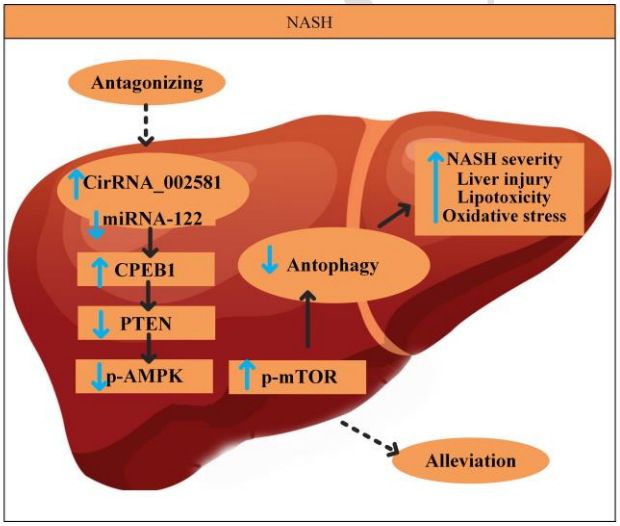

Figure 4. A proposed model showing how antagonizing CircRNA_002581 alleviates NASH progression.

Adapted from Jin et al. (2020), Cell Death & Disease, with permission from the publisher [135].

In NASH, CircRNA_002581 binds miR-122, boosting CPEB1 expression and impairing autophagy via the PTEN–AMPK–mTOR pathway, worsening NASH. Inhibiting CircRNA_002581 decreases miR-122 sequestration, reducing CPEB1 levels and partly restoring autophagy through PTEN–AMPK–mTOR, easing NASH.