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REVIEW ARTICLE

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Human antigen R: Exploring its inflammatory response impact and significance in cardiometabolic disorders

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Abstract

RNA-binding proteins (RBPs) play a crucial role in the regulation of post-transcriptional RNA networks, which can undergo dysregulation in many pathological conditions. Human antigen R (HuR) is a highly researched RBP that plays a crucial role as a posttranscriptional regulator. HuR plays a crucial role in the amplification of inflammatory signals by stabilizing the messenger RNA of diverse inflammatory mediators and key molecular players. The noteworthy correlations between HuR and its target molecules, coupled with the remarkable impacts reported on the pathogenesis and advancement of multiple diseases, position HuR as a promising candidate for therapeutic intervention in diverse inflammatory conditions. This review article examines the significance of HuR as a member of the RBP family, its regulatory mechanisms, and its implications in the pathophysiology of inflammation and cardiometabolic illnesses. Our objective is to illuminate potential directions for future research and drug development by conducting a comprehensive analysis of the existing body of research on HuR.

KEYWORDS

abnormal vision Drosophila-like 1 (ELAVL1), cardiometabolic disease, HuR, inflammation, RNA-binding proteins (RBPs)

Shahenda Salah Abdelsam and Sarah Khalaf Ghanem are co-first authors who contributed equally to this study.

1 | INTRODUCTION

The process of transcription, which involves the irreversible conversion of genetic information from DNA to transitory RNA molecules, is an essential initial stage in the expression of endogenous genes. The predominant variant of these ephemeral RNAs is messenger RNA (mRNA), which serves as the carrier of essential instructions for synthesizing particular proteins. Furthermore, it is worth noting that there exist other categories of RNA molecules that fulfill distinct roles within cellular processes. For instance, transfer RNA acts as a carrier molecule, facilitating the transportation of specific amino acids during protein synthesis. Moreover, ribosomal RNA plays a crucial role as a structural component inside the machinery responsible for protein synthesis. Over time, catalytic RNAs and a vast array of noncoding RNA species have been discovered, highlighting the versatility of RNA in performing various regulatory functions within cells (Palazzo & Lee, 2015). Posttranscriptional gene regulation (PTGR) plays a crucial role in sustaining cellular metabolism by coordinating the maturation, transport, localization, stability, and degradation of all classes of RNAs. Mechanistically, these events are regulated by the formation of ribonucleoprotein (RNP) complexes, with RNA-binding proteins (RBPs) at their core. RNAs interact with proteins to form RNPs. With hundreds of different RBPs forming complexes with tens of thousands of different mRNA sequences, RNPs are one of the most compositionally diverse groups of RNPs (Lukong et al., 2008). The structurally well-defined RNA-binding domains such as the RNA recognition motif (RRM), hnRNP K homology domain (KH), or DEAD-box helicase domain bind to common structural elements or to specific sequence motifs of mRNA (Corley et al., 2020). The interaction could also be sequence-independent where secondary or tertiary structural elements or a processing step result in the interaction between RBPs and RNA. The dynamics of interaction also vary, from forming stable complexes in the structural organization of RNA to transient interaction to modulate only one step of posttranscriptional gene expression. While the ORF transcribed in the mRNA dictates the amino acid sequence of the polypeptide, all other aspects of the mRNA life, including biogenesis, localization, nucleocytoplasmic transport, stability, and decay, are dictated by the presence of RBPs in complex with mRNA (Pereira et al., 2017). By regulating these aspects of the mRNA life cycle, RBPs play an important role in the regulation of posttranscriptional gene expression, and dysregulated RBPs may lead to different disease states (Lukong et al., 2008).

After mRNA biogenesis, three key areas of significance in mRNA function are its localization, translation, and degradation. These three processes are closely interconnected, as mRNAs do not begin translation until they are localized, and translation is halted before degradation. Mechanistically, a group of RBPs is involved in both translation repression and decapping, playing a crucial role in coupling the processes of translation and degradation (Coller & Parker, 2005). The control of different fates for different mRNAs, including differences in localization, translation, and degradation, is mediated by the interactions of the mRNAs with distinct RBPs within the cell. mRNA localization is determined by the interaction of the mRNA and its associated RBPs with molecular motors and anchors within the cell (Palacios, 2007). Translation is influenced by the strength of the interaction between the RNP and translation factors, while degradation is determined by the interaction between the RBP and the degradation machinery. There are intrinsic differences in the direct binding of mRNAs and RBP-dependent interactions with either the translation or degradation machinery. The initial draft of the human genome predicted more than 1000 RBPs, but this is likely an underestimate, as many sequence-independent RBPs have since been discovered (Hentze et al., 2018).

In general, RBPs bind more frequently to the 3′ UTR than the 5′ UTR for two reasons. First, the 5′ end of the message and the ORF are evolutionarily constrained by their role in translation, and they must maintain the proper coding region for protein synthesis. As a result, ribosomes passing through these regions can dislodge any regulatory protein that binds to them (Harvey et al., 2018). Second, the 3′ UTR tends to be longer, providing more space for RBPs to bind and regulate mRNA function. However, the number of RBPs that bind to the UTR is still an open question. For instance, the average 3′ UTR in humans is approximately 740 nucleotides, varying widely from 68 to 4000 nucleotides. A conservative estimate might suggest that one RBP binds to every 100 nucleotides, resulting in a total of 7 RBPs. Nevertheless, we know that proteins bind to sequence elements of around 10 nucleotides, while microRNAs (miRNAs) bind to around 20 nucleotides (Mayr, 2019). A more optimistic estimate would suggest that 1 RBP binds to every 20 nucleotides, resulting in 37 RBPs bound. However, even the low estimate of seven RBPs suggests that multiple regulatory factors will bind to the 3′ UTR of an average message, affecting its control of localization, translation, and degradation. It is worth noting that one RBP can impact multiple processes. For instance, Puf3 can promote decay and localize mRNA to the mitochondria. Additionally, RBPs regulate mRNAs with related functions, affecting related functional pathways (Schneider-Lunitz et al., 2021).

Research on RBPs offers a crucial insight into deciphering the complex molecular mechanisms that underlie diverse diseases. As main influencers of the fate and eventual function of RNA molecules within the cell, the dysregulation of RBPs has been associated with the pathogenesis of several disease states, including malignancies (Qin et al., 2020), neurodegenerative disorders (Cookson, 2017), and autoimmune conditions (Hashimoto & Kishimoto, 2022). Different RBPs have been proposed as potential biomarkers for early disease detection and prognosis (Yang et al., 2021). Moreover, they can pose as novel therapeutic targets themselves, whereby controlling their expression can alleviate the disease (Yang et al., 2020). Consequently, research on RBPs offers a wide spectrum of vital outcomes, from enhancing the current understanding of basic cellular processes to potential advancements in the diagnosis, treatment, and prevention of an array of human diseases.

Human antigen R (HuR) is a well-characterized RBP, encoded by the embryonic lethal abnormal vision Drosophila-like 1 (ELAVL1) gene, which is ubiquitously expressed in all tissues. In contrast, other members of the ELAVL family are primarily expressed in neuronal

tissue (Good, 1995; Hinman & Lou, 2008). Due to the ubiquitous expression of HuR, it has been associated with diverse disease states that stem from different cells and tissues (Srikantan, 2012; Wang et al., 2013). The binding of HuR to its target mRNAs is attributed to the presence of three RRMs in HuR and Adenylate-uridylate-Rich Elements (AREs) in the 3′ UTR region of the target mRNA. AREs are known to destabilize the mRNA, but HuR competes against destabilizing modulators to increase the stability and translation of the mRNA. This mechanism highlights the important role of HuR in PTGR by regulating the fate of ARE-containing mRNAs. It should also be noted that HuR can bind to other sequence elements besides AREs and can regulate the stability and translation of non-ARE-containing mRNAs as well (Mukherjee et al., 2011). The shuttling of HuR between the nucleus and cytoplasm is guided by the HuR Nucleocytoplasmic Shuttling (HNS) sequence and is regulated mostly by the posttranslational modification in this region (Fan & Steitz, 1998). Stimuli such as cellular stress can result in the cytoplasmic localization of HuR through posttranslational modifications of specific residues in the protein. The interaction between HuR and its cofactor proteins, such as transportin and importin α1 (also known as transportin1), is also involved in this process (Brennan et al., 2000).

2 | BIOLOGY OF HuR

2.1 | Hu proteins family and HuR

HuR is a ubiquitously expressed RBP. It was identified for the first time in Drosophila as a critical mediator of neuronal development (Lal et al., 2004). HuR is also referred to as ELAVL1 or HuA. It belongs to the embryonic lethal abnormal vision (ELAV) family. It is one of the best-characterized RBPs among its family, consisting of HuB, HuC, and HuD (Schultz et al., 2020). The latter is mainly expressed in the nervous system, while HuR is widely expressed in the respiratory, gastrointestinal tract, and endocrine tissue, encoded by the *ELAVL1* gene (Lachiondo-Ortega et al., 2022). Hu proteins selectively bind with high affinity to mRNAs that bear ARE in their 3′ UTR, such as cytokines with a short half-life, tumor-promoting genes, and growth factor mRNAs resulting in the modification of their expression either by increasing transcripts' stability, varying the translation, or carrying out both actions (Chen et al., 2001; Lal et al., 2004).

2.2 | Structure and function of HuR

Ubiquitously expressed, HuR drives several biological functions through its posttranscriptional modulation of multiple targets involved in the control of cellular growth and proliferation. HuR protein belongs to the classical RBPs group based on its amino acid sequence, where the similarity in sequence among family members exceeds 90%. HuR has three RRMs; RRM1, RRM2, and RRM3. The three RRMs have an orthodox topology βαββαβ (β1α1β2β3α2β4), with β-sheets made up of four antiparallel strands folded against double α-helices. For each RRM, the central β-strands contain an RNP motif that is critical for binding to RNA/DNA. β3 strand contains RNP-1 while the β1 strand contains the RNP-2 motif, which binds to RNA by hydrogen bond and stacking interactions. X-ray crystallography revealed that RRM1 and RRM2 are linked by a 10-residue connection. RRM1/2 is essential for binding HuR to the ARE region on the target mRNAs inducing their stability, while RRM3 is involved in the recognition of the ARE region. RRM1/2 and RRM3 are separated by a less conserved 50–60 residue hinge region, which contains the HNS sequence. HNS is responsible for the localization of HuR where phosphorylation at HNS results in the interaction of HuR with the nucleocytoplasmic shuttling proteins, triggering the transport and accumulation of HuR through the nucleopore into the cytosol. HuR is a protein with multiple actions involved in the regulation of RNA in both cellular compartments. HuR works as a posttranscriptional regulator, influencing a variety of RNA metabolism processes, from splicing to translation (Hinman & Lou, 2008; Lachiondo-Ortega et al., 2022; Majumder et al., 2022).

Under normal physiological conditions, HuR is principally located in the nucleus, where it plays a role in the splicing of pre-mRNA and the export of mature mRNAs. Upon stimuli such as stress or mitogenic signals, HuR is shuttled to the cytoplasm with the aid of transportin-1, transportin-2, and the adapter proteins ANP32A and ANP32B. In the cytosol, HuR stabilizes and modulates the translation of the target RNAs (Lachiondo-Ortega et al., 2022; Schultz et al., 2020). The continuous activation and heightened cytoplasmic localization of HuR result in a notable pro-inflammatory reaction. The stabilization of pro-inflammatory proteins, such as cyclooxygenase (COX)-2 and inducible nitric oxide (NO) synthase (iNOS), as well as several pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, interferon (IFN)-γ, and transforming growth factor (TGF)-β, can be attributed to the action of HuR (Schultz et al., 2020).

HuR plays a critical role in governing various cellular mechanisms. For instance, HuR plays a crucial role in cell division by stabilizing mRNAs encoding key cell cycle regulators. Wang et al. (2000) showed that HuR regulates cyclin A and cyclin B1 mRNA stability and hence promotes efficient cell cycle progression. Moreover, it has been shown that HuR plays a crucial role in the immune response. For instance, specific deletion of HuR in B cells resulted in a failed B cell antibody response, which is a critical response to produce antibodies to fight infections (Diaz-Muñoz et al., 2015). Similar effects were observed in natural killer (NK) cells specifically deleted for HuR. NKs play a major role in fighting long-term infections. To do so, NKs need to proliferate and expand. Specific deletion of HuR in NK cells results in defective expansion, leading to impaired response (Piersma et al., 2023). This highlights the important role of HuR in a normal immune response. Furthermore, HuR is a key player in the cellular response to several stressors. In response to oxidative stress, HuR stabilizes heme oxygenase-1, a pivotal enzyme in the defense against oxidative stress (Dery et al., 2020). In addition, p53, a tumor suppressor gene, is a key player in the response against multiple stressors, such as genotoxic, metabolic, and hypoxic stress. HuR was

shown to stabilize and enhance the translation of p53 (Mazan-Mamczarz et al., 2003). Altogether, these findings emphasize the significant role of HuR in diverse cellular responses.

Multiple studies have provided evidence indicating that HuR plays a crucial role in the stabilization of more than 80 target mRNAs. These mRNAs encode a diverse range of proteins, including cyclin A, cyclin B1, c-fos, vascular endothelial growth factor (VEGF), TNF-α, β-catenin, c-myc, COX-2, myogenin, myoblast determination protein 1, granulocyte-macrophage colony-stimulating factor, ILs, p21, p27, p53, and 70 kilodalton heat shock protein.

2.3 | The regulation of HuR

HuR expression is tightly regulated to promote healthy cell survival and prevent pathological proliferation. Remarkably, the expression of HuR is intricately regulated at multiple stages: transcriptional, posttranscriptional, translational, and posttranslational (Figure 1) (Govindaraju & Lee, 2013).

Despite the extensive study on HuR's role in various disorders, a thorough knowledge of the regulatory mechanisms controlling HuR expression is still lacking. HuR is thought to be controlled by two main mechanisms: autoregulation and regulation by other molecules at different phases. RBPs frequently use autoregulation to control the expression of their own mRNA. For instance, the preservation of HuR homeostasis in actively dividing cells is a pivotal mechanism controlled by autoregulation. Several polyadenylated versions of its mRNA facilitate this activity through a negative feedback mechanism. The nuclear HuR protein engages with a GU-rich element (GRE) situated in close proximity to HuR's primary polyadenylation signal. The upregulation of cellular HuR protein at a significant cellular level leads to the promotion of longer HuR mRNA variants

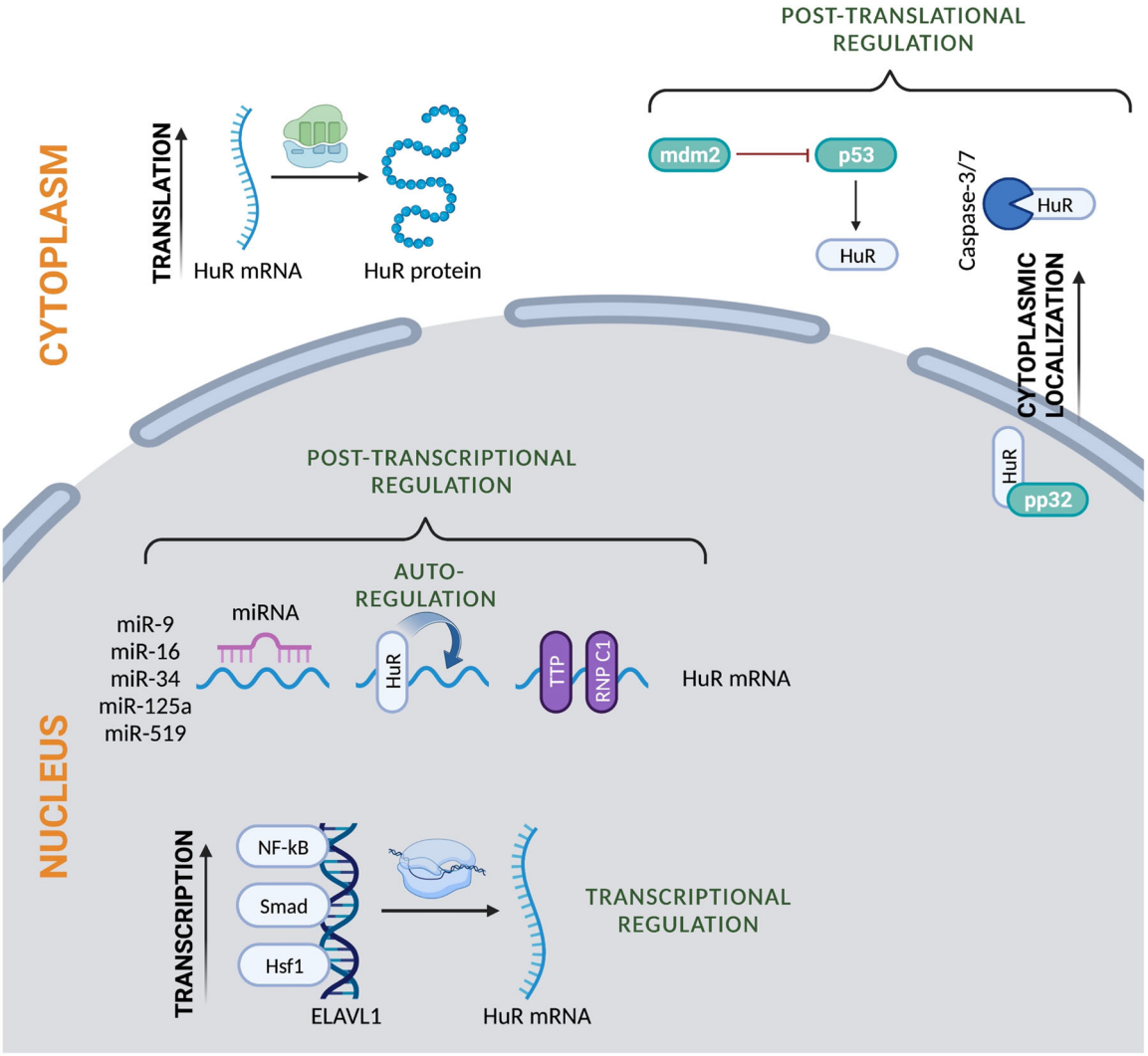

FIGURE 1 Regulation of HuR expression at different stages of its protein synthesis. HuR is transcriptionally regulated via NF-κB, Smad, and Hsf1. Posttranscriptional regulation of HuR's mRNA (product of transcription) is imposed by its own protein, via the actions of various miRNAs, and by other RBPs (TTP, RNP C1). Mdm2 and pp32 are posttranslational regulators of HuR. HuR, human antigen R; mRNA, messenger RNA; miRNAs, microRNAs; RNP, ribonucleoprotein; TTP, tristetraprolin.

that possess an ARE, resulting in the destabilization of HuR protein synthesis through the destabilization of its corresponding mRNAs (Al-Ahmadi et al., 2009; Dai et al., 2012; Mansfield & Keene, 2012). Nevertheless, the specific mechanisms that govern HuR autoregulation remain unclear. To fully comprehend the complex regulation of HuR expression and its implications in various pathological conditions, more research is essential (Müller-McNicoll et al., 2019).

Although there have been significant advancements in comprehending the regulation of HuR expression and its consequential effects on diverse cellular mechanisms, it is evident that the complicated array of molecules implicated in the regulation of HuR remains incompletely elucidated. Hence, additional research is important to elucidate the intricate interaction between HuR and its regulators, as well as to investigate possible therapeutic targets for diverse diseases linked to HuR dysregulation.

3 | THE ROLE OF HuR IN CELLULAR INFLAMMATION

HuR assumes a pivotal role in numerous cellular processes, while its downstream actions are contingent upon the specific mRNA targets it connects with. The aforementioned processes encompass inflammation, control of the cell cycle, cancer pathogenesis, cell survival, and apoptosis. The interaction between HuR and the mRNAs of diverse inflammatory mediators has been observed, underscoring the importance of HuR in the modulation of the inflammatory response. Consequently, the current review will focus on HuR's role in inflammation. The review will emphasize the interactions of HuR with distinct mRNA targets. These targets play critical roles in inflammatory signaling pathways. Future research on HuR and inflammation has the potential to offer insights into the complicated molecular pathways that regulate inflammatory responses, opening the door for possible therapeutic approaches in inflammatory diseases. Continued exploration into the unique regulatory activities of HuR in regulating major inflammatory mediators, such as cytokines and chemokines, might reveal the precise dynamics of its interactions with target mRNAs. Furthermore, investigating the interactions between HuR and other inflammatory regulators may reveal extensive regulatory networks. These understandings might direct the development of novel therapeutic approaches targeted at regulating HuR's activity to precisely regulate inflammatory responses. Specific examples of mRNAs/proteins affected by different functions of ELAVL1 are illustrated in Figure 2.

3.1 | AMP-activated protein kinase (AMPK)

The role of AMPK in inflammation is well defined (Mancini & Salt, 2018). Overall, an increased function of AMPK has a negative association with the cytoplasmic levels of HuR in various ailments (Liu et al., 2015; Wang et al., 2002, 2004). In patients diagnosed with amyotrophic lateral sclerosis, abnormal localization of HuR was associated with enhanced AMPK activity in the motor neurons. This observation was established in vitro by inducing the activity of AMPK via different experimental techniques. The effect was mediated via the phosphorylation of importin-α1, a major nuclear protein importer. The recognition of importin-α1 as a key player in AMPK-mediated HuR localization was first established in 2004 by Wang et al. (2004) in a colon cancer cell line. The aberrant activation of AMPK in motor neurons perturbed HuR's physiological distribution, resulting in an imbalance of RNA metabolism. The stimulation of the A2A adenosine receptor normalized the AMPK-evoked redistribution of HuR (Liu et al., 2015). Wang et al. (2004) showed that importin-α1 exerts its action on HuR with the aid of two AMPK-modulated mechanisms. First, AMPK triggers the acetylation of importin-α1 on Lys22, a process dependent on the acetylase activity of p300. Second, AMPK phosphorylates importin-α1 at Ser105 (Wang et al., 2004). Further investigations are necessary to examine the interplay between AMPK and HuR in various disease states, as well as to explore additional potential contributors, beyond importin-α1.

3.2 | COX-2

The role of COX-2 in inflammation was identified several decades ago (Simon, 1999). The enzyme facilitates the conversion of arachidonic acid into prostaglandins, which are implicated in the pathogenesis of various inflammatory disorders. Numerous studies have investigated the association between COX-2 and HuR in various clinical contexts. According to Hashemi Goradel et al. (2019), COX-2 is a significant factor in the initiation and advancement of several forms of cancer. A notable correlation between the cytoplasmic expression of HuR and elevated COX-2 expression levels was indicated, which subsequently correlates with low cell survival. Such correlation was demonstrated in multiple cancer types, including stomach, colorectal cancers, lymphatic invasion, and lymph node metastases (Hashemi Goradel et al., 2019; Mrena et al., 2005). However, this correlation is not observed with nuclear HuR. The results of this study indicate that cytoplasmic HuR and COX-2 may have significant implications for the advancement and spread of colorectal cancer (Lim et al., 2009). In another investigation pertaining to colorectal cancer, a significant correlation between cytoplasmic HuR expression and elevated COX-2 expression, as well as advanced tumor stage has been observed. The findings of this study indicate that HuR may play a role in a regulatory system that governs the stability of *COX-2* mRNA, hence facilitating the advancement of the disease (Denkert et al., 2006). The role of HuR in the regulation of COX-2 expression in serous ovarian cancer has been identified. Elevated levels of COX-2 expression have been linked to worse prognosis in ovarian cancer, while HuR has demonstrated the ability to augment COX-2 expression both in vitro and in over 50% of serous-type ovarian carcinoma samples. In previous in vitro studies involving ovarian cancer cells, it was

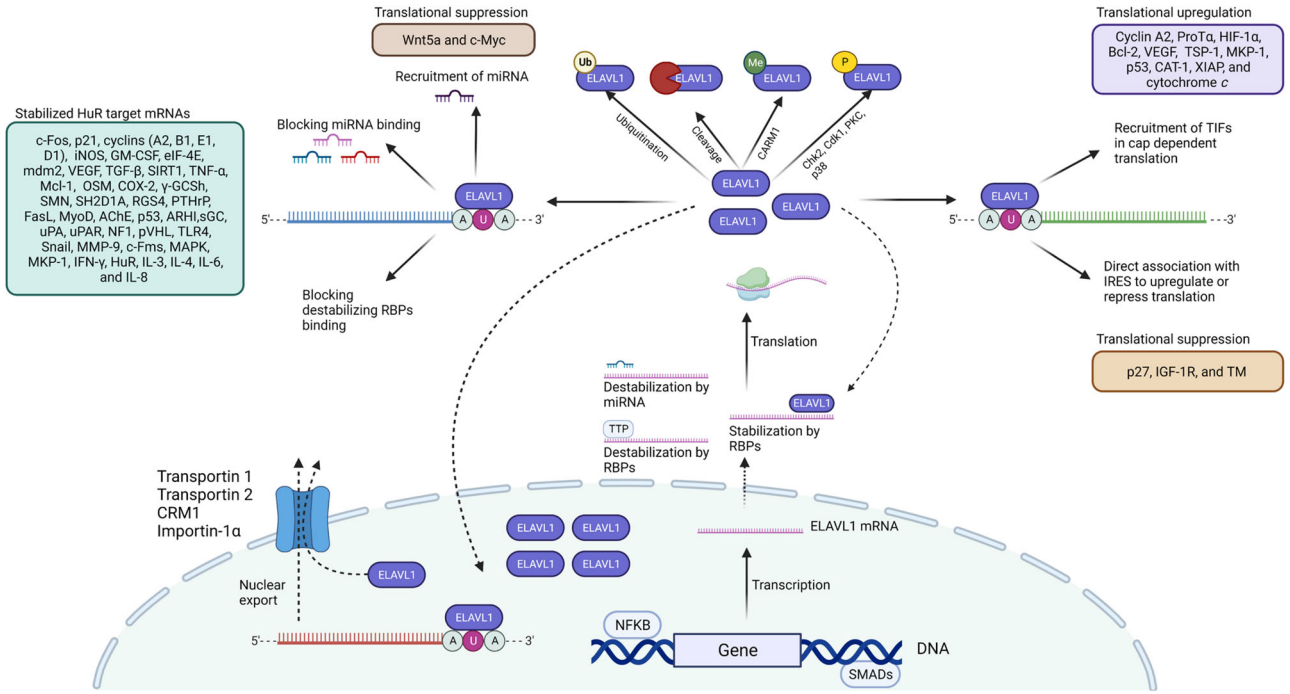

FIGURE 2 ELAVL1 mRNA regulation and posttranslational modifications affect its stability and function in stabilizing or destabilizing target proteins. RNA-binding proteins and miRNA regulate the stability of the ELAVL1 mRNA, stabilizing or destabilizing it depending on the cellular conditions. After translation, ELAVL1 undergoes posttranslational modifications that affect its function and stability. The proteasome may target ELAVL1 for degradation as a result of ubiquitination. The RNA-binding activity of ELAVL1 can be affected by CRAM1 methylation. The localization and function of ELAVL1 are influenced by the phosphorylation of certain enzymes. ELAVL1 binds to different regions of mRNA, and its binding affects how the mRNA functions in a variety of ways. To promote cap-dependent translation, binding to the 5′ end UTR recruits translation initiation factors. To initiate translation without the need for a 5′ cap, ELAVL1 can also bind to internal ribosome entry sites (IRES) in the mRNA. When ELAVL1 binds to IRES, translation can be repressed. On the other hand, binding to the 3′ end UTR can play a role in regulating mRNA stability and translation through several mechanisms. ELAVL1 plays a role in the transport of mRNA from the nucleus to the cytoplasm. By binding to the 3′ end UTR of certain mRNAs, ELAVL1 can protect certain mRNAs from degradation and facilitate their transport to the cytoplasm, where they can be translated. ELAVL1, embryonic lethal abnormal vision Drosophila-like 1; HuR, Human antigen R; mRNA, messenger RNA; miRNAs, microRNAs.

observed that the application of small interfering RNA (siRNA) targeting the *HuR* effectively suppressed the production of COX-2. These findings indicate that the inhibition of HuR could serve as a promising treatment approach for ovarian cancer, especially in instances where there is an upregulation of COX-2 (Erkinheimo et al., 2003).

HuR's cytoplasmic localization significantly affected overall survival, suggesting its involvement in pathological processes. For instance, the cytoplasmic localization of HuR and high levels of COX2 expression were found in mesothelioma tumor tissues (Stoppoloni et al., 2008). The main localization of HuR was observed within the nucleus in typical microvascular endothelial cells. On the other hand, HuR expression was observed in both the cytoplasm and nucleus of malignant melanoma and oral cancer cells. The expression of HuR was observed solely within the nucleus of normal endothelial cells in a mouse model, which is consistent with the expression pattern observed in human microvascular endothelial cells. The findings of Kurosu et al. (2011) indicate a correlation between the subcellular distribution of HuR and the process of endothelial cell transformation into a malignant phenotype.

3.3 | TNF-α

TNF-α is a multifunctional cytokine that exerts diverse effects on different cellular types. As a significant modulator of inflammatory reactions, it has been implicated in the development of certain inflammatory and autoimmune disorders (Bradley, 2008). TNF-α association with HuR has been observed in several autoimmune disorders. The study conducted by Suzuki et al. (2006) revealed the presence of high gene expression of both *HuR* and *TNF-α* in the synovial tissues of patients with rheumatoid arthritis and osteoarthritis.

In airway epithelial cells, the regulation of eotaxin, a CC chemokine, involves the enhancement of its mRNA stability, which is strongly increased by TNF-α and IL-4. An increase in cytoplasmic levels of HuR was observed in cells treated with TNF-α and IL-4 in vitro. Furthermore, HuR binds to endogenous eotaxin mRNA in vivo. Notably, the binding of HuR with eotaxin increases after treatment with TNF-α and IL-4. Overexpression of HuR in vitro increases significantly eotaxin mRNA and protein levels (Atasoy et al., 2003). These findings suggest that HuR plays a pivotal role in the regulation of eotaxin expression when airway epithelial cells are exposed to inflammatory stimuli.

HuR's role in atherosclerosis was studied in relation to its interaction with TNF-α and protease inhibitors (PIs) for the human immunodeficiency virus (HIV). One study demonstrated that the majority of HIV PIs, with the exception of amprenavir, exhibited varying degrees of enhanced expression of TNF-α and IL-6. These two molecules are recognized as significant contributors to the inflammatory response. Atazanavir has the ability to elevate the cytoplasmic concentrations of HuR and augment its interaction with the mRNAs of *TNF-α* and *IL-6*. This finding was further supported by the use of siRNA to downregulate the expression of *HuR*, which prevented atazanavir-induced elevation of cytokine upregulation (Zhou et al., 2007).

3.4 | VEGF

The identification of VEGF occurred approximately 30 years ago, establishing its significance as a crucial element in facilitating angiogenesis within both normal physiological contexts and pathological states. There are different subtypes of VEGF, among which VEGF-A has been thoroughly investigated and acknowledged for its crucial involvement in the promotion of angiogenesis (Apte et al., 2019).

The relationship between HuR and VEGF has been established in multiple research studies. According to a study conducted by Wang et al. (2009), a strong association was observed between increased cytoplasmic HuR levels and the production of VEGF-C in tumor tissue among patients with advanced operable nonsmall cell lung cancer (NSCLC). In previous studies, it was shown that the excessive production of HuR leads to an increase in the stability of *VEGF* mRNA, which was solely detected in cells with hypoxia. Additional research has provided further evidence to substantiate the involvement of HuR in the regulation of *VEGF* mRNA stability. The experimental studies conducted utilizing recombinant HuR in vitro have shown evidence that HuR plays a substantial role in facilitating the effects of VEGF under hypoxic conditions inside the cellular environment (Levy et al., 1998). Subsequently, a study conducted several years later successfully identified a 40-base pair sequence motif located in the 3′-untranslated region of *VEGF* mRNA. This particular motif was found to have a crucial role in enhancing the stability of *VEGF* mRNA when subjected to hypoxic circumstances. Such a study showed that HuR exhibits a binding affinity toward this specific region, hence facilitating the augmentation of *VEGF* mRNA stability. HuR exhibits nuclear localization during hypoxia and co-localizes with VEGF protein in specific nuclear compartments, suggesting a potential involvement of HuR in the regulation of *VEGF* transcription under hypoxic circumstances (Lejbkowicz et al., 2005).

According to Dixon et al. (2001), there is a correlation between HuR upregulation, VEGF increased expression, and other inflammatory mediators in colon cancer cells. Expression of HuR bound to the ARE-mRNA of *VEGF* in tumor endothelial cells increases compared to normal endothelial cells. This suggests a potential role for HuR in promoting angiogenesis and tumor growth in melanoma (Kurosu et al., 2011). HuR modulates the degree of posttranscriptional regulation of *VEGF* mRNA by competitive interaction with miR-200b. HuR acts as an antagonist to miR-200b inhibitory effects, downregulates miR-200b expression, and promotes VEGF-A production. *VEGF-A* and other transcripts associated with angiogenesis were downregulated in defective bone-marrow derived macrophages. As anticipated, a notable decrease in tumor growth characteristics, such as angiogenesis, sprouting, branching, and vascular permeability, was observed (Chang et al., 2013).

3.5 | NOS

NO is a gas that is produced by the enzyme NOS and plays a prominent role in the regulation of inflammation (Evans, 1995). There are three different isoforms of NOS: endothelial NOS (eNOS/NOS3), neuronal NOS (nNOS/NOS1), and iNOS (iNOS/NOS2). Among them, iNOS is the most commonly implicated form in inflammatory processes (Zamora et al., 2000). HuR has been implicated in the posttranscriptional regulation of iNOS mRNA in cachexia, a major consequence of various chronic conditions. HuR upregulation in skeletal muscle during cachexia is accompanied by an increased expression of iNOS. HuR silencing results in decreased expression of iNOS, indicating that HuR positively regulates iNOS mRNA stability in cachexia. Therefore, targeting HuR could be a potential therapeutic strategy for cachexia prevention or treatment in chronic conditions (Di Marco et al., 2005).

Other binding proteins interact with HuR to bind to the iNOS mRNA. In the DLD-1 colon cancer cell line, the interaction between HuR and other RBPs on iNOS mRNA was investigated. It was found that HuR competes with RNA destabilizing factors such as KSRP and tristetraprolin (TTP) for binding sites. After cytokine treatment, the intracellular binding to iNOS mRNA was reduced for KSRP but enhanced for HuR. Moreover, a complex interplay of KSRP with TTP and HuR appeared to be essential for the stabilization of iNOS mRNA following cytokine stimulation (Linker et al., 2005). In the cytoplasm of rat hepatocytes, HuR was shown to colocalize with iNOS mRNA. However, another RBP, hnRNP L, was also found to be present (Matsui et al., 2008). Another study investigating the association between HuR and iNOS found that berberine, a natural compound, suppressed lipopolysaccharide (LPS)-induced iNOS protein expression via a reduction of iNOS mRNA stability mediated by HuR. This effect was found to be due to the inhibition of the cytoplasmic translocation of HuR (Shin et al., 2016).

3.6 | Toll-like receptors (TLRs)

TLRs are a set of PRRs that have a significant function in the recognition of various PAMPs, including bacterial and viral components, as well as endogenous ligands (Kawasaki & Kawai, 2014). The posttranscriptional regulatory mechanism of TLR3 in the context of TLR3-mediated innate responses requires further investigation. According to Zainol et al. (2019), HuR correlates to the 3′ UTR of

Atp6v0d2 mRNA, which plays a crucial role in the initiation of TLR3's innate immune response. HuR has a heightened level of interaction with the 3′ UTR of TLR4 mRNA following exposure to LPS. Knocking down *HuR* decreases the stability of *TLR4* mRNA in human airway human aortic smooth muscle cells (HASMCs) which leads to a decrease in the production of the luciferase reporter gene in HASMCs transfected with CMV-Luciferase-TLR4 3′ UTR (Lin et al., 2006).

4 | THE ROLE OF HuR IN THE PATHOGENESIS OF CARDIOMETABOLIC DISORDERS

Cardiometabolic diseases encompass a cluster of disorders that emerge as a result of the interplay between genetic predisposition, behavioral patterns, and environmental influences. These conditions include obesity, hypertension, impaired glucose regulation, and dyslipidemia, all of which have the potential to induce detrimental effects on cardiovascular health and arterial function. Chronic low-grade inflammation serves as a fundamental pathophysiological process that is commonly observed across a range of cardiometabolic disorders. Indeed, there exists a correlation between inflammatory processes and various diseases, including but not limited to type 2 diabetes, chronic renal disease, and cardiovascular disease (Gerdts & Regitz-Zagrosek, 2019; Sumida et al., 2022). HuR, as a versatile protein that assumes multiple functions and exerts a pivotal role in the control of gene expression at the posttranscriptional level, plays a crucial role in the control of many genes associated with inflammatory processes, stress responses, and metabolic functions. Consequently, it presents an appealing prospect for therapeutic intervention in pathologies related to the cardiovascular system and metabolism. The dysregulation of HuR expression and activity has been associated with the pathogenesis of various cardiometabolic disorders, such as obesity, type 2 diabetes, cardiovascular disease, and chronic kidney disease (Nutter & Kuyumcu-Martinez, 2018). HuR exerts regulatory control over many cellular processes, including inflammation, insulin sensitivity, and lipid metabolism, which play pivotal roles in the pathogenesis and development of cardiometabolic diseases, by engaging with specific mRNA targets. Targeting HuR and its downstream pathways may provide a promising therapeutic strategy for the prevention and treatment of cardiometabolic diseases.

4.1 | Atherosclerosis

Atherosclerosis is a chronic degenerative condition that affects the arterial wall, especially the medium to large arteries, and is the primary cause of cardiovascular disease, which continues to be the dominant cause of morbidity and mortality worldwide. Maintaining arterial endothelial homeostasis is critical for preventing vascular pathology. The healthy arterial endothelium serves as a crucial barrier against vascular disorders, and several vascular disorders are directly linked to endothelial dysfunction, such as atherosclerosis. Proatherogenic substances such as oxidized lipids, TNF-α, and IL-1 usually increase endothelial activation, which is a cellular condition that precedes its failure and leads to the production of pro-inflammatory signaling responses and elevated expression of surface adhesion molecules. These pathogenic events work together to increase lipid permeability and leukocyte recruitment to the artery wall, resulting in intimal lipid accumulation and local inflammation, which ultimately promotes the onset and progression of atherosclerosis (Cheng et al., 2019; Fu et al., 2018)

HuR has been shown to mediate endothelial activation and play a key role in atherosclerosis through various mechanisms (Cheng et al., 2019). This includes the inhibition of eNOS activity. This leads to reduced production of NO, a key regulator of endothelial function and vascular homeostasis, and increased endothelial activation and inflammation (Fernández-Hernando et al., 2013). Furthermore, it has been observed that HuR plays a role in the modulation of gene expression related to lipid metabolism, inflammation, and oxidative stress, which are significant factors in the progression of atherosclerosis (Lin et al., 2006). Hence, the strategic targeting of HuR may offer a promising therapeutic approach in the prevention and treatment of atherosclerosis and other vascular disorders.

In a study aimed at examining the involvement of HuR in the pathogenesis of atherosclerosis, investigators conducted a comparative analysis of HuR expression levels in human coronary arteries afflicted with and devoid of atherosclerotic lesions. The study revealed that HuR protein levels were notably elevated in atherosclerotic coronary arteries (ACAs) in comparison to non-ACAs. Further examination uncovered that ACAs exhibited elevated expression levels of mRNAs established to be bound and stabilized by the HuR, including *COX-2*, *TNF-α*, *IL-17*, and *TLR4*, in comparison to non-ACAs. HuR has a significant impact on the development of atherosclerosis through its regulation of pro-inflammatory gene expression (Cheng et al., 2019). The development of atherosclerosis exhibits a slowed pace in animals lacking endothelium HuR, according to an experimental model of atherosclerosis-prone apolipoprotein E-deficient ($ApoE^{-/-}$) mice. Decreased levels of proatherogenic substances, which are known to play a role in processes such as inflammation, adherence, and recruitment of leukocytes, can be linked to this phenomenon. Deficiency of HuR in endothelial cells results in decreased concentrations of inflammatory cytokines and chemokines, including IL-6, IL-17, and TNF-α. These molecules play a role in the atherogenic mechanisms of monocyte polarization and macrophage M1 polarization. The decrease of these molecules through the deletion of endothelial HuR may serve as a therapeutic strategy for the prevention or treatment of atherosclerosis (Fu et al., 2018). HuR expression has a potential involvement in the progression of atherosclerosis as it was higher in the aortas of $ApoE^{-/-}$ mice than in wild-type mice. Both endothelial cells and vascular smooth muscle cells (VSMCs) contain HuR, with endothelial cells exhibiting a notable abundance. This finding underscores HuR's distinct functional role in different regions of arteries, particularly

within the endothelium. The results of in vitro experiments conducted on human aortic endothelial cells demonstrated that the proatherogenic inflammatory cytokines TNF-α and IL-1 have the ability to stimulate *HuR* mRNA expression and protein levels. In the study conducted by Cheng et al. (2019), it was shown that mice fed a high-fat diet for different durations had elevated levels of HuR protein expression and enhanced RNA-binding activity in isolated aortic endothelial cells in comparison to mice that were fed a standard chow diet (Cheng et al., 2019).

Significant phenotypic changes in VSMCs were observed in response to environmental signals. Vascular injury in pathological settings can lead to changes in proliferation, migration, and the production of extracellular matrix (ECM), which contribute to the onset and development of vascular disorders. Accumulation of proliferative VSMCs is the primary cause of various vascular diseases such as in-stent restenosis, transplant vasculopathy, and atherosclerosis. The proliferative phenotype of VSMCs in both healthy and pathological conditions results from critical modifications in the gene expression patterns of the proliferating cells. In normal coronary tissues, low HuR expression was seen in medial and intimal VSMCs, and HuR was primarily localized in the nucleus with little expression in the cytoplasm. However, in samples from individuals with atherosclerotic plaques, intimal hyperplasia, and neointimal proliferation, an overall increase in HuR signal was observed in both the nucleus and cytoplasm, with notable prevalence in the cytoplasm. Inhibition of HuR expression was found to decrease hVSMC proliferation in culture (Pullmann et al., 2005). In a study using a balloon-injured rabbit aorta as an inflammatory model, it was found that LPS interacts with TLR4 to stimulate the growth of VSMCs, which can contribute to atherogenesis. The expression of HuR was increased in response to LPS, and it was found to mediate the stabilization and enhanced translation of several inflammatory genes that contribute to vascular inflammation and are implicated in the atherogenic process (Lin et al., 2006).

4.2 | Heart failure (HF)

HF is a serious medical condition that can arise from several underlying conditions, including hypertension, coronary artery disease, and myocardial infarction. A common precursor to HF is the hypertrophy of the cardiac muscle. Under hemodynamic stress, this structural adaptation initially serves to maintain cardiac output. However, this pattern of growth is not viable and results in increased cardiac fibrosis, elevated susceptibility to arrhythmias, and ultimately the initiation of HF. The ECM is remolded because of myocytes' release of TGF-β in response to hypertrophic stimuli, which plays a pivotal role in myofibroblast activation and signaling of fibrosis. Researchers employed a murine model of transverse aortic constriction (TAC) to create pressure overload in the left ventricle (LV) to investigate the involvement of HuR in HF. They found that HuR activity colocalized with areas of fibrosis in the hypertrophic heart. Following TAC, cardiac-specific HuR-deleted mice were significantly protected from pathology, exhibiting reduced LV hypertrophy, preserved cardiac function, reduced LV chamber dilation, and decreased cardiac fibrosis. HuR was also found to directly interact with TGF-β, stabilizing *TGF-β* mRNA and promoting fibrosis. Deletion or pharmacological suppression of HuR slowed down the progression of fibrosis, halted the progression of LV hypertrophy, and improved survival rates, highlighting the protective role of HuR against pathological remodeling and functional deterioration in HF (Green et al., 2019). Krishnamurthy et al. (2010) have demonstrated that HuR protein interacts directly with the mRNAs that encode *TGF-β*. In hypertrophic neonatal rat ventricular myocytes, HuR appears to be activated, as evidenced by increased HuR translocation to the cytoplasm. *HuR* knockdown reduced the increase in cell area and completely blocked the rise in atrial natriuretic factor expression, which is a common marker of cardiac myocyte hypertrophic development. On the other hand, overexpression of HuR alone is enough to promote hypertrophic cell growth (Slone et al., 2016).

Following a myocardial infarction, inflammation can lead to unfavorable remodeling changes such as LV dilation and fibrosis, due to the production of pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, IFN-induced protein 10, and monocyte chemoattractant protein (MCP)-1, among others. HuR is implicated in stabilizing mRNA molecules encoding pro-inflammatory cytokines, hence exerting a significant influence on the regulation of the heart's homeostasis following tissue injury. In an experimental mouse model of MI, the inhibition of HuR resulted in a significant reduction in the levels of pro-inflammatory cytokines, including TNF-α, IL-1, and MCP-1. These cytokines have been involved in the progression of LV dysfunction. The suppression of HuR additionally resulted in the resolution of inflammatory cell infiltration, a decrease in the size of the infarct, and mitigation of LV dysfunction during myocardial infarction (Krishnamurthy et al., 2010).

4.3 | Diabetes and its major complications

Diabetes mellitus (DM) is a metabolic condition characterized by elevated blood glucose levels as a consequence of insulin resistance and diminished pancreatic insulin secretion. The primary contributors to the morbidity and mortality of individuals with DM are problems that impact both macrovascular and microvascular systems, leading to adverse effects on multiple organs, including the kidneys, eyes, and liver (Raguraman et al., 2021). According to a study conducted by Amadio et al. (2009), HuR expression increases in the tissues of diabetic rats. A study by Govindappa et al. (2020) showed that hyperglycemia can induce HuR activation and promote its relocation from the nucleus to the cytoplasm. Following the induction of diabetes, there was an upregulation in the expression of HuR protein and its subsequent binding to *VEGF-A* mRNA. This upregulation resulted in an increase in the production of VEGF-A protein, hence contributing to the occurrence of aberrant angiogenesis in individuals with diabetes. In vivo experiments have demonstrated that the

coadministration of a specific inhibitor of protein kinase C, an upstream activator of HuR, can mitigate these effects (Amadio et al., 2016). In this review, we will examine the involvement of HuR in complications induced by diabetes.

4.3.1 | Diabetic kidney disease

Clinical indicators of diabetic nephropathy (DN) include increasing protein albuminuria and a subsequent reduction in glomerular filtration rate. DN prevalence has increased globally due to the rising incidence of type 2 DM. Ultimately, interstitial fibrosis is the final damage pathway for all commonly occurring renal disorders that lead to end-stage renal disease (Yu et al., 2015). DN is preceded by structural changes in the kidney, including renal hypertrophy, glomerular capillary enlargement, and glomerular basement membrane thickening. The expansion of the ECM in the glomeruli is responsible for these hallmarks. Reactive oxygen species (ROS) play a crucial role in the pathogenesis of renal and other vascular disorders, particularly in DN. NADPH oxidases (NOX), a significant generator of ROS in various organs, produce ROS in the kidney, including the main isoform NOX4, which participates in the adverse effects of hyperglycemia associated with microvascular problems in diabetes. HuR can regulate NOX4 mRNA stability by binding to its 3′-UTR and affecting its translational efficacy, leading to increased ROS generation and glomerular microvascular fibrosis. In DN patients, HuR is upregulated, underscoring its involvement in the disease's pathophysiology (Shi et al., 2020).

DN is characterized by renal fibrosis resulting from the process of epithelial-mesenchymal transition (EMT). EMT is a phenotypic change in renal tubular cells that causes the formation of alpha-smooth muscle actin and collagen-secreting myofibroblasts. TGF-β is a well-known profibrotic cytokine and the primary pathogenic driver that promotes EMT. HuR is crucial for controlling the post-transcriptional expression of EMT genes. HuR expression was significantly increased in patients with DN, particularly in the cytoplasm of tubular epithelial cells. The mRNA transcripts of *TGF-β1*, *CTGF*, *c-fos*, and *Snail*, which are genes crucial for the regulation of the EMT process, have been demonstrated to exert a stabilizing effect by HuR. Therefore, it can be inferred that HuR facilitates kidney disease progression (Yu et al., 2015).

The role of NOD2 in the signal transduction pathway linking renal injury and inflammation is significant in DN. The reduction in diabetes-related renal damage in mice deficient in *NOD2* serves as empirical evidence in favor of this. Additionally, kidney biopsies obtained from patients with diabetes showed an upregulation of NOD2 expression. Elevated expression of HuR in renal tissues of patients with DN and its association with the presence of proteinuria play a role in the development of DN. HuR targets *NOD2* mRNA and NOX4 gene suppression lowers both HuR levels and *NOD2* mRNA stability. The expression and translocation of HuR, and the stability of *NOD2* mRNA are mediated through the formation of ROS by NOX. The silencing of *HuR* leads to a decrease in NOD2 expression, while high glucose levels promote mRNA stability. These findings highlight the significant involvement of HuR in the signal transduction pathway that links renal injury to the inflammatory response in DN, which is mediated by NOD2 (Shang et al., 2015).

4.3.2 | Diabetic retinopathy (DR)

DR is a significant contributor to adult visual impairment, which has two distinct stages: nonproliferative and proliferative. The presence of microaneurysms and retinal hemorrhages are the primary indications of nonproliferative DR. As the condition advances, increased capillary nonperfusion results in cotton-wool patches, venous beading, and intraretinal microvascular abnormalities. Proliferative DR manifests as the exacerbation of retinal ischemia, resulting in the emergence of anomalous blood vessels on the retinal surface or optic disc. These vessels have a tendency to experience hemorrhaging, which can lead to various problems, including vitreous hemorrhage, fibrosis, and tractional retinal detachment. VEGF-A is synthesized in response to retinal ischemia, leading to the stimulation of endothelial cell proliferation, migration, and tube formation. Consequently, this process contributes to the construction of delicate blood vessels. Although DR is a serious condition, the current strategies for prevention and treatment mostly focus on maintaining appropriate blood pressure and glucose levels. Unfortunately, there is currently no specific medication available to directly address this disease (Amadio et al., 2010). The upregulation of HuR is implicated in the pathogenesis of DR through its ability to facilitate angiogenesis. This phenomenon can be attributed to the capacity of HuR to stabilize the mRNA of *VEGF-A*, resulting in an augmentation of the angiogenic potential of endothelial cells. According to Si et al. (2021), HuR plays a substantial role in the development of DR. In a murine model of retinopathy, the expression of HuR was observed to be elevated, concomitant with an upregulation in the expression of VEGF-A and an enhanced angiogenic response. The silencing of *HuR* resulted in a decrease in the expression of VEGF-A and a reduction in angiogenesis, thereby emphasizing the pivotal regulatory role of HuR in retinopathy and pathological angiogenesis (Huang et al., 2023). To assess the onset of DR using fundoscopic examinations, a study was conducted on streptozotcin (STZ)-induced diabetic rats, which serves as model for DR. It was found that the onset of DR was accompanied by an increase in *HuR* mRNA expression, indicating upregulation of HuR in DR. HuR mRNA levels were also significantly reduced after HuR siRNA treatment in STZ-induced diabetic rats (Supe et al., 2023).

5 | FUTURE RESEARCH DIRECTIONS

Research on HuR is a dynamic field with various areas that require further exploration. Among these is the elucidation of the mechanisms governing HuR's regulation which would add an intriguing dimension to our current understanding of the protein. Besides the focus on its self-regulatory mechanisms which constitute most of the

literature in this aspect, more research should be conducted to investigate its posttranslational modifications, associated molecules and proteins, and the effect of intricate cellular signaling pathways on its expression and action. Moreover, the identification and characterization of HuR's broad range of RNA targets, preferably via the use of advanced techniques like crosslinking immunoprecipitation-sequencing (Kapral et al., 2022), remains an essential part of comprehending its full scope of action. Lastly, these exploratory efforts would allow us to selectively modulate HuR's activity, especially in inflammatory disorders; thereby, offering a promising opportunity for achieving advancements in the scientific body aiming to decipher HuR's biology, and hence, unleash new avenues for novel therapeutic interventions.

6 | CONCLUSIONS

Understanding the pathogenesis of various diseases has been greatly improved by the identification of key molecular regulators that control dysregulated gene expression programs. RBPs have become an intriguing research topic due to their ability to regulate RNA. This regulation is achieved through their control over several processes, including RNA splicing localization, stability, and translation. However, because RBP regulation is dependent on the microenvironment and events such as stress response and metabolism, binding affinities, and the resulting RNA-RBP networks may be influenced. Consequently, a variety of illnesses, including diabetes, and cardiovascular disease (Nutter et al., 2016), in addition to other conditions like cancer (Qin et al., 2020) and neurological diseases (Xue et al., 2020), can result from any dysregulation and disruption in the properties of RNA and its associated homeostasis. In light of this, proper control of RNA and RBPs is essential for optimal health since RBP loss of function can lead to pathogenesis (Huang et al., 2023; Kelaini et al., 2021).

HuR is an essential posttranscriptional modulator of gene expression. Given its critical involvement in key cellular activities, HuR's participation in disorders characterized by abnormal responses is becoming increasingly recognized. This highlights HuR as an effective therapeutic target (Srikantan, 2012). HuR has been inhibited through three main methods that have been investigated in the field: first, by inhibiting its cytoplasmic localization; second, by preventing it from binding to its target mRNAs; and third, by reducing its expression, which is typically achieved through silencing by the delivery of siRNA oligonucleotides (Schultz et al., 2020).

One of the first identified inhibitors of HuR translocation is MS-444, derived from *Actinomyces* species microbial broths (Meisner et al., 2007). In glioblastoma cells, MS-444 was found to reduce cytoplasmic HuR, which led to the inhibition of mRNAs that drive glioma progression. MS-444 inhibition of HuR translocation resulted in cytotoxicity, apoptosis, and impaired invasion of glioblastoma cells (Wang et al., 2019). Similar effects were observed upon treatment of colorectal cancer cells with MS-444 (Blanco et al., 2016). Another example of inhibitors of HuR translocation is the US Food and Drug Administration (FDA)-approved drug pyrvinium pamoate. It targets the AMPK/importin 1 cascade and the Chk1/Cdk1 pathway to prevent the cytoplasmic accumulation of HuR (Guo et al., 2016). The significance of cytoplasmic localization in HuR's tumor-promoting activity is underscored by these HuR inhibitor-based studies. This demonstrates the need for more research to validate these inhibitors and advance them toward clinical use.

Another promising candidate to target HuR is CMLD-2, a small molecule identified that prevents HuR from binding to its target mRNAs. In an NSCLC model, treatment with CMLD-2 resulted in decreased mRNAs of HuR-regulated genes. This resulted in elevated cytotoxicity and apoptosis (Muralidharan et al., 2017). Furthermore, new indole derivatives (VP12/14 and VP12/110) were identified to reduce HuR expression and inhibit its binding to VEGF-A and TNF-α mRNAs. The treatment of high-glucose-challenged human retinal endothelial cells with these indoles reduced the release of TNF-α and VEGF-A and altered the expression of HuR (Platania et al., 2020). This shows that these indoles have anti-inflammatory and antiangiogenic effects, indicating that targeting HuR may be used as an innovative treatment for DR.

RNA interference has been quickly embraced for the identification and confirmation of gene function through cell culture and animal model research using sequence-specific siRNA duplexes. The increased success of siRNA as a research tool has sparked significant interest in employing siRNA as a therapeutic agent (Kim et al., 2016). Using siRNA, HuR was knocked down in radioresistant triple-negative breast cancer (TNBC) cells. Silencing HuR dramatically lowered HuR mRNA and protein levels, which affected HuR's downstream targets. Moreover, the knockdown of HuR increased the radiosensitivity of TNBC cells (Mehta et al., 2016). Furthermore, melanoma cells treated with lipid nanoparticles encapsulating HuR siRNA, showed that the expression of HuR and HuR-regulated oncoproteins was dramatically downregulated, leading to cell cycle arrest at the G1 phase, activating the cascade of apoptotic signaling, and lessening the aggressiveness of melanoma cells (Ahmed et al., 2021). Liposome-polyethyleneimine complexes have been used to deliver HuR siRNA by injection into the eyes of diabetic rats with retinopathy. The disease-causing overexpression of VEGF, which is controlled by HuR, was overcome via the HuR siRNA duplexes (Supe et al., 2023). Overall, these strategies targeting HuR provide a promising therapeutic approach in the treatment of several pathologies, including cardiometabolic disorders. However, a clinically viable method for inhibiting HuR expression has not been fully manifested. This is due to several reasons; most importantly, siRNA is subjected to breakdown by nucleases in the vascular system, bombardment by immune cells due to immunostimulation, and degradation by components of the ECM. Another vital barrier is degradation ensued by endosomes and lysosomes, from which siRNA molecules must escape. Lastly, the choice of an optimal delivery system still poses an obstacle as it needs to offer a combination of high stability along with maximal on-target actions (i.e., therapeutic), and minimal off-target effects (Guo et al., 2024).

Because each targeting strategy necessitates its own distinct and specific approach to the process of validation and testing, additional research endeavors must be undertaken to definitively ascertain the underlying mechanism of action and to accurately identify any potential on- and off-target effects that may arise. Given the ever-evolving nature of this particular field and its constant progression, the act of validating these strategies, particularly in terms of their capacity to effectively modify and alter a given disease phenotype, will undoubtedly emerge as an absolutely crucial and indispensable component.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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