

Review

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Review

Multifaceted Human Antigen R: A Key Player in Liver Metabolism and MASLD

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Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the leading cause of chronic liver disease worldwide, posing a substantial public health burden and underscoring the urgent need for effective therapeutic and preventive strategies. MASLD is defined by excessive hepatic lipid accumulation and, in a subset of patients, progresses to metabolic dysfunction-associated steatohepatitis (MASH), a pro-inflammatory and pro-fibrotic condition associated with increased risk of fibrosis, cirrhosis, and hepatocellular carcinoma. Although the mechanisms driving MASLD progression remain incompletely understood, dysregulation of key metabolic pathways, including triglyceride handling, cholesterol catabolism, bile acid metabolism, mitochondrial function, and autophagy, has been consistently observed in MASLD livers. Human antigen R (HuR), a ubiquitously expressed mRNA-binding protein, is a post-transcriptional regulator of diverse cellular processes, including nutrient metabolism, cell survival, and stress responses. Recent evidence highlights HuR's critical role in maintaining hepatic homeostasis, particularly under conditions of metabolic stress, such as those found in MASLD. Moreover, comorbid metabolic diseases, including obesity, type 2 diabetes mellitus, and cardiovascular disease, not only exacerbate MASLD severity but also involve HuR dysregulation in extrahepatic tissues, further contributing to hepatic dysfunction. This review explores the dynamic and cell-type-specific roles of HuR in MASLD pathogenesis and its associated metabolic comorbidities. A deeper understanding of HuR's post-transcriptional regulatory networks across metabolic tissues may inform the development of targeted therapies aimed at preventing or reversing MASLD progression.

Keywords: RNA binding protein; Human antigen R; metabolic dysfunction-associated steatotic liver disease (MASLD); metabolic syndrome

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now recognized as the most common cause of chronic liver disease globally [1]. Its growing prevalence poses a substantial socio-economic burden, prompting medical societies and public health agencies to prioritize the development of effective interventions and preventive strategies [2,3]. MASLD encompasses a spectrum of disease severity, ranging from simple, non-inflammatory metabolic dysfunction-associated steatotic liver (MASL) to metabolic dysfunction-associated steatohepatitis (MASH), which is characterized by liver inflammation and fibrosis [4]. Progression to MASH significantly increases the risk of end-stage liver disease, cardiovascular events, and extrahepatic malignancies [5,6]. Despite the high prevalence of MASLD, only 10–30% of affected individuals develop MASH [1]. While lifestyle modifications such as dietary intervention and increased physical activity are effective in reversing MASLD phenotypes, poor adherence limits their long-term success [7]. Understanding the mechanisms by which hepatic steatosis leads to inflammation, hepatocyte death, and fibrogenesis in a subset of patients is therefore critical to reducing MASLD-related morbidity and mortality. Moreover, MASLD frequently coexists with other metabolic disorders, including obesity and type 2

diabetes mellitus (T2DM), both of which are associated with increased MASLD severity [8,9]. These associations underscore the importance of investigating how metabolic dysfunction in one tissue can exacerbate disease in another.

Human antigen R (HuR), encoded by the embryonic lethal abnormal vision-like 1 (*Elavl1*) gene, is a member of the Hu family of RNA-binding proteins (RBPs) [10]. The *Elavl* gene family was first identified in *Drosophila* as essential for embryonic and ocular development [11]. In humans, Hu proteins selectively bind adenine- and uridine-rich elements (AREs) within the 3' untranslated regions (3' UTRs) of mature mRNAs and in intronic sequences of pre-mRNAs [10,12,13]. AREs are present in approximately 22% of human 3' UTRs and 25% of introns [14], and are typically found in transcripts encoding proteins involved in development, inflammation, metabolism, and signal transduction [15]. While Hu family members HuB, HuC, and HuD are predominantly expressed in the nervous system [16], HuR is ubiquitously expressed and essential for normal development and homeostasis [10,17]. HuR was initially identified as a regulator of early-response gene mRNA stability [18], but has since emerged as a dynamic, context-dependent modulator of numerous biological processes, including cell cycle progression [19–21], differentiation [22,23], apoptosis [24,25], and senescence [26,27]. HuR deficiency in mice is embryonically lethal [28], underscoring its essential role in development. HuR activity is regulated by various factors, including cell type, subcellular localization, and environmental cues. For example, in liver-resident hepatic stellate cells (HSCs), HuR induction and cytoplasmic translocation promote HSC activation and liver fibrosis [29,30], while reduced HuR expression in adipose tissue has been linked to obesity and insulin resistance [31,32]. Given its role in regulating thousands of transcripts [13,33], much remains to be learned about HuR's functions in tissue-specific homeostasis and disease progression.

The rationale for this review stems from HuR's emerging role as a key post-transcriptional regulator of metabolic homeostasis, inflammation, and fibrosis, hallmark features of MASLD and its progression to MASH. Given HuR's cell-type-specific and stimulus-responsive activity, its function in different tissues may either promote or protect against MASLD depending on the biological context. This review provides a comprehensive synthesis of current evidence on HuR's role in liver pathophysiology, focusing on its regulation of lipid metabolism, bile acid synthesis, mitochondrial function, oxidative stress, autophagy, inflammation, and fibrogenesis. We also highlight HuR's involvement in extrahepatic metabolic tissues, including adipose, cardiac, and immune cells, where its dysregulation contributes to comorbid conditions such as obesity, cardiovascular disease, and T2DM, all of which exacerbate MASLD. Ultimately, we discuss the therapeutic potential and challenges of targeting HuR in MASLD and related metabolic disorders, emphasizing the need for cell-specific strategies that preserve HuR's protective roles while mitigating its pathogenic effects.

2. HuR Structure and Subcellular Localization

As a ubiquitously expressed RNA binding protein with diverse roles in physiological and pathological processes [17], HuR is comprised of multiple domains that facilitate high affinity and specificity binding to AREs found within target transcripts [10,34]. HuR was first cloned and characterized by who used degenerate oligonucleotide-directed PCR to amplify a 140 nucleotide product from HeLa cells [10]. This gene product was called HuR and was highly similar, but distinct, in sequence to mRNAs encoding HuB, HuC, and HuD. The protein encoded by *HuR/Elavl1* is comprised of a short 20 amino acid long N-terminus that precedes three RNA recognition motifs (RRMs) (Figure 1). RRM1 and RRM2 are connected via a 12 amino acid linker domain, while a much longer 60 amino acid hinge domain connects RRM2 to RRM3 [10,34,35]. All three RRM domains are highly conserved among Hu protein family members and have high affinity and specificity for AREs that are prevalent within the 3' UTR and intronic regions of many labile and stress-inducible mRNAs [36]. Interdomain cooperation is essential to RNA binding protein function and localization within the cell [37]. Based on the crystal structure of RNA-bound HuR, binding of RRM2 or RRM3 to an ARE is dependent upon the conformational changes to HuR that accompany initial binding of RRM1 to the ARE [34,35]. Although non-covalent interactions between RRM1/2 and AREs act as adhesive to

temporarily anchor HuR to target transcripts, maximum HuR function cannot be achieved without involvement of RRM3. For instance, both binding of the RRM3 domain of HuR to the poly(A) tail of mRNAs [38] and HuR dimerization via the RRM3 domain have been shown to increase the binding affinity of HuR for its target transcripts, in part by facilitating binding of multiple HuR proteins to tandem AREs [34]. HuR binding to other proteins, including SET α , SET β , and APRIL, is also RRM3 dependent [39]. Specific interactions between the structural domains of HuR and other cellular factors, including RNA and protein, dictate HuR function, localization, and stability.

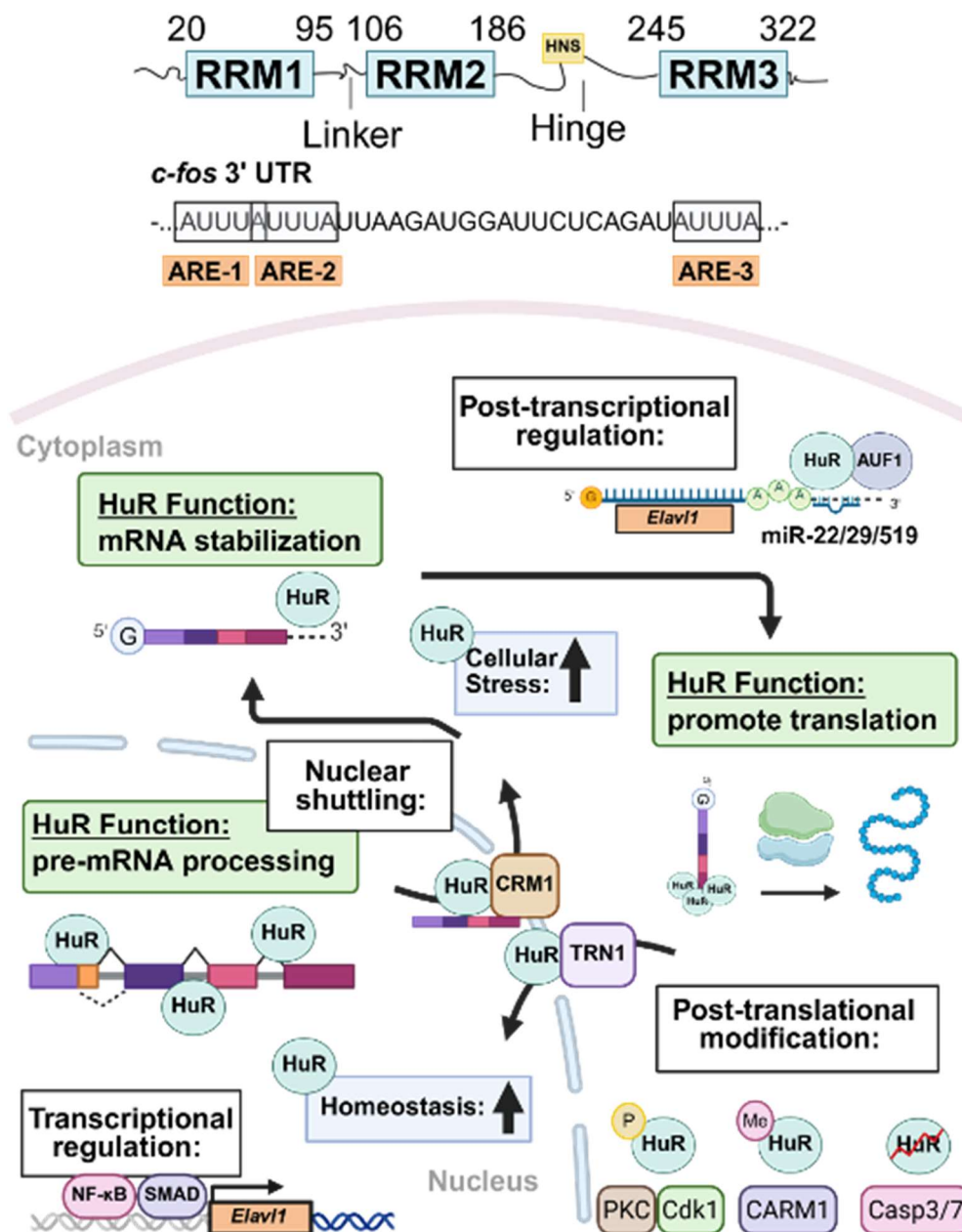


Figure 1. Schematic overview of HuR structure, function, and regulatory mechanisms. HuR (Human antigen R) contains three highly conserved RNA recognition motifs (RRMs) connected by flexible hinge and linker domains. The HuR nucleocytoplasmic shuttling sequence (HNS) enables HuR to dynamically move between the nucleus and cytoplasm. HuR binds directly to target mRNAs by recognizing adenine- and uridine-rich elements (AREs) through its RRM3, classically exemplified by its interaction with transcripts such as *c-fos*. HuR expression and activity are regulated at multiple levels, including transcriptional, post-transcriptional, post-translational, and protein-protein interactions, which collectively govern its localization and functional output. Under homeostatic conditions, HuR is predominantly localized in the nucleus, where it binds to introns and splice sites

of pre-mRNAs to regulate pre-mRNA processing. In response to cellular stress, HuR translocates to the cytoplasm, where it enhances stability and translation of mature mRNA targets involved in stress response, survival, inflammation, and metabolism.

Early on, subcellular localization of HuR in both human and mouse cell lines was established as predominantly nuclear [40]. For instance, immunofluorescence staining of HuR revealed that only 2% of the HuR protein detected was localized to the cytoplasm of the HeLa cell line under normal culture conditions [41]. However, ARE-mediated mRNA decay is believed to be primarily cytosolic, leaving question as to how HuR could perform its mRNA stabilizing function if retained within the nucleus [36]. To address this question, Fan *et. al.* used a heterokaryon fusion experiment to show that flag-tagged HuR can shuttle back and forth between the nucleus and cytoplasm [40]. Later, this same group generated deletion mutants of HuR to identify both the nuclear localization signal (NLS) and the nuclear export signal (NES) of HuR [42]. Deletion of RRM3 and the hinge domain, but not RRM3 alone, inhibited nucleocytoplasmic shuttling of HuR, indicating that the hinge domain, connecting RRM2 and RRM3 of HuR, was necessary for nucleocytoplasmic shuttling. Further study of HuR deletion mutants revealed the HuR nucleocytoplasmic shuttling sequence (HNS) to be a 32 amino acid stretch within the hinge domain that is necessary and sufficient for HuR nucleocytoplasmic shuttling [42]. Initially, shuttling of HuR from the nucleus to the cytoplasm was thought to play an important role in protecting HuR-bound mRNAs from ARE-associated degradation machinery [42]. Association of HuR with poly(A) tail-enriched mRNA in both the nucleus and cytoplasm, as well as association of HuR with polysome fractions provided further support for HuR's mRNA stabilizing role [41]. However, nucleocytoplasmic shuttling of both RNAs and proteins, such as HuR, through the nuclear pore complex (NPC) is largely nuclear transport factor, or karyopherin, dependent [43,44]. Therefore, identifying karyopherin-HuR interactions is essential to understanding mechanisms underlying HuR nucleocytoplasmic shuttling. Both A proliferation-inducing ligand (APRIL) and pp32 were found to directly bind HuR and mediate an interaction between HuR and the nuclear exportin, chromosomal region maintenance 1 (CRM1) [39,45]. Following heat shock, nuclear export of HuR into the cytoplasm of HeLa cells was shown to be CRM1-dependent [45]. Likewise, multiple pathways mediate import of HuR into the nucleus, including transport by nuclear importins, including transportin 1 and 2 (TRN1/2) and the karyopherin adaptor protein, importin- α (IMP α) [46,47]. Interestingly, AMPK activation and negative energy balance were associated with importin-mediated transport of HuR into the nucleus, while CRM1-mediated export of HuR into the cytoplasm occurred under conditions of heightened cellular stress [45,47], in both cases intracellular HuR localization impacting HuR-mediated regulation of gene expression.

3. Regulation of HuR Expression

Various regulatory mechanisms govern HuR expression, localization, and function. Transcriptional regulation of HuR expression has important implications for the cellular stress response and tumorigenesis. There are four annotated HuR transcripts in mice (NCBI Gene ID: 15568). However, all four transcripts encode the same 326 amino acid protein, with transcript variation due to differences in sequence and secondary structure of both the 3' and 5' untranslated regions (UTR) [48–50]. The HuR gene contains three putative transcriptional start sites located upstream of the methionine start codon. These sites are flanked by transcription factor binding motifs, including c-ets, CREB, and AP1 elements [51]. Several transcription factors have been shown to bind directly to the *HuR* promoter (Figure 1). For example, nuclear factor $\kappa\beta$ (NF $\kappa\beta$) enhances transcription of the long HuR variant by direct binding of the p65 subunit to the promoter, promoting cell survival and proliferation in MKN74 gastric cancer cells [52]. Similarly, ATP depletion activates SMAD-mediated transcription of the short HuR variant in LLC-PK1 porcine kidney proximal tubule cells, also contributing to cell survival [53]. The presence and differential regulation of both short and long *HuR* transcript variants enable context-specific fine-tuning of HuR expression [50].

Beyond transcriptional control, *HuR* expression is further regulated at the post-transcriptional level by RNA-binding proteins and microRNAs (miRNAs) that modulate mRNA stability, translation, and subcellular localization through direct interaction with AU-rich elements in the *HuR* transcript [54,55] (Figure 1). In fact, HuR can positively autoregulate its own expression by binding to its cognate mRNA, enhancing its stability, cytoplasmic localization, and translation [27,54]. In contrast, decay-promoting RNA-binding proteins such as AUF1 (ARE/poly(U)-binding degradation factor 1) bind to the same ARE regions to destabilize *HuR* mRNA and simultaneously modulate broader gene expression patterns [54,56]. Several miRNAs, including miR-22, miR-29, and miR-519, have also been identified as key post-transcriptional regulators of *HuR* expression [57–59]. More specifically, miR-519 binds directly to both the 3' untranslated region (UTR) and coding sequence of *HuR* mRNA, repressing translation without affecting mRNA stability across multiple cancer cell lines, including HeLa cells [59].

While transcriptional and post-transcriptional mechanisms regulate *HuR* expression, its functional activity is more strongly influenced by post-translational modifications, protein–protein interactions, and interactions with noncoding RNAs [34,55,60] (Figure 1). Phosphorylation of *HuR* by kinases such as protein kinase C (PKC), cyclin-dependent kinase 1 (Cdk1), p38 mitogen-activated protein kinase (MAPK), and checkpoint kinase 2 (Chk2) modulates both its nucleocytoplasmic shuttling and its binding affinity for target transcripts, ultimately impacting cell survival [61–66]. Methylation of *HuR* enhances the stability of its target mRNAs and promotes cytoplasmic accumulation in cancer cells [26]. In contrast, ubiquitination marks *HuR* for proteasomal degradation under cellular stress, while caspase-mediated cleavage during apoptosis generates *HuR* fragments with distinct RNA-binding profiles compared to the full-length protein [24,67]. Biophysical and biochemical analyses using techniques such as fluorescence resonance energy transfer (FRET), X-ray crystallography, and immunoprecipitation have shown that *HuR* engages in non-covalent interactions with itself and other proteins to enhance binding to longer AREs and promote expression of target transcripts through oligomerization [34,68–70]. Additionally, in intestinal epithelial cells, transient interactions between *HuR* and various noncoding RNAs, including long noncoding RNAs, miRNAs, and circular RNAs, can modulate *HuR*'s affinity for its mRNA targets [55]. Together, these multilayered regulatory mechanisms underscore the complexity of *HuR* function, enabling dynamic and context-specific control of its activity in response to diverse cellular signals.

4. Overview of *HuR* Function during Physiological and Pathological Conditions

Under physiological conditions, *HuR* is predominantly localized to the nucleus, where it plays key roles in splicing, 3' end processing, pre-mRNA stabilization, and nuclear export of target transcripts [33] (Figure 1). Although *HuR* was originally characterized for its cytoplasmic role in stabilizing mature mRNAs [71], its nuclear functions in gene regulation are increasingly recognized. For instance, approximately 35% of *HuR* binding sites identified in unstressed HeLa cells by photoactivatable ribonucleotide crosslinking and immunoprecipitation (PAR-CLIP) were located within intronic regions, suggesting a major role in pre-mRNA processing [13]. Consistent with this, *HuR* knockdown in human embryonic kidney (HEK293) cells induces widespread changes in exon usage, further supporting its involvement in alternative splicing [33]. More specifically, nuclear *HuR* has been implicated in regulating transcripts involved in metabolism and mitochondrial function. In HEK293 cells, *HuR* binds to the long noncoding RNA (lncRNA) RNA component of mitochondrial RNA processing endoribonuclease (*RMRP*), facilitating its export to the cytoplasm where it regulates mitochondrial DNA replication and RNA processing [72]. Similarly, in activated B cells, *HuR* regulates expression of Dihydroliipoamide S-Succinyltransferase (*Dlst*), a critical component of the alpha-ketoglutarate dehydrogenase (α -KGDH) complex in the tricarboxylic acid (TCA) cycle, by binding to introns within *Dlst* pre-mRNA, thereby preventing the production of non-functional transcript variants [73].

During cellular stress, *HuR* plays an increasingly prominent role in regulating mature mRNA stability within the cytoplasm [17]. Translocation of *HuR* from the nucleus to the cytoplasm is

observed in various pathological and stress-related contexts, including cancer progression [74], oxidative injury [75], inflammation [76,77], fibrosis [29], and cell death [24]. Once in the cytoplasm, HuR stabilizes and enhances the translation of thousands of ARE-containing transcripts, many of which encode cell survival proteins and pro-inflammatory cytokines [13,71]. Although a basal level of cytoplasmic HuR is present under homeostatic conditions [41], both its upregulation and increased cytoplasmic localization have been implicated in the pathogenesis of inflammatory diseases such as rheumatoid arthritis [78], atherosclerosis [79], and inflammatory bowel disease [80], as well as in cancer progression [74]. Stabilized mRNAs include those encoding key regulators of proliferation (e.g., *c-Fos*, *p21*, *Cyclins B1*, *D1*, *E1*, *mdm2*) and inflammation (e.g., *iNOS*, *GM-CSF*, *TNF α* , *COX-2*) [17]. In some cases, HuR enhances the translation of target mRNAs without altering their stability, as seen with *X-linked inhibitor of apoptosis (XIAP)* [81], while in rare instances such as with internal ribosome entry site (IRES)-containing transcripts like *p27*, HuR binding suppresses translation [82].

Beyond its pro-inflammatory and pro-tumorigenic targets, HuR also regulates mRNAs encoding other RNA-binding proteins, mRNA processing factors, transcription factors, and cytokines, reflecting its broad influence on gene expression across disease states [33]. For instance, HuR stabilizes forkhead box Q1 (*FOXQ1*) mRNA in MDA-MB-231 triple negative breast cancer cells, promoting tumorigenesis and metastases [83], and stabilizes *transforming growth factor beta (TGF- β)* mRNA in activated hepatic stellate cells (HSCs), contributing to fibrosis in chronic liver disease [30]. Importantly, cytoplasmic HuR is not always pathogenic. It also supports adaptive cellular responses by stabilizing transcripts that encode metabolic enzymes [31], structural proteins [84], and signaling mediators [85]. In fact, reduced HuR expression is linked to the progression of certain disorders, including obesity and MASLD [31,85–87], underscoring its potential protective role in maintaining cellular homeostasis. Despite these advances, the full scope of HuR's function in cellular homeostasis and disease remains to be fully elucidated.

5. Role of HuR in Liver Homeostasis and MASLD

5.1. MASLD Epidemiology and Prevalence

MASLD is the most common cause of chronic liver disease today, with MASLD incidence continuing to increase across all populations [1,2]. In 2019, the global prevalence of MASLD was estimated at 23.4–30% of adults, with incidence also increasing in children and adolescents [2,88–90]. Although originally referred to as Non-Alcoholic Fatty Liver Disease (NAFLD), the term MASLD was adopted in 2023 by major international liver societies and patient advocacy groups to better reflect the heterogeneity of steatotic liver disease and its close association with other metabolic disorders [91]. Importantly, >96% of individuals who originally met NAFLD-diagnostic criteria also meet MASLD-diagnostic criteria, allowing for continuity between NAFLD-related and MASLD-related studies [92]. MASLD is defined as excessive hepatic triglyceride accumulation (>5% liver weight) in the presence of at least one additional cardiometabolic risk factor and absence of excess alcohol consumption [91]. The adult diagnostic criteria for MASLD-related cardiometabolic risk factors include 1) Body mass index (BMI) ≥ 25 kg/m² or waist circumference > 94 cm in men and > 80 cm in women, with ethnicity taken into account, 2) Fasting blood glucose ≥ 100 mg/dl or 2-hrs post-load glucose level ≥ 140 mg/dl or HbA1c $\geq 5.7\%$, 3) Blood pressure $\geq 130/85$ mmHg, 4) Plasma triglycerides ≥ 150 mg/dl, and 5) Plasma high-density lipoprotein (HDL) cholesterol < 40 mg/dl for men or < 50 mg/dl for women [91]. The MASLD spectrum ranges in severity from simple, non-inflammatory hepatic steatosis (>5% liver lipid), termed MASL, to the pro-inflammatory and pro-fibrotic phenotype of MASH [4]. Liver fibrosis is associated with increasing MASH severity and progression to cirrhosis and/or hepatocellular carcinoma (HCC) characterizes the progressive end of the MASLD spectrum [1].

MASLD presents an increasingly significant socioeconomic burden [88]. For instance, in 2016 alone, direct medical costs associated with MASLD were estimated to be about \$103 billion in the United States [3]. Likewise, despite the effectiveness of lifestyle interventions, such as weight loss,

increased exercise, and dietary restrictions, on reversing deleterious MASLD phenotypes, poor adherence to lifestyle interventions results in continued MASLD progression in many [1,7]. Although MASLD progresses to MASH in only 10-30% of human MASLD patients [1], MASH -and its subsequent fibrotic manifestations- greatly increases the risk for development of end-stage liver diseases, such as liver cirrhosis and hepatocellular carcinoma, and both fatal and non-fatal cardiovascular events [1,5,6]. Indicative of the increasing impact of MASLD on human health outcomes, MASH was the second most common cause of liver transplantation within the United States in 2019, and was also the most rapidly increasing liver transplantation etiology at that time [93]. Also indicative of the urgency to address the growing MASLD problem, as of January 2025, over 500 MASLD/MASH related clinical trials were currently ongoing or actively recruiting participants (clinicaltrials.gov). However, despite significant efforts, in 2024, approval of the β thyroid hormone receptor agonist, resmetirom marked the first -and only- Food and Drug Administration (FDA) approved pharmacotherapeutic for use in MASLD patients [94]. Importantly, resmetirom use is restricted to a small subset of MASLD patients and much uncertainty remains regarding its long term efficacy and side effect profile, pointing to the need for further MASLD-related pharmacotherapeutic development [94].

The pathogenesis and progression of MASLD are complex and multifactorial. Although significant progress has been made in understanding the molecular mechanisms underlying MASLD, the factors that drive the progression from non-inflammatory, simple steatosis to MASH in some individuals—but not others—remain poorly understood [4]. This knowledge gap continues to hinder effective therapeutic development. In this context, exploring the role of HuR, a dynamic and multifaceted RNA-binding protein, in a heterogeneous and multisystem disease like MASLD may offer valuable insights. Importantly, the loss of hepatic HuR expression observed in both MASLD patients and preclinical mouse models suggests a potential role for HuR in maintaining liver homeostasis and protecting against MASLD development [86]. Consistently, liver-specific *HuR* knockout mice show increased susceptibility to diet-induced MASLD, highlighting HuR and its downstream pathways as promising therapeutic targets [85–87,95]. The remainder of this review will explore HuR's regulatory functions in key pathways commonly disrupted in MASLD (Figure 2).

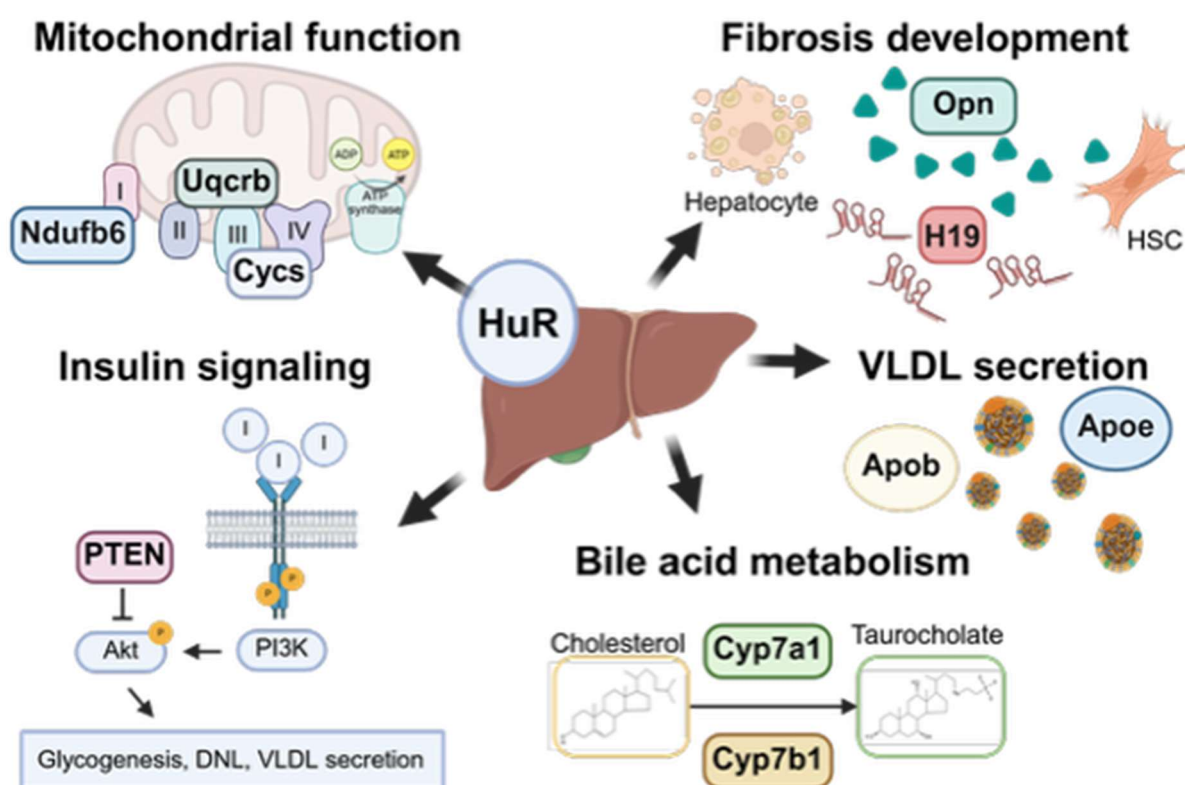


Figure 2. Graphical summary of HuR's roles in liver homeostasis and MASLD pathogenesis. HuR plays a multifaceted role in maintaining hepatic homeostasis and regulating key processes implicated in MASLD development. These include electron transport chain activity and mitochondrial function, hepatic stellate cell (HSC) activation and fibrogenesis, insulin signaling via the PI3K/Akt pathway, lipoprotein assembly and VLDL secretion, and bile acid synthesis and metabolism. HuR directly or indirectly regulates the expression of a wide array of target transcripts involved in these pathways, including *Ndufb6*, *Uqcrb*, *Cycs* (mitochondrial function), *Opn*, *H19* (fibrosis signaling), *PTEN* (insulin signaling), *Apob*, *Apoe* (lipid export), and *Cyp7a1*, *Cyp7b1* (bile acid synthesis). Collectively, these regulatory activities position HuR as a key post-transcriptional mediator in both physiological liver function and MASLD progression.

5.2. Role of HuR in Hepatic Steatosis

In MASLD, hepatic steatosis arises from an imbalance between lipid acquisition and elimination in the liver [96]. In human MASLD patients, approximately 60% of hepatic lipids are derived from adipose tissue lipolysis, 25% from hepatic *de novo* lipogenesis (DNL), and 15% from dietary intake [97]. In mouse models, liver-specific *HuR* deficiency exacerbates high-fat diet-induced steatosis, suggesting a protective role for HuR in lipid homeostasis [85–87,95]. In the following section, we will examine the potential mechanisms contributing to steatosis development in *HuR*-deficient livers.

5.2.1. HuR Regulates Insulin Signaling and Hepatic Steatosis

MASLD is strongly associated with insulin resistance and hyperinsulinemia [98]. More than 60% of individuals with type 2 diabetes mellitus (T2DM) also develop MASLD, placing them at significantly elevated risk for progression to pro-fibrotic MASH [99]. Insulin resistance in adipose tissue, liver, and skeletal muscle contributes to the metabolic disturbances that drive hepatic steatosis in MASLD [100]. In adipose tissue, insulin resistance impairs the anti-lipolytic effects of insulin, resulting in sustained lipolysis and increased circulating free fatty acids (FFAs), which promote ectopic lipid deposition in the liver [101]. In parallel, hepatic insulin resistance enhances DNL [100], while insulin resistance in skeletal muscle reduces glucose uptake and glycogen synthesis, leading to systemic hyperglycemia and further stimulating hepatic DNL [102].

Paradoxically, liver-specific *HuR*-deficient mice display enhanced insulin sensitivity and lower blood glucose levels compared to wild-type controls following 24 weeks of high-fat diet (HFD) feeding, despite exhibiting more pronounced hepatic steatosis [85]. To elucidate the underlying mechanisms, hepatic expression and activation of insulin signaling mediators including components of the phosphoinositide 3-kinase (PI3K)/Akt pathway were assessed in *HuR*-deficient mice [85]. Under normal conditions, hepatic insulin signaling via the PI3K/Akt axis inhibits glucose production and promotes glucose utilization through glycogenesis, DNL, and triglyceride export [100]. In *HuR*-deficient livers, Akt activation was elevated, and the expression of genes involved in glycolysis and DNL was increased, while genes related to hepatic glucose production were suppressed—indicating heightened sensitivity to insulin signaling [85]. Phosphatases such as phosphatase and tensin homolog (PTEN) act as negative regulators of the PI3K/Akt pathway and thereby reduce hepatic insulin sensitivity [103]. Like *HuR*-deficient mice, liver-specific *Pten* knockout mice show increased insulin sensitivity but develop more severe hepatic steatosis [104]. PTEN expression was decreased in *HuR*-deficient livers, and *Pten* mRNA was shown to associate with HuR in ribonucleoprotein immunoprecipitation (RNP-IP) assays from hepatocytes [85]. These findings suggest that HuR stabilizes *Pten* transcripts and that its loss leads to reduced PTEN expression, enhanced PI3K/Akt signaling, and increased hepatic insulin sensitivity, thereby promoting DNL. However, overexpression of PTEN in *HuR*-deficient livers did not reduce serum alanine aminotransferase (ALT) levels following HFD feeding, indicating that loss of *HuR*-mediated PTEN stabilization does not fully explain the susceptibility to liver injury in this model [85]. Supporting this, two additional studies using liver-specific *HuR* knockout mice reported significant upregulation of DNL-related genes, such as *acetyl-CoA carboxylase 1 (Acc1)* and *fatty acid synthase (Fasn)*, compared to wild-type controls, under both normal chow and Western diet conditions (42 kcal% fat, 0.1% cholesterol) [86,87].

These findings collectively suggest that hepatic HuR plays a critical role in modulating insulin signaling and lipid metabolism, where its loss enhances insulin sensitivity but simultaneously promotes hepatic lipogenesis and steatosis.

5.2.2. HuR Regulation of Very Low-Density Lipoprotein Secretion

The assembly and secretion of very low-density lipoprotein (VLDL) particles represent the primary pathway for hepatic lipid export and are essential for maintaining liver lipid homeostasis [105]. Impaired VLDL secretion leads to lipid accumulation, lipotoxicity, and exacerbation of MASLD [106–108]. In hepatocytes, VLDL particles are synthesized through microsomal triglyceride transfer protein (MTTP)-mediated lipidation of apolipoprotein B-100 (APOB-100), followed by the incorporation of storage lipids such as triglycerides and cholesterol esters [105]. Additional apolipoproteins, including apolipoprotein E (APOE), contribute to the stabilization and distribution of VLDL particles [109]. Enhanced VLDL secretion is generally protective against hepatic steatosis, as evidenced by the increased prevalence of MASLD in individuals with loss-of-function mutations in *MTTP* or *APOB* [110]. However, chronic overproduction of VLDL in MASLD patients is also linked to dyslipidemia and heightened cardiovascular risk [6,106].

In a recent study using liver-specific *HuR*-deficient mice, increased hepatic steatosis was accompanied by reduced expression of both APOB-100 and APOE, as well as decreased serum lipid levels [95]. Supporting a direct regulatory role for HuR, the authors demonstrated HuR binding to *ApoB* pre-mRNA, which enhanced APOB expression in a human hepatoma cell line [95]. Similarly, another study using the same Alb-Cre-driven *HuR* knockout model found elevated hepatic steatosis under normal chow conditions, though this effect was not observed after 6 weeks of choline-deficient high-fat diet (HFD-CD) feeding [86]. Because choline deficiency impairs hepatic VLDL secretion [111], this dietary context may have masked the effect of *HuR* loss on lipid export. Further supporting a role for HuR in VLDL regulation, shotgun lipidomic analysis revealed increased levels of major VLDL components such as various triglyceride and cholesterol ester species in *HuR*-deficient livers, with lipid profiles resembling those observed in human MASLD [86]. In addition, ER stress and dysregulated FXR signaling, both known to impair VLDL secretion and promote steatosis in MASLD [105], were also observed in *HuR*-deficient livers. Bulk RNA-seq analysis confirmed disruption of FXR target gene expression, lipid export pathways, and ER stress response genes, further supporting the hypothesis that impaired VLDL secretion contributes to lipid accumulation in the absence of hepatic HuR [86].

5.3. Role of HuR in Cholesterol Metabolism

Hepatic steatosis is considered the “first hit” in MASLD pathogenesis [112]. However, only 10–30% of individuals with MASLD progress to the inflammatory and fibrotic stage of MASH [1]. As shown in human clinical trials [1], improvements in hepatic steatosis do not necessarily correlate with reductions in liver injury or disease severity. This highlights the importance of identifying additional molecular “hits” that drive disease progression and may serve as therapeutic targets [113]. While overall hepatic fat accumulation defines MASLD, dysregulation of cholesterol metabolism is increasingly recognized as a critical driver of disease progression [114,115]. Cholesterol homeostasis in the liver is governed by a balance between assimilation (uptake, synthesis, esterification, storage) and elimination (lipoprotein secretion, bile acid synthesis, and excretion) [114]. In human MASLD, hepatic cholesterol accumulation is frequently linked to increased endogenous cholesterol synthesis [114,116]. This process is regulated by sterol regulatory element-binding protein 2 (*SREBP-2/Srebf2*), an ER-resident transcription factor activated under low sterol conditions [117]. Hepatic cholesterol biosynthesis involves a multi-step pathway, beginning with the conversion of acetyl-CoA to mevalonate by HMG-CoA reductase (*HMGCR/Hmgcr*), the rate-limiting step of the pathway and a major control point [118]. Cholesterol metabolites, glucagon, and statins inhibit HMGCR, whereas insulin and SREBP-2 activate [118,119]. While hepatic cholesterol accumulation normally suppresses

SREBP-2 activation, inflammation and insulin resistance can override this feedback, resulting in sustained cholesterol synthesis during MASLD [120,121].

Paradoxically, although *HuR*-deficient mouse livers show increased hepatic cholesterol content under MASLD-inducing diets [86,87], transcriptomic analysis revealed that cholesterol synthesis pathways were significantly downregulated in *HuR*-deficient livers under normal dietary conditions [86]. In the same study, RNP-IP sequencing (GEO access ID: GSE143703) in healthy murine liver tissue revealed direct binding of HuR to the *Hmgcr* mRNA, indicative of HuR-mediated post-transcriptional regulation of *Hmgcr*. These findings suggest that HuR loss alters the regulatory landscape of cholesterol metabolism even before overt MASLD develops, though further investigation is needed to clarify how HuR influences *Hmgcr* expression and cholesterol synthesis under different dietary conditions.

Following synthesis, cholesterol can be stored or utilized in various cellular processes, including bile acid (BA) synthesis and steroidogenesis. Excess free cholesterol is esterified by acyl-CoA:cholesterol acyltransferase (ACAT) for storage in lipid droplets [122]. Alternatively, unesterified cholesterol is distributed to cellular membranes to maintain membrane fluidity and serve as a precursor for cholesterol derivatives [122]. In hepatocytes, free cholesterol predominantly accumulates in the plasma membrane, while its accumulation in organelle membranes, particularly the mitochondrial and ER membranes, is tightly restricted to preserve membrane integrity [118]. During MASLD, excess accumulation of free cholesterol in the mitochondrial and ER membranes leads to mitochondrial dysfunction and ER stress, promoting inflammation, cell death, and MASLD progression [123]. Although membrane-specific free cholesterol distribution has not yet been assessed in *HuR*-deficient mouse livers, elevated total hepatic cholesterol levels in these mice are accompanied by increased mitochondrial dysfunction [95] and ER stress [86], raising the possibility that disrupted cholesterol compartmentalization, including excess free cholesterol, contributes to liver injury in this model. This warrants further investigation into the role of HuR in regulating intracellular cholesterol distribution and its implications for MASLD progression.

5.4. Role of *HuR* in Bile Acid Metabolism

Metabolism of cholesterol into bile acids represents the primary route for cholesterol elimination in the body [124]. Bile acid synthesis occurs mainly in the liver and involves two distinct pathways: the classical and the alternative pathways [124]. The classical pathway predominates in the adult human liver, while the alternative pathway is more active in infants and becomes increasingly relevant in MASLD [125]. In the classical synthesis pathway, both microsomal and mitochondrial cytochrome P-450s (CYPs), including 7α -hydroxylase (CYP7A1), 3β -hydroxy- Δ^5 -C₂₇-steroid dehydrogenase (3β -HSD), sterol 12α -hydroxylase (CYP8B1), aldo-keto reductase 1D1 (AKR1D1) and sterol 27 -hydroxylase (CYP27A1), oxidize cholesterol into the bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA). In contrast, the alternative pathway is initiated by sterol hydroxylases that metabolize cholesterol into various oxysterols, including 24 -, 25 -, and 27 -hydroxycholesterol [126]. Mitochondrial CYP7B1 then further hydroxylates these oxysterols into 3β , 7α -dihydroxy-5-cholestenoic acid, which subsequently enters the classical synthesis pathway for further metabolism by AKR1D1 and CYP27A1 to generate CDCA [124]. In humans, most CA and CDCA are conjugated with glycine or taurine at a 3:1 ratio by the peroxisomal enzymes bile acid-CoA synthase (BACS) and bile acid *N*-acyltransferase (BAAT) [127]. In mice, however, CDCA is further converted to α - and β muricholic acids (MCAs) by *Cyp2c70* before conjugation [128]. Additionally, murine BAAT preferentially conjugates bile acids with taurine, resulting in nearly all primary bile acids being taurine-conjugated [129]. These species-specific differences in bile acid synthesis and conjugation significantly influence bile acid pool composition and signaling, which limits the direct applicability of findings from murine models to human physiology [124].

MASLD development is associated with a progressive increase in serum bile acid levels and alterations in bile acid pool composition [130,131]. However, the underlying mechanisms driving bile acid induction in MASLD remain controversial and incompletely understood [132]. For instance,

upregulation of bile acid synthesis genes, including *CYP7A1*, *CYP8B1*, and *CYP27A1* [133], along with elevated levels of bile acid synthesis marker 7- α -hydroxy-4-cholesten-3-one (C4) [134], has been linked to increased bile acid pool size in two human MASLD cohorts. In contrast, another study reported that although serum primary bile acids increased with higher MASH activity scores and fibrosis progression, C4 levels remained unchanged [130]. Similar discrepancies have been observed in diet-induced rodent MASLD models. In rats, MASLD induction led to increased expression of *Cyp7a1* and *Cyp8b1* [133], whereas a MASLD mouse model showed elevated hepatic bile acid levels despite decreased expression of classical bile acid synthesis genes, including *Cyp27a1* and *Cyp8b1* [135].

HuR appears to play a regulatory role in hepatic BA synthesis [86,87]. In hepatocyte- and cholangiocyte-specific *HuR*-deficient mouse livers, key genes involved in both classical and alternative BA synthesis pathways such as *Cyp7a1* and *Cyp7b1* are downregulated. RNP-IP from healthy murine liver tissue confirms that HuR directly binds to both *Cyp7a1* and *Cyp7b1* transcripts, suggesting post-transcriptional regulation by HuR [86]. *Cyp7b1* repression is commonly observed during MASLD and is associated with induction of the alternative BA synthesis pathway, leading to oxysterol accumulation, which contributes to hepatic inflammation and fibrosis [126,136,137]. Whether *Cyp7b1* suppression in *HuR*-deficient livers promotes oxysterol accumulation during MASLD remains to be determined. In addition to gene repression, hepatocyte- and cholangiocyte-specific *HuR*-deficient livers show reduced levels of conjugated primary bile acids, including tauro-CDCA (TCDCA) and tauroursodeoxycholic acid (TUDCA) [86]. Contrastingly, hepatocyte-specific *HuR*-deficient mice exhibit increased levels of conjugated primary and secondary bile acids in both liver and serum following MASLD-inducing diet feeding [87]. The authors of that study hypothesized that this accumulation may promote MASH fibrosis by activating sphingosine-1-phosphate receptor 2 (S1PR2) and upregulating H19 expression [87]. The discrepancies between these two studies may be attributed to differences in the scope of *HuR* deletion (hepatocyte-specific vs. hepatocyte-and-cholangiocyte-specific) as well as variations in diet feeding conditions.

Enterohepatic bile acid circulation that recycles bile acids between the liver and the intestine is essential to not only disposition of lipid-soluble metabolites, but also to bile acid-mediated regulation of metabolic homeostasis [125]. Around 95% of the bile acids that enter the small intestine are reabsorbed by ileal enterocytes. Prior to recycling, some bile acids are metabolized by gut bacteria in the distal ileum and large intestine into secondary BAs, including DCA, hyocholic acid (HCA), lithocholic acid (LCA), ursodeoxycholic acid (UDCA) and ω -MCA. Indicative of impaired enterohepatic bile acid circulation, conjugated bile acids including TCA are elevated in the liver and serum of hepatocyte-specific *HuR*-deficient mice compared to wild-type controls, while primary and secondary bile acids are reduced in the cecum following MASLD-inducing diet feeding [87]. These findings suggest that HuR plays a multifaceted role in regulating bile acid metabolism by modulating the expression of key synthetic enzymes and maintaining proper enterohepatic circulation. Its deficiency disrupts BA synthesis, alters BA pool composition, and impairs metabolic signaling, collectively contributing to MASLD progression.

5.5. *HuR* Regulates Mitochondrial Function and Oxidative Stress

Mitochondrial dysfunction is a key contributor to MASLD progression toward MASH [138]. As central regulators of lipid metabolism and cellular energy homeostasis, mitochondria act both as protectors of liver function and as drivers of MASLD under metabolic stress [139,140]. For instance, mitochondrial fatty acid oxidation (FAO) is initially upregulated in response to increased intrahepatic lipid accumulation during early MASLD development [139]. However, as the disease progresses to MASH, mitochondrial oxidative metabolism becomes impaired, resulting in reduced ATP production and increased reactive oxygen species (ROS) generation [138–142].

HuR appears to play a hepatocyte-specific role in regulating mitochondrial function. In liver-specific *HuR*-deficient mice, increased hepatic steatosis is associated with significantly reduced ATP levels and downregulation of electron transport chain (ETC) proteins, including cytochrome c (Cycs),

NADH: ubiquinone oxidoreductase subunit B6 (*Ndufb6*), and ubiquinol-cytochrome c reductase binding protein (*Uqcrcb*), following four weeks of high-fat diet feeding [95]. Direct binding of HuR to the mRNAs of *Cytc*, *Ndufb6*, and *Uqcrcb* was also demonstrated in Hepa1-6 cells, supporting a post-transcriptional regulatory role for HuR [95]. However, overexpression of *Cytc* alone did not restore mitochondrial ATP production in *HuR*-deficient livers, suggesting that HuR may influence mitochondrial function through multiple pathways [95].

Accumulation of ROS in dysfunctional mitochondria contributes to oxidative injury in MASLD [143]. To mitigate oxidative stress, the nuclear factor erythroid 2-related factor 2 (*Nrf2*, *Nfe2l2*) pathway is activated, inducing the expression of key cytoprotective genes such as superoxide dismutase 2 (*Sod2*) and heme oxygenase-1 (*HO-1*) [144]. HuR has been shown to enhance this antioxidant response; HuR-mediated upregulation of *HO-1* is associated with improved survival in liver transplant recipients [75]. Furthermore, in rats fed a methionine- and choline-deficient (MCD) diet for six weeks, a positive correlation between hepatic HuR expression and both *HO-1* and *Sod2* expression was observed, further supporting HuR's role in regulating oxidative stress responses in vivo [145].

In summary, HuR helps preserve mitochondrial function and protects against oxidative injury by regulating components of the electron transport chain and key antioxidant defense pathways, underscoring its potential role in preventing MASLD progression.

5.6. Role of HuR in Autophagy

Autophagic degradation of lipids (lipophagy) and damaged mitochondria (mitophagy) plays a protective role in preventing MASLD progression to MASH [146]. Although autophagy is constitutively active in all cell types, it is strongly induced under conditions of cellular stress and energy depletion [147]. During autophagy, autophagy-related proteins including Atg8/ microtubule-associated protein 1A/1B light chain (LC3) and selective autophagy receptors (SARs) such as sequestosome 1 (SQSTM1/p62) target cellular components for sequestration into double-membraned vesicles called autophagosomes [146]. Fusion of autophagosomes with lysosomes enables degradation of the sequestered materials [147]. In autophagy-deficient livers, clearance of lipid droplets and dysfunctional mitochondria is impaired, contributing to increased hepatic steatosis and mitochondrial dysfunction during MASLD progression [147,148].

While HuR's specific role in autophagy during MASLD remains to be defined, growing evidence suggests that HuR functions as a positive regulator of autophagy in various cell types and disease contexts, particularly under oxidative and metabolic stress [149]. In liver cancer cell lines such as L-02 and Hep3B, HuR deficiency reduces autophagosome formation and autophagic flux. RNP-IP revealed direct HuR binding to the 3' UTRs of *Atg5*, *Atg12*, and *Atg16* mRNAs in Hep3B cells [150]. Similarly, in *HuR*-deficient mouse livers, reduced expression of *Atg3*, *Atg5*, and *Atg7* was observed alongside more severe liver injury following acetaminophen (APAP) overdose and the direct binding of HuR to the 3' UTRs of these genes was also confirmed in Hepa1-6 cells [151]. Given HuR's established role in regulating autophagy across multiple tissues and models of liver injury, further investigation into its function in autophagy during MASLD development is highly warranted.

5.7. HuR Regulates Apoptosis and Cell Survival

As MASLD progresses to MASH, worsening liver dysfunction triggers activation of cell death pathways, particularly apoptosis. Apoptosis is considered the predominant mode of cell death in MASLD livers, and caspase substrates, such as cytokeratin-18, have been proposed as potential serum biomarkers for human MASH [4,152]. HuR, widely recognized as a survival-promoting factor in various cancers, regulates the stability of both pro-apoptotic transcripts (e.g., p53, p27, caspase-8, caspase-9, Fas, c-Myc) and anti-apoptotic transcripts (e.g., Bcl-2, SIRT1, Prothymosin α) [153–155]. However, under conditions of lethal cellular stress, HuR itself is cleaved and adopts a pro-apoptotic role by directly binding to and stabilizing *Caspase-9* mRNA [24,25].

Apoptosis induction in MASLD is strongly associated with the accumulation of non-storage lipids, including FFAs and free cholesterol, in the liver [156,157]. Although HuR's specific role in hepatocyte apoptosis during MASLD remains to be fully elucidated, elevated hepatic FFA and cholesterol levels have been observed in *HuR*-deficient mouse livers, correlating with increased liver injury after 24 weeks of high-fat diet feeding [85]. These non-storage lipids contribute to hepatocyte apoptosis by activating both intrinsic (organelle-mediated) and extrinsic (death receptor-mediated) apoptotic pathways [123,158,159]. Intrinsic apoptosis is initiated when FFAs and free cholesterol accumulate in organelle membranes, particularly the ER, mitochondria, and lysosomes, triggering ER stress, mitochondrial dysfunction, and release of lysosomal proteases [158]. RNP-IP analysis from healthy murine livers revealed direct binding of HuR to transcripts involved in the ER stress response, suggesting a potential role for HuR in regulating organelle stress pathways during MASLD [86]. In parallel, non-storage lipids also activate extrinsic apoptosis signaling. FFAs sensitize hepatocytes to apoptosis via JNK activation, upregulation of death receptor 5 (DR5) and Fas receptor, and activation of Bax [160,161]. Similarly, excessive free cholesterol accumulation within mitochondrial membranes increases mitochondrial sensitivity to oxidative stress and enhances hepatocyte susceptibility to TNF α - and Fas ligand-mediated apoptosis [123]. Both DR5 and Fas are highly expressed in human MASH livers, which also exhibit greater degrees of mitochondrial dysfunction [141,156,160]. In liver cancer models, HuR has been shown to inhibit apoptosis by directly binding to the 3' UTR of Fas mRNA in HepG2 cells and repressing its translation [162]. Whether HuR plays a similar survival-promoting and anti-apoptotic role in hepatocytes during MASLD progression remains an important area for future investigation.

5.8. *HuR* in Hepatic Inflammation

Chronic liver injury and cell death during MASLD progression to MASH are accompanied by sustained immune activation, contributing to aberrant wound healing, inflammation, and fibrosis [4]. In MASLD, damage-associated molecular patterns (DAMPs) released from stressed or dying hepatocytes and pathogen-associated molecular patterns (PAMPs) from gut-derived microbial products activate Toll-like receptors (TLRs) on various hepatic cell types to initiate immune responses [163]. For instance, TLR4 activation by FFAs and unesterified cholesterol triggers pro-inflammatory signaling cascades, particularly in macrophages [164]. This leads to increased expression of pro-inflammatory cytokines and chemokines such as tumor necrosis factor alpha (Tnfa), interleukin 6 (IL-6), interleukin 1 β (IL-1 β), and C-C motif chemokine ligand 2 (Ccl2), the molecules tightly linked to MASLD progression and fibrosis [163]. TNF α acts on both parenchymal and non-parenchymal cells to promote immune cell recruitment, activation, and fibrogenic remodeling in the liver [163,165]. HuR has been shown to bind directly to the *Tnf* mRNA 3' UTR in RAW 264.7 macrophages, and its expression is essential for LPS-induced Tnfa production in bone marrow-derived macrophages (BMDMs) [166–168]. Additional pro-inflammatory targets of HuR include *Ccl2*, inducible nitric oxide synthase (iNOS, *Nos2*), vascular endothelial growth factor (VEGF, *vegfa*), and cyclo-oxygenase 2 (COX-2, *Ptgs2*) [169]. Although HuR is generally regarded as a positive regulator of inflammation, studies in myeloid-specific *HuR* knockout models suggest a more nuanced role. In these models, *HuR* depletion exacerbates inflammation and mortality in response to LPS-induced endotoxemia and chemically induced colitis [170–172]. While the role of myeloid HuR in MASLD has not yet been studied, hepatocyte-specific *HuR*-deficient mice fed a WD diet for four weeks exhibit increased liver inflammation, characterized by F4/80-positive macrophage infiltration and upregulation of *Ccl2*, *Tnf*, *Il6*, and *Il1b* [87].

Beyond macrophages, the roles of other immune cells, including natural killer T (NKT) cells and adaptive immune populations, are gaining recognition in MASLD pathogenesis [173]. NKT cells exert both pro- and anti-inflammatory effects but are enriched in the liver during MASLD progression to MASH and fibrosis [173,174]. Adaptive immune subsets, including Th1, Th17, and B cells, also increase in abundance and activity with worsening disease severity [173]. HuR has been shown to influence the adaptive immune response; *HuR*-deficient T and B cells exhibit impaired activation and

proliferation upon inflammatory stimulation [73,175,176]. Moreover, postnatal *HuR* depletion results in apoptosis of immune progenitor cells in the bone marrow and thymus, highlighting *HuR*'s essential role in immune cell survival [23]. In the context of MASLD, inflammation and tumorigenesis are exacerbated in hepatocyte- and cholangiocyte-specific *HuR*-deficient mice after 14 months of HFD-CD feeding [86]. These livers show increased infiltration of NKT cells and CD8⁺ T cells, immune subsets commonly associated with severe inflammation and fibrosis in MASLD [86,173,174].

In summary, *HuR* exerts a context-dependent and multifaceted influence on inflammation, regulating both innate and adaptive immune responses. However, its specific roles within individual immune cell populations in the context of MASLD remain unexplored. Further investigation is warranted to elucidate how immune cell-specific *HuR* activity contributes to immune-mediated mechanisms underlying MASLD progression.

5.9. *HuR* in Liver Fibrosis

Fibrosis is the major predictor of liver-related morbidity and mortality in MASLD patients, significantly increasing the risk of liver failure and hepatocellular carcinoma (HCC) [177,178]. Hepatic fibrosis develops when chronic inflammation, sustained cell death, and aberrant wound healing activate normally quiescent fibroblasts, primarily hepatic stellate cells (HSCs), into highly proliferative, contractile, and collagen-secreting myofibroblasts [179,180]. HSC activation is driven by various profibrotic signals, including transforming growth factor β 1 (TGF β 1) and platelet-derived growth factor (PDGF) [180,181]. In MASLD, free cholesterol accumulation within HSCs enhances their activation, while other pro-fibrotic cues, such as Notch signaling activation in hepatocytes and lncRNA H19 induction in cholangiocytes, further amplify fibrogenic responses [87,182–184].

HuR plays a complex and cell type-specific role in liver fibrosis. In hepatocytes, *HuR* appears protective, as its deficiency exacerbates fibrosis progression in MASLD mouse models [86,87]. Hepatocyte- and cholangiocyte-specific *HuR* deficiency leads to hepatic cholesterol accumulation and marked dysregulation of cholesterol metabolism, conditions known to promote HSC activation [86]. These *HuR*-deficient mice also show elevated expression of the Notch signaling mediator osteopontin (OPN) [86] and, under WDSW diet feeding, increased H19 expression [87], both associated with more severe fibrosis.

In contrast, *HuR* expression in hepatic myofibroblasts (activated HSCs) promotes both bile duct ligation and CCl₄-induced fibrosis development [29,30]. In murine HSCs, TGF β 1 and PDGF both induce cytoplasmic localization of *HuR*, while PDGF specifically increases *HuR* expression [29,30]. In *HuR*-deficient rat HSCs, PDGF-induced proliferation and migration are significantly impaired [29]. RNP-IP experiments in the activated HSC line CFSC-8B revealed that *HuR* binds directly to transcripts encoding pro-proliferative (e.g., cyclin D1, cyclin B1) and motility-related proteins (e.g., MMP9, actin) following PDGF stimulation [29]. Similarly, *HuR* directly binds to sphingosine kinase 1 (*Sphk1*) mRNA, which is required for TGF β 1-mediated induction of *Colla1* and α -SMA in both human HSCs LX-2 cells and murine primary HSCs [30]. In addition to promoting HSC activation, *HuR* may also contribute to fibrosis resolution. In a recent study, sorafenib-induced ferroptosis in HSCs was dependent on *HuR*-mediated stabilization of the autophagy gene beclin 1 (*Becn1*), suggesting a role for *HuR* in promoting autophagy and cell death in activated HSCs under therapeutic stress [185].

The transition of HSCs from a quiescent to a myofibroblast-like phenotype is a critical determinant of both fibrosis progression and resolution in the liver [177]. *HuR* has been shown to regulate differentiation in various cell types, including enterocytes and immune cells, and is implicated in Wnt/ β -catenin signaling during cancer progression [179,186,187]. Although *HuR*'s role in HSC differentiation remains incompletely defined, there is growing interest in its interaction with key developmental signaling pathways such as Notch, Wnt, and Hedgehog, which are known to influence fibrogenesis. In summary, *HuR* functions as a pivotal post-transcriptional regulator of liver fibrosis, with cell-type-specific effects that may drive both the progression and resolution of fibrogenic responses in MASLD. Future research should aim to dissect the signaling networks

through which HuR modulates HSC plasticity, with the goal of identifying new therapeutic strategies to prevent or reverse hepatic fibrosis.

6. Role of HuR in Extrahepatic Metabolic Comorbidities

MASLD is closely linked to a range of extrahepatic metabolic disorders, including obesity, T2DM, and cardiovascular disease [1]. Reflecting the central role of systemic metabolic dysfunction in MASLD pathogenesis, current diagnostic criteria require the presence of at least one additional cardiometabolic risk factor, such as obesity or insulin resistance, in conjunction with hepatic steatosis to establish a MASLD diagnosis [91]. In this section, we provide a brief overview of HuR's emerging roles in extrahepatic metabolic diseases commonly associated with MASLD, highlighting its potential contribution to the broader metabolic syndrome context.

6.1. Obesity

6.1.1. Overview of Obesity and Its Association with MASLD

Obesity is a well-established independent risk factor for MASLD progression to MASH, even in the absence of other metabolic comorbidities [9]. The global prevalence of obesity has increased dramatically over the past 50 years, driven by a complex interplay of genetic, behavioral, environmental, and socioeconomic factors [188]. Understanding the mechanisms linking obesity to metabolic disease progression is essential for improving both survival and quality of life in affected individuals. While chronic low-grade inflammation, insulin resistance, and dyslipidemia are recognized contributors to MASLD development in obese individuals, the molecular drivers of these pathophysiological changes remain incompletely defined [188]. For instance, although adipokine signaling dysregulation is known to exacerbate hepatic steatosis and insulin resistance [9], the specific regulatory networks involved are still not fully understood [189]. Given these knowledge gaps, investigating the role of HuR in adipose tissue function and obesity development may offer novel insights into the mechanisms driving MASLD and identify potential therapeutic targets.

6.1.2. Role of HuR in Adipocyte Differentiation and Obesity

HuR is a key post-transcriptional regulator of adipocyte function, and its expression is dynamically regulated during adipocyte differentiation and obesity development. In vitro differentiation of 3T3-L1 pre-adipocytes is associated with increased HuR expression and cytoplasmic localization [22]. In contrast, in vivo studies show that mature adipocytes express lower levels of HuR compared to pre-adipocytes residing in the stromal vascular fraction [31]. Importantly, obesity is associated with further suppression of HuR expression in adipose tissue in both humans and mice [31]. In this section, we highlight HuR's role in adipocyte differentiation and dysfunction, with an emphasis on mechanisms relevant to MASLD [22,31,32,190–192].

Adipocyte differentiation from pre-adipocytes into mature and lipid-storing adipocytes is essential for maintaining lipid homeostasis. HuR supports this process by stabilizing mRNAs encoding key adipogenic regulators, including CCAAT/enhancer-binding protein beta (*C/EBPβ*) and solute carrier family 2 member 1 (*Slc2a1*, also known as *GLUT1*) [22]. In addition, HuR directly stabilizes transcripts encoding peroxisome proliferator-activated receptor gamma (*Pparγ*) and adiponectin (*Adipoq*), both of which are critical for adipocyte function and insulin sensitivity [190]. The activity and localization of HuR during adipocyte differentiation are modulated by regulatory signals, including *Pparγ* and the long non-coding RNA *CAAInc1*. Binding of *CAAInc1* to HuR interferes with HuR-mediated stabilization of adipogenic transcription factor mRNAs in C3H10 cells [192].

In vivo, HuR is essential for maintaining adipose tissue health and systemic metabolic balance. Adipocyte-specific *HuR* deletion in mice leads to exacerbation of obesity, MASLD, and cardiovascular disease [31,32,191]. Following 16 weeks of high-fat diet feeding, adipocyte-specific

HuR-deficient mice exhibited significantly greater hepatic steatosis than wild-type controls. This was partly attributed to reduced expression of patatin-like phospholipase domain-containing 2 (*Pnpla2*), which encodes adipose triglyceride lipase (ATGL), a key enzyme in adipocyte lipolysis [31]. Impaired ATGL activity resulted in adipocyte hypertrophy, inflammation, and systemic insulin resistance, all of which promote MASLD progression. Further studies demonstrated that *HuR* deficiency selectively impacted abdominal (epididymal) adipose depots, but not subcutaneous (inguinal) depots. This regional *HuR* loss was associated with increased adipogenesis and pro-inflammatory cytokine expression, a pattern closely linked to obesity-associated MASLD in humans [32]. In the context of cardiovascular disease, *HuR* deficiency in adipocytes led to cardiac hypertrophy and fibrosis, despite unaltered *HuR* expression in heart tissue. Transcriptomic analyses revealed significant alterations in both adipose and cardiac gene expression, and the pro-inflammatory environment in *HuR*-deficient adipose tissue likely contributed to a systemic inflammatory state, promoting pathological cardiac remodeling [191].

In summary, adipocyte-specific *HuR* is a critical regulator of adipocyte differentiation, lipid metabolism, and systemic inflammation. Its loss not only promotes adipose tissue dysfunction and obesity but also contributes to the development of MASLD and cardiovascular disease, underscoring *HuR*'s central role in metabolic health [31,32,191].

6.2. Cardiovascular Disease and Type II Diabetes Mellitus

6.2.1. Overview of Cardiovascular Disease, Diabetic Cardiomyopathy and Their Link to MASLD

Similar to obesity, T2DM and MASLD are closely interconnected metabolic disorders [193]. While approximately 30% of the global adult population is estimated to have MASLD, the prevalence rises to nearly 60% among individuals with T2DM, underscoring their frequent coexistence [1]. Key pathophysiological contributors to this relationship include systemic insulin resistance and hyperglycemia, both hallmark features of T2DM [100]. Conversely, growing evidence suggests that MASLD itself may act as a precursor to T2DM, rather than merely a consequence [194]. Mechanistically, hepatic steatosis contributes to systemic insulin resistance, chronic low-grade inflammation, and dyslipidemia, all of which drive T2DM pathogenesis. Moreover, progression of MASLD to MASH and advanced fibrosis further increases the risk for developing T2DM [194].

Cardiovascular disease (CVD), including myocardial infarction, ischemic stroke, and heart failure, is the leading cause of death in patients with both MASLD [195] and T2DM [196]. In T2DM, chronic hyperglycemia-induced vascular injury underlies multiple cardiovascular complications, including atherosclerotic cardiovascular disease and diabetic cardiomyopathy [197]. In diabetic cardiomyopathy, insulin resistance and hyperglycemia contribute to persistent inflammation, oxidative stress, cardiomyocyte death, and cardiac remodeling, leading to heart failure independent of atherosclerosis [198]. However, atherosclerosis frequently co-occurs with T2DM and contributes to the 2-fold or greater increase in CVD risk observed in this population [196]. Similarly, MASLD contributes to CVD development through shared mechanisms, including hepatic steatosis-induced insulin resistance, chronic systemic inflammation, and atherogenic dyslipidemia [5]. These overlapping metabolic disturbances suggest that MASLD is not only a liver disease but also a significant contributor to cardiometabolic risk.

6.2.2. Role of *HuR* in Metabolic Dysfunction-associated Cardiovascular Disease

HuR expression and cytoplasmic localization in cardiac tissue are associated with CVD development in both human patients and experimental animal models [199]. While some discrepancies in the literature exist regarding the direction of *HuR*'s effects [200], the majority of studies suggest that *HuR* induction contributes to cardiac dysfunction in conditions such as ischemia/reperfusion (I/R) injury [201–203], pressure overload-induced cardiac remodeling [204,205], and myocardial infarction (MI) [206]. In diabetic (db/db) mice, *HuR* is upregulated not only in cardiomyocytes but also in infiltrating immune cells within the heart [203]. Correspondingly,

elevated HuR expression has been observed in myocardial tissue from heart failure patients [203,204], including those with diabetes [67].

HuR contributes to CVD pathogenesis through several mechanisms, including cardiomyocyte death, inflammatory cytokine production, and immune cell infiltration, all of which drive adverse cardiac remodeling and progression to heart failure [198]. Following ischemic injury, HuR induction in the infarct zone is associated with increased expression of pro-inflammatory cytokines such as $TNF\alpha$, $IL-1\beta$, $CCL2$, and the pro-apoptotic factor p53. In mice with cardiomyocyte-specific *HuR* depletion, infarct-associated cell death and inflammation were significantly reduced compared to controls [206]. In a coronary artery-ablation model of murine I/R injury, pharmacological inhibition of HuR led to reduced $Il6$ and $Tnfa$ expression in the infarcted region [201]. Interestingly, while cardiomyocyte apoptosis (as measured by TUNEL staining) remained unchanged between treatment groups, $CD68^+$ immune cell infiltration into the infarct site was reduced in HuR-inhibited mice, correlating with improved cardiac function and attenuated fibrosis [201]. Prolonged inflammation contributes to fibrotic remodeling and heart failure. In diabetic patients with heart failure, an increased number of HuR^+ and $F4/80^+$ macrophages has been observed in failing hearts [203]. In mouse models, macrophage-specific *HuR* deletion led to reduced pro-inflammatory cytokine expression and fibrosis in an angiotensin II-induced model of cardiac injury [203]. Similarly, fibroblast-specific *HuR* deletion resulted in decreased myofibroblast activation (e.g., reduced α -SMA expression), less fibrosis, and preserved cardiac function following pressure overload-induced injury [205]. In a separate study, cardiomyocyte-specific *HuR* deletion protected against cardiac hypertrophy and fibrosis in a pressure overload model, in part by suppressing $TGF-\beta$ expression in cardiomyocytes [204].

In summary, HuR contributes to the development and progression of cardiovascular disease under conditions of metabolic stress by promoting inflammation, cell death, immune infiltration, and fibrotic remodeling in the heart. Its cell-specific functions in cardiomyocytes, macrophages, and fibroblasts highlight HuR as a multifaceted regulator of cardiac pathology in metabolic disease contexts such as MASLD and T2DM.

7. Conclusions and Future Perspectives

As a ubiquitously expressed and highly dynamic regulator of post-transcriptional gene expression, HuR plays a critical role in numerous cellular processes. Expanding our understanding of HuR function in the context of MASLD holds significant potential for informing the development of novel therapeutic strategies. However, HuR's essential role in maintaining homeostasis across multiple tissues and cell types presents a substantial challenge for its therapeutic targeting. This complexity is exemplified by the opposing effects of HuR in different liver cell populations. While hepatocyte-specific HuR protects against diet-induced MASLD progression [86], HuR activation in HSCs promotes fibrogenesis and chronic liver injury [29]. As such, indiscriminate modulation of HuR in both hepatocytes and HSCs could inadvertently exacerbate disease progression or produce limited therapeutic benefit. Similarly, although reduced hepatic HuR expression is associated with worsening MASLD [85], HuR induction and cytoplasmic localization are poor prognostic markers in both hepatocellular carcinoma [207] and heart failure [203], underscoring the need for context- and cell-specific therapeutic approaches.

To address this challenge, several strategies have been proposed to enhance therapeutic specificity. One approach involves cell-targeted delivery, such as conjugating small-molecule inhibitors to retinol for selective uptake by retinol-storing HSCs, thereby limiting off-target effects while inhibiting fibrosis progression [208]. Additionally, rather than targeting HuR expression broadly, interventions could focus on specific functional aspects of HuR, including nuclear-to-cytoplasmic translocation, dimerization, post-translational modifications, or mRNA-binding activity—each of which may contribute differentially to HuR's role in disease [209]. Importantly, genetic HuR depletion in metabolic tissues such as the liver, heart, and adipose tissue typically does not disrupt basal tissue function unless triggered by metabolic stressors like lipid overload

[31,95,204]. This observation suggests that therapeutic inhibition of HuR may be selectively toxic under pathological conditions, allowing for dose titration strategies to minimize effects on healthy tissue. For example, KH-3, a small-molecule HuR inhibitor that blocks mRNA binding, has shown promise in selectively inhibiting HuR in tumor cells with high HuR expression, while sparing normal tissues [83].

Although further research is necessary to develop safe and effective HuR-targeted therapies, a deeper understanding of HuR's multifaceted role in metabolic disease offers new opportunities for precision medicine. At the very least, this insight highlights the need for caution in the use of HuR inhibitors for treating cancer or age- and inflammation-related diseases. Ultimately, unraveling the mechanisms by which HuR contributes to metabolic homeostasis and dysfunction may yield novel therapeutic targets for MASLD and related cardiometabolic disorders.

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Abbreviations

The following abbreviations are used in this manuscript:

BMDMs: Bone Marrow-Derived Macrophages; CCL2: Chemokine (C-C Motif) Ligand 2; DAMP: Damage-Associated Molecular Patterns; HCC: hepatocellular carcinoma; HSC: hepatic stellate cell; IL: interleukin; LPS: lipopolysaccharide; MASH: metabolic dysfunction-associated steatohepatitis; MASL: metabolic dysfunction-associated steatotic liver; MASLD: metabolic dysfunction-associated steatotic liver disease; MCD: Methionine Choline Deficient; NAFLD: nonalcoholic fatty liver disease; NF- κ B: Nuclear Factor Kappa B; NLRP3: NLR Family Pyrin Domain Containing 3; NOS2: Nitric Oxide Synthase 2; PPAR: Peroxisome Proliferator-Activated Receptor; ROS: reactive oxygen species; T2DM: Type II Diabetes Mellitus; TGF- β : Transforming Growth Factor Beta; TLR: Toll-like receptor; TNF α : Tumor Necrosis Factor Alpha.

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