

Review

Hu Antigen R (HuR) Protein Structure, Function and Regulation in Hepatobiliary Tumors

Sofia Lachiondo-Ortega ¹, Teresa Cardoso Delgado ¹, Blanca Baños-Jaime ², Alejandro Velázquez-Cruz ², Irene Díaz-Moreno ² and María Luz Martínez-Chantar ^{1,3,*}

¹ Liver Disease Lab, Center for Cooperative Research in Biosciences (CIC bioGUNE), Basque Research and Technology Alliance (BRTA), 48160 Derio, Spain; slachiondo@cicbiogune.es (S.L.-O.); tcardoso@cicbiogune.es (T.C.D.)

² Centro de Investigaciones Científicas Isla de la Cartuja (cicCartuja), Instituto de Investigaciones Químicas (IIQ), Universidad de Sevilla, Consejo Superior de Investigaciones Científicas (CSIC), 41092 Sevilla, Spain; blanca.banos@iiq.csic.es (B.B.-J.); alejandro.velazquez@iiq.csic.es (A.V.-C.); idiazmoreno@us.es (I.D.-M.)

³ Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Carlos III National Health Institute, 28029 Madrid, Spain

* Correspondence: mlmartinez@cicbiogune.es; Tel.: +34-944-061318; Fax: +34-944-061301

Simple Summary: Hepatobiliary tumors are a group of primary malignancies encompassing the liver, the intra- and extra-hepatic biliary tracts, and the gall bladder. Within the liver, hepatocellular carcinoma (HCC) is the most common type of primary cancer, which is, also, representing the third-most recurrent cause of cancer-associated death and the sixth-most prevalent type of tumor worldwide, nowadays. Although less frequent, cholangiocarcinoma (CCA) is, currently, a fatal cancer with limited therapeutic options. Here, we review the regulatory role of Hu antigen R (HuR), a ubiquitous member of the ELAV/Hu family of RNA-binding proteins (RBPs), in the pathogenesis, progression, and treatment of HCC and CCA. Overall, HuR is proposed as a valuable diagnostic and prognostic marker, as well as a therapeutic target in hepatobiliary cancers. Therefore, novel therapeutic approaches that can selectively modulate HuR function appear to be highly attractive for the clinical management of these types of tumors.

Abstract: Hu antigen R (HuR) is a 36-kDa ubiquitous member of the ELAV/Hu family of RNA-binding proteins (RBPs), which plays an important role as a post-transcriptional regulator of specific RNAs under physiological and pathological conditions, including cancer. Herein, we review HuR protein structure, function, and its regulation, as well as its implications in the pathogenesis, progression, and treatment of hepatobiliary cancers. In particular, we focus on hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), tumors where the increased cytoplasmic localization of HuR and activity are proposed, as valuable diagnostic and prognostic markers. An overview of the main regulatory axes involving HuR, which are associated with cell proliferation, invasion, metastasis, apoptosis, and autophagy in HCC, is provided. These include the transcriptional, post-transcriptional, and post-translational modulators of HuR function, in addition to HuR target transcripts. Finally, whereas studies addressing the relevance of targeting HuR in CCA are limited, in the past few years, HuR has emerged as a potential therapeutic target in HCC. In fact, the therapeutic efficacy of some pharmacological inhibitors of HuR has been evaluated, in early experimental models of HCC. We, further, discuss the major findings and future perspectives of therapeutic approaches that specifically block HuR interactions, either with post-translational modifiers or cognate transcripts in hepatobiliary cancers.

Keywords: ELAV-like protein 1; RNA-binding protein; hepatocellular carcinoma; cholangiocarcinoma



Citation: Lachiondo-Ortega, S.; Delgado, T.C.; Baños-Jaime, B.; Velázquez-Cruz, A.; Díaz-Moreno, I.; Martínez-Chantar, M.L. Hu Antigen R (HuR) Protein Structure, Function and Regulation in Hepatobiliary Tumors. *Cancers* **2022**, *14*, 2666. <https://doi.org/10.3390/cancers14112666>

Academic Editor: Claudio Tiribelli

Received: 15 April 2022

Accepted: 23 May 2022

Published: 27 May 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Hu antigen R (HuR), also known as HuA or embryonic lethal abnormal vision-like protein 1 (ELAVL1), is a 36-kDa ubiquitous member of the ELAV/Hu family of RNA-binding proteins (RBPs), which, also, includes HuB, HuC and HuD [1,2]. In humans, this protein is encoded by the ELAVL1 gene. In healthy individuals, HuR protein is, mostly, expressed in human endocrine tissues, the respiratory system, and the gastrointestinal tract [3].

1.1. HuR Protein Structure

HuR structure is, mainly, comprised of three RNA-recognition motifs (RRMs) (Figure 1A) [4]. The first two domains (RRM1 and RRM2) are connected by a 10-residue linker in a tandem structure, as revealed by its X-ray crystallographic model (Figure 1B, middle panel), and are the main domains involved in RNA recognition [5]. Despite the high dynamics of the N-terminal unstructured 20-residue stretch of HuR, nuclear magnetic resonance (NMR) experimental restraints revealed that it was folded towards the RRM1 β -sheet (Figure 1B, left panel) [6]. Interestingly, it harbors the HuR redox sensor Cys13, which is conserved among ELAVL1 orthologous proteins and is involved in HuR RRM1 and RRM1-2 homodimerization and, to some extent, in the regulation of the antioxidant response by HuR (Figure 1C) [7,8]. A 60-residue disordered hinge region spaces out the C-terminal RRM3 domain from the tandem RRM1-2. This linker region contains the HuR nucleocytoplasmic shuttling sequence (HNS) (Figure 1A), whose length enables transient contacts between RRM3 and RRM1-2 [9]. Phosphorylation at HNS modifies HuR interaction with nucleo-cytoplasmic transport proteins, triggering HuR accumulation in the cytosol [10,11]. HuR RRM3, also, forms dimers through its evolutionary well-conserved Trp261 residue along evolution (Figure 1C), which is located in helix α_1 of RRM3 (Figure 1B, right panel) [12,13].

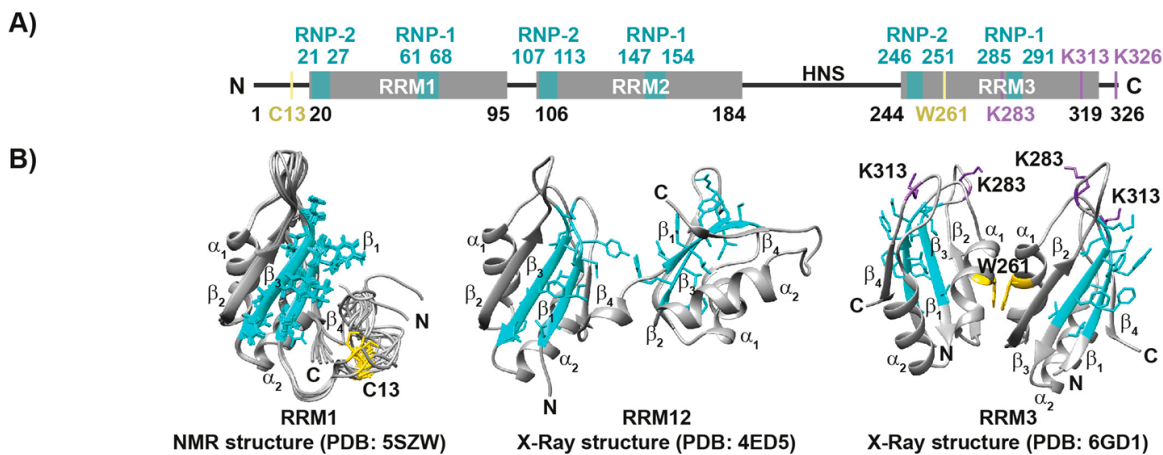


Figure 1. Cont.

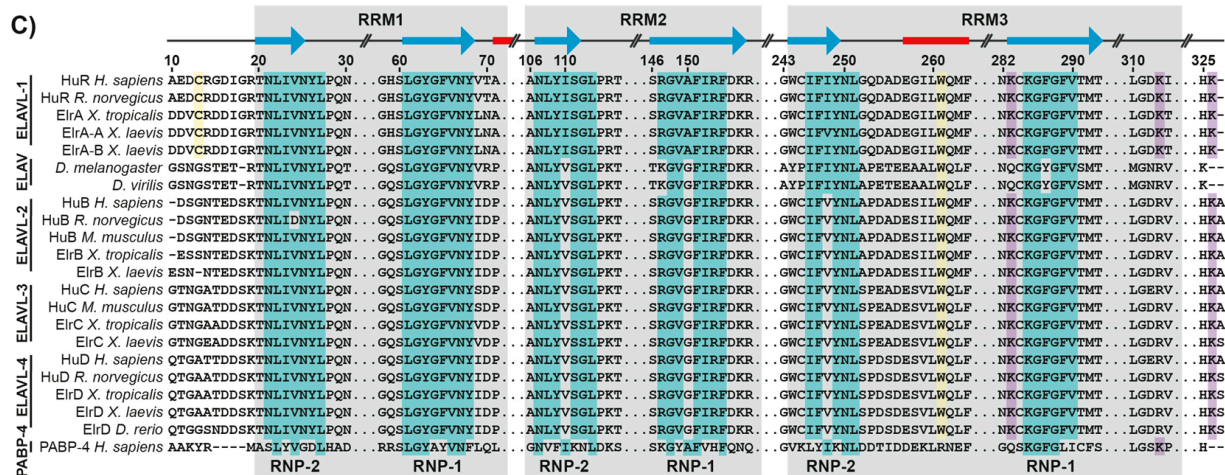


Figure 1. HuR domain organization, structures, and sequence alignment. (A) Schematic domain organization of human HuR. Black numbers indicate the residues flanking each domain. RNPs and residues flanking RNPs are colored in cyan. C13 and W261, implicated in dimerization, are highlighted in yellow. Susceptible lysines to become NEDDylated are highlighted in purple. N and C indicate N-terminal and C-terminal endings, respectively. (B) Ribbon structures of human HuR RRM domains. Side-chains of residues at RNPs are colored in cyan, those of C13 and W261 are highlighted in yellow; NEDDylated lysines are shown in purple. β-strands and α-helices numbers are indicated. Left panel: NMR structure of RRM1 domain. Ten models are shown (PDB: 5SZW) [14]. Middle panel: X-ray structure of RRM12 tandem of HuR (PDB: 4ED5) [5]. Right panel: X-ray structure of RRM3 domain, in its dimeric form (PDB: 6GD1) [15]. (C) Sequence alignment of HuR, with homologous RNA binding proteins (ELAV, ELAVL-1, ELAVL-2, ELAVL-3, ELAVL-4, and PABP-4), from human and related organisms. Residues belonging to each RRM domain are shaded in grey. RNPs residues from HuR are highlighted in cyan, whereas C13 and W261 are in yellow. K283, K313, and K326 are highlighted in purple. Blue arrows represent β-strands, and red rectangles represent α-helices of HuR.

All three RRMs show the canonical $\beta_1\alpha_1\beta_2\beta_3\alpha_2\beta_4$ topology, with a β-sheet formed by four antiparallel β-strands folded against two α-helices. The two central β-strands (β₁ and β₃) of each RRM contain the ribonucleoprotein (RNP) motifs RNP-1 (in β₃) and RNP-2 (in β₁), which are essential for RNA/DNA binding (Figure 1B,C) [15,16]. HuR RRM domains bind single-stranded RNA/DNA, by means of stacking interactions and hydrogen bonds between RNP motifs and nucleic acids [17]. RNP motif sequences are indicated in Figure 1C and, even though they differ for each RRM of HuR, they have been extensively conserved in ELAV-like proteins, through evolution from *Drosophila* to vertebrates [18].

1.2. HuR Protein Function

HuR functions as a post-transcriptional regulator, affecting many aspects of RNA metabolism, from splicing to translation, by binding through its RRMs to AU-rich elements (AREs), typically present in the 3'-untranslated region (UTR) of its target transcripts [19,20]. Under physiological conditions, HuR is, predominantly, located in the nucleus, where it participates in pre-mRNA splicing and nuclear export of mature mRNAs [21–25]. Notably, its nuclear functions remain poorly understood. Upon specific stimuli (such as stress signals and mitogens), HuR translocates to the cytoplasm and develops its main biological functions, which are mRNA stabilization and modulation of translation. HuR nucleocytoplasmic shuttling, through the nucleopore, is aided by the import factors transportin-1 (Trn1) and -2 (Trn2), and the adaptor proteins ANP32A (pp32/PHAP-I) and ANP32B (APRIL), both independently mediating HuR association with the nuclear export receptor chromosome region maintenance 1 (CRM1) [22,26,27].

In the cytoplasm, it is thought that HuR might control RNA stability, by competing with other RBPs and, thus, preventing mRNA degradation and deadenylation. To date, over 80 HuR-stabilized target mRNAs have been described and reviewed in [28,29], which include those that encode c-Fos [30], p21 [31–33], cyclins A2 [30,34], B1 [30,34], E1 [35,36], D1 [30,37], inducible nitric oxide synthase (iNOS) [38,39], granulocyte macrophage-colony stimulating factor (GM-CSF) [40,41], eukaryotic initiation factor (eIF)-4E [42], murine double minute (Mdm)2 [43,44], vascular endothelial growth factor (VEGF) [45–50], transforming growth factor (TGF)- β [45], sirtuin 1 (SIRT1) [51,52], tumor necrosis factor (TNF)- α [40,45,53], B-cell leukemia (Bcl)-2 [54,55], myeloid leukemia cell differentiation protein (Mcl)-1 [54], oncostatin M (OSM) [56], cyclooxygenase (COX)-2 [30,45,52,57–62], γ -glutamylcysteine synthetase heavy subunit (γ -GCSH) [63], survival of motor neuron (SMN) [64], SH2D1A [65], the regulator of G-protein signaling 4 (RGS4) [66], parathyroid hormone-related protein (PTHrP) [67], Fas ligand (FasL) [68], Myogenin [69,70], MyoD [69,70], acetylcholinesterase (AChE) [71,72], p53 [73,74], ARHI [aplasia Ras homolog member I (DIRAS3)] [58], nitric oxide/soluble guanylyl cyclase (sGC) [75], urokinase plasminogen activator (uPA) and its receptor (uPAR) [76], neurofibromatosis type 1 (NF1) [77], von Hippel-Lindau protein (pVHL) [67,78], toll-like receptor 4 (TLR4) [79], Snail [80], matrix metalloproteinase (MMP)-9 [81–85], c-Fms [86], the MAPK phosphatase (MKP)-1 [87], interferon (IFN)- γ [88], interleukin (IL)-3 [89], IL-4 [90], IL-6 [45,91,92], IL-8 [45,57,93], and HuR itself [25,94,95].

Regarding the control of translation, HuR can promote the expression of many mRNAs that are templates for proteins, such as cyclin A2 [30,34,96], prothymosin α (ProT α) [97], hypoxia-inducible factor (HIF)-1 α [98], Bcl-2 [54,55,99], VEGF [45–47,49,100–102], thrombospondin (TSP)-1 [103], MKP-1 [87], p53 [73,74], the cationic amino acid transporter (CAT)-1 [104], the intrinsic cellular caspase inhibitor XIAP [37], and cytochrome c [105]. Importantly, HuR can also bind to the 5'-UTR of a small subset of target transcripts (e.g., p27, IGF-1R and thrombomodulin) and disrupt the internal ribosome entry site (IRES)-dependent translation, eventually resulting in the repression of protein expression [106–108]. HuR was, also, found to bind to the 3'-UTR of Wnt5a and c-Myc mRNAs and repress their translation [109,110].

In addition to coding transcripts, HuR has the ability to bind and regulate the function of microRNAs (miRNAs) [111–114] and long non-coding RNAs (lncRNAs) [111,115–117].

1.3. Regulation of HuR Protein Function

The function of HuR is regulated through transcriptional, post-transcriptional, and post-translational mechanisms, as discussed below.

1.3.1. Transcriptional Control of HuR

The ELAVL1 gene displays alternate transcriptional start sites, leading to at least two distinct transcripts with distinct 5'-UTRs [99,118], the shorter of them being expressed in stress conditions under the influence of bone morphogenetic protein-7 (BMP-7) and the Smad 1/5/8 route [118]. Expression of the long HuR isoform relies on nuclear factor κ of activated B-cells (NF- κ B). The HuR promoter region contains a target of NF- κ B, to which one of its members—p65/RelA—binds upon the induction of the phosphatidylinositol 3-kinase (PI3K)/AKT signaling route, resulting in the abnormal upregulation of HuR gene expression in gastric tumors [119].

1.3.2. Post-Transcriptional Control of HuR

The stability of HuR mRNA is another key factor controlling its protein levels. HuR can both up- and down-regulate its expression, by interacting with its own transcript [25,94,95,120]. In addition, the existence of both positive and negative feedback loops between HuR and the protein product of its target mRNAs have been reported [121–124].

HuR abundance can, also, be regulated by miRNAs. An assortment of miRNAs (miR-125 [125], miR-519 [126], miR-9 [127], 291b-3p [128], miR-570-3 [129], miR-16 [130],

and miR-22 [131]) has been found to target the coding region and 3'-UTR of *HuR* mRNA, suppressing its expression. Conversely, *HuR* 3'-UTR comprises a binding site for miRNA-155-5p, which stabilizes the transcript and favors HT-29 colorectal cancer (CRC) cell migration [132].

1.3.3. Post-Translational Control of HuR

Post-translational modifications (PTMs) account for the main mechanism of regulation for *HuR* function, allowing the protein to elicit quick changes in gene-expression programs [10,11]. *HuR* protein abundance, subcellular localization, and RNA-binding affinity can be modulated by methylation [133–136], phosphorylation [24,33,44,51,137–157], proteolytic cleavage [158–160], ubiquitination [78,147,161,162], PARylation [163,164], sulfhydrylation [165], and arginylation [166].

More recently, it was described that circular RNAs (circRNAs) may comprise various binding motifs for one or several RBPs, including *HuR*, acting as sponges, where the RBP is prevented from binding to other targets while tethered to the circRNA [167]. For instance, it was shown that circPABPN1 competes with *PABP1* mRNA for binding to *HuR*, affecting the expression of p53, c-myc, and bcl-2, besides *PABP1* [168].

1.3.4. HuR Protein Oligomerization

HuR and functionally related proteins, such as *AUF1*, form dimers and multimers both free and bound to target sequences [12,15,153,169–171]. *HuR* dimers have been detected by fluorescence resonance energy transfer (FRET), both in the cell nucleus and cytoplasm. Importantly, the *HuR* oligomerization state strongly affects the stability of its target mRNAs. Fluorescence anisotropy analyses suggested that *HuR* RRM1-2 is able to form dimers with high affinity (K_D ca. 0.1 nM). These data indicate that RRM1-2 dimerization could be an important feature of the interaction mechanism between *HuR* and its target RNAs [172]. Furthermore, a structural analysis revealed that RRM1 alone forms homodimers as well, since Cys13 is exposed to and capable of establishing disulfide bonds, thus enabling *HuR* to respond to oxidative stress [7]. Beyond dimerization, cytoplasmic multimerization of *HuR* has been observed in glioma cells. A thorough analysis using distinct *HuR* constructs bound to fluorescent and bioluminescent probes enabled a model to be constructed, in which Cys13 is responsible for covalent dimerization, although the hinge region and RRM3 are still necessary for further oligomerization [173]. Indeed, the C-terminal domain of *HuR* is, also, prominently involved in its dimerization [12,13,15,170], as well as in the cooperative formation of *HuR* oligomers on ARE motifs [12,153,170]. According to small-angle X-ray scattering (SAXS) and NMR data, a single site-directed mutation (W261E) in RRM3 was enough to hinder its dimerization, under reducing conditions [15]. Moreover, deletion of RRM3 critically impaired the ability of the RBP to stabilize reporter β -globin mRNA constructs containing different AREs [9]. Altogether, experimental evidence points to *HuR* dimerizing through RRM1 and RRM3 in an independent way, while requiring both domains for oligomerization.

2. HuR and Hepatobiliary Cancers

HuR owns the post-transcriptional control of a large number of RNAs, enabling the protein to play pivotal roles that are dictated by the molecular functions of the transcripts. *HuR* targets, chiefly, include many mRNAs encoding proteins involved in cell proliferation, senescence, apoptosis, differentiation, stress, and immune responses. In turn, *HuR* was found to be involved not only in physiological processes (e.g., adipogenesis and muscle differentiation) [69,174–176] but also in disease (primarily, cancer and inflammation) [28,29,177]. Indeed, the relevance of *HuR* in some types of hepatobiliary tumors has been constantly described during the last decade. The major findings to date and future perspectives on the applications of *HuR* as a protein marker for the diagnosis, prognosis, and therapy of hepatobiliary cancers are the main topic of this review.

2.1. Hepatobiliary Cancers

Hepatobiliary cancers are a group of primary malignancies encompassing the liver, the intra- and extra-hepatic biliary tracts, and the gall bladder. Within the liver, the most common primary cancer is hepatocellular carcinoma (HCC). HCC, usually, arises in patients with an underlying chronic liver disease, such as chronic infection with the hepatitis B (HBV) or C virus (HCV), cirrhosis, excessive alcohol consumption, metabolic syndrome, diabetes, and non-alcoholic fatty liver disease (NAFLD) [178]. Even though the clinical management of HCC has improved in the past ten years, particularly for patients at advanced stages, HCC is still the third-most common cause of cancer-associated death and the sixth-most prevalent type of cancer worldwide [179]. Of relevance, in the past few years, important studies on immunotherapy in HCC have been carried out, resulting in novel guidelines for its treatment [180–182].

On the other hand, cholangiocarcinoma (CCA) encompasses a group of malignancies, arising at any point in the hepatic biliary tree. Biliary tract cancers, including intrahepatic (ICC), perihilar (PCC), and distal cholangiocarcinoma (DCC), as well as gallbladder cancer, are low-incidence malignancies in most high-income countries, but represent a major health problem in endemic areas. Indeed, ICC is the second-leading cause of primary liver cancer [183]. Nowadays, CCA is a fatal cancer, with a survival rate beyond a year of diagnosis inferior to 5% [184]. Therapeutic options are limited and surgery is the cornerstone of cure for CCA, even though most patients present with locally advanced or metastatic disease [185]. In the past few years, druggable alterations such as fibroblast growth factor receptor 2 (FGFR2) gene fusions and rearrangements, or isocitrate dehydrogenase-1 (IDH-1) and BRAF mutations, have been widely described in CCA patients, further indicating the important differences between iCCA and PCC/DCC, as thoroughly reviewed in [186].

2.2. HuR as a Prognostic and Diagnostic Biomarker in Hepatobiliary Cancers

HuR protein is, either, overexpressed in most human cancers or overactivated, as denoted by its increased cytoplasmic localization and the translation of various mRNAs involved in carcinogenesis. Regarding liver cancer, Embade et al. [187], reported significantly higher HuR protein levels in the mouse liver progenitor 29 (MLP29) cell line and in the S-adenosylmethionine-deficient (SAME-D) cell line, isolated from the *methionine adenosyltransferase (MAT)1A* knockout (*MAT1A-KO*) mouse model of HCC, compared with primary mouse hepatocytes. Accordingly, higher HuR expression levels were found in human hepatoma cells (e.g., HepG2, Hep3B, SNU398, SNU449, SNU182, and SNU475), than in normal CRL4020 cells [188]. Moreover, in a human liver cancer tissue microarray (TMA) of 59 liver tissue cores from 44 patients, also by Zhu et al. [188], HCC tumor tissues showed significantly higher overall and cytoplasmic HuR staining, compared to normal liver tissues, and this high HuR staining score correlated with worse survival of patients with early-stage HCC. Furthermore, immunofluorescence analyses of normal versus malignant liver tissue revealed that HuR protein is down-regulated in normal human liver samples and up-regulated in HCC samples of different aetiologies (cirrhotic patients with HCV, alcoholic steatohepatitis, and non-alcoholic steatohepatitis (NASH)), where HuR concentration increased, proportionately, to their transformation status [189]. Finally, the expression of *ELAVL1* gene is highly induced in the tumor tissue of a cohort of CCA patients, according to The Cancer Genome Atlas (TCGA) mRNA expression repository [190]. Likewise, high cytoplasmic HuR levels are associated with poor survival in patients with surgically resected CCA, treated with adjuvant gemcitabine-based chemotherapy [191].

In sum, HuR overexpression, along with its cytoplasmic localization, are hallmarks of both HCC and CCA, correlating with disease progression and overall survival. Even though the role of HuR in HCC has been widely investigated, with some studies revealing HuR targets and regulators under these conditions, the function of HuR in CCA remains rather unexplored to date.

2.3. Signaling Pathways Implicated in HCC Involving HuR

The oncogenic-gene-expression programs that allow cancer cells to develop, survive, proliferate, and colonize other tissues are strongly dependent on post-transcriptional mechanisms [28]. As has been previously described, HuR is highly involved in many types of cancer, including HCC and CCA, and so are the numerous HuR-regulated RNAs, which are known to contribute to the main cancer hallmark functions (i.e., enhanced cell proliferation and survival, elevated local angiogenesis, evasion of immune recognition, facilitated cancer cell invasion, and metastasis). Furthermore, a series of transcriptional, post-transcriptional, and post-translational regulators of HuR function have been found to be altered during HCC. Herein, we aimed to analyze the main regulatory axes involving HuR that are associated with hepatobiliary tumors, which can be classified into those related with cell proliferation, invasion, and metastasis; apoptosis; and autophagy (Figure 2). In the process, some of the previously reported HuR RNA targets and regulators of HuR function have been confirmed in the specific context of HCC, while others have been newly identified in this type of tumor.

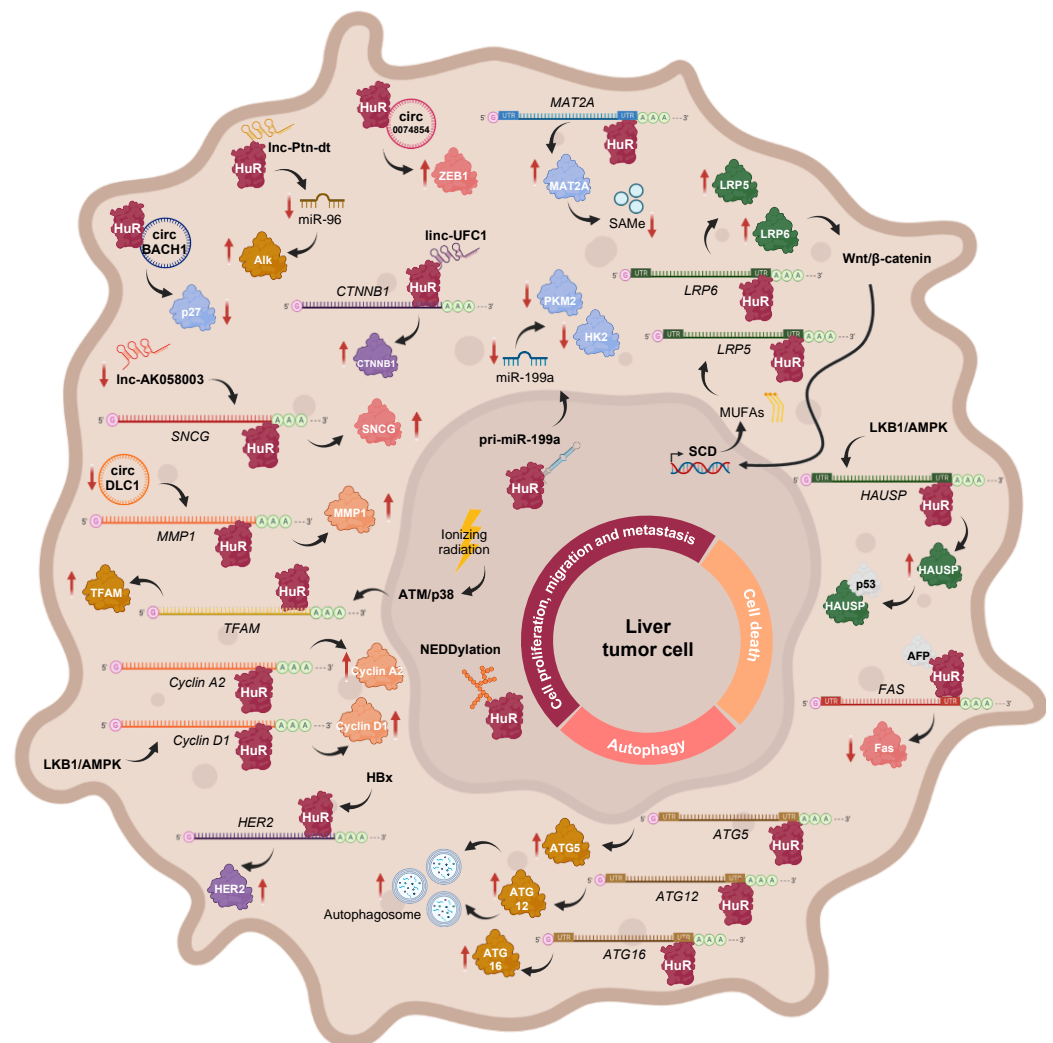


Figure 2. Main regulatory axes involving HuR, which are associated with cell proliferation, invasion, metastasis, apoptosis, and autophagy during HCC. These include the transcriptional, post-transcriptional, and post-translational modulators of HuR function, in addition to HuR target transcripts.

2.3.1. The Role of HuR in Cell Proliferation, Migration, and Metastasis during HCC Pathways Involving Coding Transcripts

The PI3K/AKT signaling route is known to be upregulated in HCC [192], and, therefore, it could be responsible for the increased expression of the long HuR mRNA isoform, through NF- κ B, as it occurs in gastric tumors [119]. However, it is likely that expression of the short HuR transcript is not observed during HCC, as reduced levels of BMP-7 and p-Smad1/5/8 were detected in patient samples [193].

During HBV-associated HCC, the HBV-encoded X (HBx) protein upregulates HuR expression, which enhances *HER2* mRNA stabilization and translation, thus contributing to the migration of HCC cells [194]. In the *MAT1A* knockout (*MAT1A*-KO) mouse model, which shows a chronic deficiency in SAME levels and, spontaneously, develops NASH and HCC, hepatic levels of LKB1 and AMPK are activated, incrementing the cytoplasmic localization of HuR, which leads to the stabilization and expression of *cyclin A2* and *D1* mRNAs, and subsequent cell cycle progression [195]. Moreover, an abnormally low ratio between methylated and unmethylated HuR was revealed in HCC samples. The two HuR isoforms can associate with the 3'-UTR of *MAT2A* mRNA, whose activity is linked to liver cell proliferation. However, while unmethylated HuR was shown to stabilize the *MAT2A* transcript, an increase in its methylation status correlated with lower *MAT2A* mRNA levels. Hence, the loss of HuR methylation may explain the increased *MAT2A* mRNA and protein expression, and the subsequent loss of SAME homeostasis that occurs during hepatocyte dedifferentiation, proliferation, and carcinogenesis [189]. Moreover, related with PTMs, NEDDylation of HuR was firstly reported in the context of liver cancer. Specifically, the E3 ligase Mdm2 catalyzes the conjugation of NEDD8 to HuR at Lys283, Lys313, and Lys326, a process that has been linked to the nuclear localization and reduced proteasomal degradation of the RBP [187]. Interestingly, the Mdm2 transcript being a described target of HuR [43,44], and considering the significantly positive correlation between Mdm2 and HuR expression in clinical HCC and human hepatoma cell lines [187], it would be highly expected that the mRNA levels of this E3 ligase were stabilized by HuR during HCC too, despite not having been verified to date.

The Wnt/ β -catenin pathway has been shown to induce stearoyl-CoA desaturase (SCD) expression in liver-tumor-initiating and HCC cells, further increasing the synthesis of mono unsaturated fatty acids (MUFAs). MUFAs can block the nuclear import of HuR, thereby increasing its protein levels in the cytoplasm, where it binds to the 3'UTR of *Lrp5* and *Lrp6* mRNAs as well as stabilizes and stimulates their translation, further providing a positive feedback loop, by amplifying Wnt/ β -catenin signaling and contributing to liver carcinogenesis [196]. Moreover, Wilms tumor 1-associated protein (WTAP) drives N6-methyladenosine (m6A) RNA methylation and epigenetic silencing of *ETS1*, by interfering with HuR-mediated stabilization of *ETS1* mRNA, further alleviating the expression of p21 and p27 G2/M checkpoint proteins, which are known downstream effectors of *ETS1*, and facilitating HCC progression [197]. Moreover, it has been reported that ionizing radiation activates the DNA damage response (DDR) via ATM/p38, which causes HuR shuttling to the cytoplasm in order to stabilize *mitochondrial transcription factor A (TFAM)* mRNA and induce its expression in HepG2 hepatoma cells. These results suggest a new pathway, which could be targeted to increase the sensitivity of liver cancer cells to radiotherapy [198].

Pathways Involving Non-Coding Transcripts

In addition to mRNAs, a few examples, whereby HuR interacts with non-coding transcripts during hepatobiliary tumors, have been reported. In human HCC cells subjected to hypoxic stress, HuR binds to the primary transcript of miR-199a (pri-miR-199a) blocking its processing into mature miR-199a. Interestingly, miR-199a is a negative regulator of *Hk2* and *Pkm2* mRNA expression. Therefore, HuR-mediated miR-199a maturation inhibition, during hypoxia, enables the metabolic reprogramming of HCC cells towards the Warburg effect, which confers favorable conditions for tumor growth, invasion, and metastasis [199]. The long intergenic noncoding RNA (lincRNA)-UFC1 plays an oncogenic role in liver

cancer, by interacting with HuR, which stabilizes and induces the expression of the *CTNNB1* mRNA, leading to increased cell-cycle progression as well as proliferation and reduced apoptosis in HCC cells [200]. The oncofetal lncRNA Ptn-dt appeared to be highly expressed in HCC tissue and was found to interact with HuR protein, further compromising the stabilization and expression of miR-96. Therefore, the reduced function of miR-96 on the post-transcriptional inhibition of anaplastic lymphoma kinase (Alk) protein contributed to HCC cell proliferation [201]. Another study, describing the tumor suppressor role of lncRNA-AK058003 in HCC, revealed *SNCG* mRNA as a potential target of HuR. It was postulated that lncRNA-AK058003 is downregulated during HCC but, if overexpressed, it can interact with HuR to suppresses its expression, further affecting *SNCG* translation and stability, thus inhibiting γ -synuclein-mediated HCC cell proliferation and metastasis, both in vitro and in vivo [202].

In an attempt to elucidate the function of circRNAs, a few circRNA-RBP-mRNA axes involving HuR were revealed in HCC. For example, circBACH1 acts as an oncogene during hepatic tumorigenesis, upon association with HuR, to facilitate its translocation to the cytoplasm, where the RBP inhibits p27 protein expression and allows cell cycle progression, eventually favoring HCC cell proliferation [203]. KIAA1429, a key component of the m6A methyltransferase complex, negatively regulates circRNA-DLC1 in HCC tissues. A mechanistic study revealed that circDLC1 competitively binds with HuR, thereby impairing HuR-mediated *MMP1* mRNA stabilization and expression, ultimately resulting in decreased hepatoma cell proliferation and metastasis [204]. Moreover, hsa_circ_0074854 physically interacts and stabilizes HuR protein in the cytoplasm, which induces ZEB1 protein expression, thereby promoting the migration, invasion, and epithelial-mesenchymal transition (EMT) of HepG2 hepatoma cells [205].

2.3.2. The Role of HuR in Cell Death during HCC

In SAMe-D cells derived from *MAT1A* KO mice, sustained LKB1 phosphorylation contributes to increased cytoplasmic HuR localization, where it, specifically, binds to the 3'-UTR of *herpesvirus-associated ubiquitin-specific protease (HAUSP)* mRNA, stabilizing it and increasing its transcription. The subsequent accumulation of HAUSP deubiquitinating enzyme in the cytoplasm allows its interaction with p53, which increases the stability of the tumor suppressor in the cytoplasm, thereby controlling the apoptotic response [206].

A recent study about a possible model, whereby alpha fetoprotein (AFP) regulates HCC progression and chemosensitivity, reported the reactivation of AFP during hepatocarcinogenesis and its interaction with HuR, resulting in the redistribution of the RBP to the cytoplasm. There, HuR would bind to the 3'-UTR of the Fas death receptor mRNA and repress its translation, without affecting its stability or splicing, which further suppresses the Fas/FADD-mediated extrinsic apoptotic program and bypasses immune surveillance in HCC-derived cell lines [188,207].

2.3.3. The Role of HuR in Autophagy during HCC

Interestingly, HuR binds to the 3'-UTR of *ATG5*, *ATG12*, and *ATG16* mRNAs and enhances their translation. As a result, autophagosome formation is enhanced, dysregulating the autophagy activity in HCC cell lines, which might possibly act as a pro-survival response and promote hepatic tumor growth [208]. On the other hand, inhibition of autophagy by *BECN1* siRNA leads to HuR-enhanced ferroptosis in HCC. HuR and *BECN1* interaction induces autophagosome formation, increasing autophagic ferritin degradation and enhancing ferroptosis in hepatic stellate cells (HSCs) [209].

3. Therapeutic Approaches to Inhibit HuR in Hepatobiliary Tumors

Given its essential role as a regulation hub of cell-fate decisions, suppression of HuR activity has become a key objective to control tumor progression and therapy resistance. Even though RBPs were, initially, considered unsuitable for drug screening, developments during the last decade have enabled the generation of distinct approaches to target RBPs, including HuR, in cancer and other human pathologies [210].

The downregulation of HuR function may be achieved through different strategies, with small molecules being the most popular class of inhibitors for this RBP. Small molecules, directly, inhibit HuR interaction with target RNAs, oligomerization, nucleocytoplasmic shuttling, or post-translational modification, further compromising its function. Dehydromutactin, MS-444, and okicenone are three low-molecular-weight molecules, found to inhibit both HuR dimerization and RNA binding, during a screening of compounds derived from *Actinomyces* cultures [172]. Among them, MS-444 showed the highest affinity and has proven to affect the viability of different cell lines [173,211–213]. Dihydrotanshinone-I (DHTS) [214], b40, and quercetin [215], as well as the coumarin derivative CMLD-2 [216–218], were, also, identified as chemical disruptors of the interaction between HuR and its target mRNAs. Other small-molecule inhibitors preventing HuR interaction with its target mRNAs include KH-3, which has been found to be promising for the treatment of breast cancer [219]. A new inhibitor is the muscone derivative ZM-32, a synthetic compound that shows antiangiogenic effects in breast cancer tumor cells, by blocking HuR association with *VEGF* and *MMP9* mRNAs [220].

Except for ZM-32, which was tested in the human hepatoma HepG2 cell line without obtaining very successful outcomes [220], surprisingly, none of the abovementioned molecules have been tested in hepatobiliary tumors. Currently, studies reporting the use of small-molecule HuR inhibitors to tackle HCC are limited (Table 1). For instance, resveratrol (RSV) increased HuR mRNA and protein-expression levels in human liver cancer cell lines, which helped to raise *MAT2B* and *SIRT1* expression, by stabilizing their mRNAs at the 3'-UTR. Importantly, the induced HuR, SIRT1, and MAT β proteins interact and stabilize each other, while compromising the binding of MAT β to MAT α 2. Eventually, this leads to an increase in SAME levels, which might favor cell growth suppression and apoptosis during liver cancer, upon treatment with RSV [221]. In another study, *N*-Benzylcantharidinamide impaired HuR translocation to the cytosol and decreased the stability of *MMP-9* mRNA and its expression, further inhibiting the invasive potential in metastatic Hep3B cells [222]. Additionally, since the nucleocytoplasmic transport of HuR depends on the interaction of this RBP with cytoskeletal proteins, the naturally occurring cytoskeletal inhibitors latrunculin A and blebbistatin have shown to exert antitumorigenic properties in human hepatoma cells, by interfering with the intracellular trafficking of HuR and its mRNA cargo [223]. Finally, the NEDDylation inhibitor Pevonedistat was shown to exert antitumoral effects in vitro and in vivo in liver cancer, partially through HuR destabilization. Importantly, overexpression of HuR in hepatoma cells offered resistance to pharmacological NEDDylation inhibition, while low levels of HuR sensitized cells to the treatment, suggesting that HuR levels determine the druggability of the NEDDylation pathway in HCC [224].

Notably, antisense oligonucleotides (ASOs) [225] and small interfering RNAs (siRNAs) exist for HuR. The latter have been widely used in the numerous studies mentioned throughout this review, in connection with HCC [187–189,194,197,199,204,206,208]. Related with siRNA technology as well, targeted delivery is, often, highly desirable and can be achieved thanks to the use of nanotechnology, for example, by means of the folate-receptor-targeted nanoparticle delivery of HuR siRNA, to reach lung cancer cells [226].

Table 1. Small-molecule inhibitors controlling HuR function, tested in hepatobiliary tumors.

Molecule	Type	Effect	Ref.
ZM-32	Synthetic muscone-derivative	Inhibition of HuR binding to target mRNAs	[220]
Resveratrol (RSV)	Naturally occurring	Increase in HuR mRNA and protein expression	[221]
N-Benzylcantharidinamide	Synthetic analogue of the naturally occurring cantharidine drug	Inhibition of HuR translocation to the cytosol	[222]
Latrunculin A	Naturally occurring	Inhibition of HuR translocation to the cytosol	[223]
Blebbistatin	Naturally occurring	Inhibition of HuR translocation to the cytosol	[223]
Pevonedistat	Synthetic NEDDylation inhibitor	HuR destabilization	[224]

4. Future Perspectives

Herein, we have reviewed the current knowledge on the role of HuR in hepatobiliary tumors, including HCC and CCA. Considering increased HuR protein expression, cytoplasmic localization, and its relationship with patient outcome, HuR is regarded as a valuable diagnostic as well as a prognostic marker in HCC. Even though we recognize the growing attention of liquid biopsy in HCC, only invasive approaches have been carried out, to address the diagnosis and prognosis of HuR in these types of tumors, to date. With regard to CCA, high cytoplasmic expression and elevated tumor-gene levels of HuR have been described. However, special care should be taken when using cytological and pathological approaches, due to the highly desmoplastic nature of these types of tumors. In fact, in biliary tract carcinomas, biopsy samples are often inadequate for molecular profiling. Additionally, tissue sampling has reported high specificity but low sensitivity in diagnosis. Thereby, to further validate the relevance of HuR as a diagnostic and prognostic marker in CCA, further *in vitro* studies and *in vivo* pre-clinical mouse models are required.

Even though the role of HuR in CCA remains, largely, unexplored, novel mechanisms underlying HuR regulation have been addressed in HCC, with special focus on the importance of the PTM NEDDylation in the stabilization of HuR, preventing it from proteasome-mediated degradation [187]. Consequently, the relevance of HuR in pathological conditions, including cancer, has gained interest, with the advent of many naturally occurring and synthetic inhibitors of HuR. Nevertheless, given the lack of studies, using the currently available HuR inhibitors for the treatment of hepatobiliary tumors, and considering the heterogenous nature of HuR as a target affecting multiple pathways in many types of human cancers, it is, somehow, expected that the inhibition of HuR may be associated with undesired side-effects. Indeed, it has been described that HuR whole-body knock-out leads to embryonic lethality in mice, suggesting that HuR is, most probably, involved in regulating the fate of mRNAs encoding proteins implicated in key processes, such as organ development and tissue homeostasis [227].

Therefore, to take advantage of HuR as a therapeutic target, we propose that it would be critical to, specifically, inhibit the diverse interactions of HuR with its transcripts, which are uniquely relevant in the context of hepatobiliary cancers. For this purpose, the first step would be to interrogate the HuR RNA-binding signature in hepatobiliary tumors, which could be achieved, for example, by using RNA sequencing (RNA-Seq) approaches after the immunoprecipitation (IP) of the RNAs interacting with HuR, in the tumor and adjacent tissues, of large cohorts of HCC and CCA patients. Additionally, considering the relevance of HuR PTMs in liver disease, the screening of HuR PTM signature, including the residues susceptible of modification in liver cancer can unravel new unexpected and druggable regulatory mechanisms of HuR function. The screening of novel HuR RNA targets and

PTMs in liver cancer as well as their clustering, according to the degree of liver disease, may, eventually, reveal subtypes of patients where certain HuR-related therapeutic approaches may be more suitable, paving the way for a more-personalized medicine. In other words, from this population-based study, we could, potentially, treat liver cancer by inhibiting the interactions of HuR either with (1) specific target RNAs or (2) peptides responsible for its PTM, which are ascribed to liver cancer. Indeed, short RNAs that compete with HuR for the binding to its target mRNAs, without affecting other HuR-mRNA binding interactions, had been previously suggested as a novel strategy for the management of HCC [228]. In this context, aptamers have, recently, emerged as small single-stranded DNA or RNA molecules that fold in a specific way, which is optimal to interact with a given target [229]. Thus, after elucidating HuR RNA targets and its PTMs in the context of liver cancer, we believe it would be possible to obtain aptamers blocking HuR interaction with both RNA and the peptides associated with PTMs, in a highly specific manner, minimizing potential adverse effects. This might be achieved through the screening of aptamer libraries, using the Systematic Evolution of Ligands by Exponential Enrichment (SELEX) selection method. For this purpose, the understanding of HuR protein structure is of great benefit to predict whether the conformation of the aptamer would be suitable to inhibit the binding of HuR to its target.

5. Concluding Remarks

In conclusion, even though, in the past few years, great efforts have been carried out, in order to better understand the function of HuR and its regulation in hepatobiliary tumors, further studies are necessary to address the therapeutic potential of HuR inhibitors or, alternatively, a more-personalized treatment based on the selected inhibition of HuR and its RNA or the protein targets in HCC and CCA.

Author Contributions: Conceptualization, S.L.-O., T.C.D., B.B.-J., A.V.-C., I.D.-M. and M.L.M.-C.; writing—review and editing, S.L.-O., T.C.D., B.B.-J., A.V.-C., I.D.-M. and M.L.M.-C. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Programa Retos-Colaboración, grant number RTC2019-007125-1 (to M.L.M.-C.); the Instituto de Salud Carlos III, Proyectos de Investigación en Salud, grant number DTS20/00138 (to M.L.M.-C.); the Departamento de Industria del Gobierno Vasco (to M.L.M.-C.); the Ministerio de Ciencia, Innovación y Universidades (MICINN), integrated in the Plan Estatal de Investigación Científica y Técnica e Innovación, grant numbers PID2020-117116RB-I00 (to M.L.M.-C.) and PGC2018-096049-B-I00 (to I.D.-M.); the Gobierno de Andalucía, grant numbers BIO-198, US-1254317, US-1257019, P18-FR-3487, and P18-HO-4091 (to I.D.-M.); the Universidad de Sevilla (to I.D.-M.); Fundación Ramón Areces (to I.D.-M.); co-funded by the Fondo Europeo de Desarrollo Regional (FEDER) (to MLM-C and I.D.-M.); and the La Caixa Foundation Program, grant number HR17-00601 (to M.L.M.-C.). We acknowledge investigator contracts granted by the Ministerio de Educación, Cultura y Deporte, grant number FPU016/01513 (to A.V.C); the Asociación Española Contra el Cáncer (AECC) (to T.C.-D.); and Gobierno Vasco (to S.L.-O.).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hinman, M.N.; Lou, H. Diverse Molecular Functions of Hu Proteins. *Cell. Mol. Life Sci.* **2008**, *65*, 3168–3181. [[CrossRef](#)] [[PubMed](#)]
2. Simone, L.E.; Keene, J.D. Mechanisms Coordinating ELAV/Hu mRNA Regulons. *Curr. Opin. Genet. Dev.* **2013**, *23*, 35–43. [[CrossRef](#)] [[PubMed](#)]
3. Uhlén, M.; Fagerberg, L.; Hallström, B.M.; Lindskog, C.; Oksvold, P.; Mardinoglu, A.; Sivertsson, Å.; Kampf, C.; Sjöstedt, E.; Asplund, A.; et al. Proteomics. Tissue-Based Map of the Human Proteome. *Science* **2015**, *347*, 1260419. [[CrossRef](#)] [[PubMed](#)]
4. Scheiba, R.M.; Aroca, A.; Díaz-Moreno, I. HuR Thermal Stability Is Dependent on Domain Binding and upon Phosphorylation. *Eur. Biophys. J.* **2012**, *41*, 597–605. [[CrossRef](#)]
5. Wang, H.; Zeng, F.; Liu, Q.; Liu, H.; Liu, Z.; Niu, L.; Teng, M.; Li, X. The Structure of the ARE-Binding Domains of Hu Antigen R (HuR) Undergoes Conformational Changes during RNA Binding. *Acta Crystallogr. D Biol. Crystallogr.* **2013**, *69*, 373–380. [[CrossRef](#)] [[PubMed](#)]

6. Mujo, A.; Lixa, C.; Carneiro, L.A.M.; Anobom, C.D.; Almeida, F.C.; Pinheiro, A.S. (1)H, (15)N and (13)C Resonance Assignments of the RRM1 Domain of the Key Post-Transcriptional Regulator HuR. *Biomol. NMR Assign.* **2015**, *9*, 281–284. [[CrossRef](#)]
7. Benoit, R.M.; Meisner, N.-C.; Kallen, J.; Graff, P.; Hemmig, R.; Cèbe, R.; Ostermeier, C.; Widmer, H.; Auer, M. The X-Ray Crystal Structure of the First RNA Recognition Motif and Site-Directed Mutagenesis Suggest a Possible HuR Redox Sensing Mechanism. *J. Mol. Biol.* **2010**, *397*, 1231–1244. [[CrossRef](#)]
8. Poganik, J.R.; Van Hall-Beauvais, A.K.; Long, M.J.C.; Disare, M.T.; Zhao, Y.; Aye, Y. The mRNA-Binding Protein HuR Is a Kinetically-Privileged Electrophile Sensor. *Helv. Chim. Acta* **2020**, *103*, e2000041. [[CrossRef](#)]
9. Fan, X.C.; Steitz, J.A. Overexpression of HuR, a Nuclear–Cytoplasmic Shuttling Protein, Increases the in Vivo Stability of ARE-Containing MRNAs. *EMBO J.* **1998**, *17*, 3448–3460. [[CrossRef](#)]
10. Grammatikakis, I.; Abdelmohsen, K.; Gorospe, M. Posttranslational Control of HuR Function. *Wiley Interdiscip. Rev. RNA* **2017**, *8*, e1372. [[CrossRef](#)]
11. Velázquez-Cruz, A.; Baños-Jaime, B.; Díaz-Quintana, A.; De la Rosa, M.A.; Díaz-Moreno, I. Post-Translational Control of RNA-Binding Proteins and Disease-Related Dysregulation. *Front. Mol. Biosci.* **2021**, *8*, 658852. [[CrossRef](#)] [[PubMed](#)]
12. Scheiba, R.M.; de Opakua, A.I.; Díaz-Quintana, A.; Cruz-Gallardo, I.; Martínez-Cruz, L.A.; Martínez-Chantar, M.L.; Blanco, F.J.; Díaz-Moreno, I. The C-Terminal RNA Binding Motif of HuR is a Multi-Functional Domain Leading to HuR Oligomerization and Binding to U-Rich RNA Targets. *RNA Biol.* **2014**, *11*, 1250–1261. [[CrossRef](#)] [[PubMed](#)]
13. Díaz-Quintana, A.; García-Mauriño, S.M.; Díaz-Moreno, I. Dimerization Model of the C-Terminal RNA Recognition Motif of HuR. *FEBS Lett.* **2015**, *589*, 1059–1066. [[CrossRef](#)] [[PubMed](#)]
14. Lixa, C.; Mujo, A.; de Magalhães, M.T.Q.; Almeida, F.C.L.; Lima, L.M.T.R.; Pinheiro, A.S. Oligomeric Transition and Dynamics of RNA Binding by the HuR RRM1 Domain in Solution. *J. Biomol. NMR* **2018**, *72*, 179–192. [[CrossRef](#)] [[PubMed](#)]
15. Pabis, M.; Popowicz, G.M.; Stehle, R.; Fernández-Ramos, D.; Asami, S.; Warner, L.; García-Mauriño, S.M.; Schlundt, A.; Martínez-Chantar, M.L.; Díaz-Moreno, I.; et al. HuR Biological Function Involves RRM3-Mediated Dimerization and RNA Binding by All Three RRMs. *Nucleic Acids Res.* **2019**, *47*, 1011–1029. [[CrossRef](#)] [[PubMed](#)]
16. Wang, X.; Tanaka Hall, T.M. Structural Basis for Recognition of AU-Rich Element RNA by the HuD Protein. *Nat. Struct. Biol.* **2001**, *8*, 141–145. [[CrossRef](#)]
17. Corley, M.; Burns, M.C.; Yeo, G.W. How RNA-Binding Proteins Interact with RNA: Molecules and Mechanisms. *Mol. Cell* **2020**, *78*, 9–29. [[CrossRef](#)]
18. Della Volpe, S.; Nasti, R.; Queirolo, M.; Unver, M.Y.; Jumde, V.K.; Dömling, A.; Vasile, F.; Potenza, D.; Ambrosio, F.A.; Costa, G.; et al. Novel Compounds Targeting the RNA-Binding Protein HuR. Structure-Based Design, Synthesis, and Interaction Studies. *ACS Med. Chem. Lett.* **2019**, *10*, 615–620. [[CrossRef](#)]
19. Mukherjee, N.; Corcoran, D.L.; Nusbaum, J.D.; Reid, D.W.; Georgiev, S.; Hafner, M.; Ascano, M.J.; Tuschl, T.; Ohler, U.; Keene, J.D. Integrative Regulatory Mapping Indicates That the RNA-Binding Protein HuR Couples Pre-mRNA Processing and mRNA Stability. *Mol. Cell* **2011**, *43*, 327–339. [[CrossRef](#)]
20. Lebedeva, S.; Jens, M.; Theil, K.; Schwanhäusser, B.; Selbach, M.; Landthaler, M.; Rajewsky, N. Transcriptome-Wide Analysis of Regulatory Interactions of the RNA-Binding Protein HuR. *Mol. Cell* **2011**, *43*, 340–352. [[CrossRef](#)]
21. Izquierdo, J.M. Hu Antigen R (HuR) Functions as an Alternative Pre-mRNA Splicing Regulator of Fas Apoptosis-Promoting Receptor on Exon Definition. *J. Biol. Chem.* **2008**, *283*, 19077–19084. [[CrossRef](#)] [[PubMed](#)]
22. Gallouzi, I.E.; Steitz, J.A. Delineation of mRNA Export Pathways by the Use of Cell-Permeable Peptides. *Science* **2001**, *294*, 1895–1901. [[CrossRef](#)] [[PubMed](#)]
23. Prechtel, A.T.; Chemnitz, J.; Schirmer, S.; Ehlers, C.; Langbein-Detsch, I.; Stülke, J.; Dabauvalle, M.-C.; Kehlenbach, R.H.; Hauber, J. Expression of CD83 Is Regulated by HuR via a Novel Cis-Active Coding Region RNA Element. *J. Biol. Chem.* **2006**, *281*, 10912–10925. [[CrossRef](#)]
24. Doller, A.; Akool, E.-S.; Huwiler, A.; Müller, R.; Radeke, H.H.; Pfeilschifter, J.; Eberhardt, W. Posttranslational Modification of the AU-Rich Element Binding Protein HuR by Protein Kinase Cdelta Elicits Angiotensin II-Induced Stabilization and Nuclear Export of Cyclooxygenase 2 mRNA. *Mol. Cell. Biol.* **2008**, *28*, 2608–2625. [[CrossRef](#)] [[PubMed](#)]
25. Yi, J.; Chang, N.; Liu, X.; Guo, G.; Xue, L.; Tong, T.; Gorospe, M.; Wang, W. Reduced Nuclear Export of HuR mRNA by HuR Is Linked to the Loss of HuR in Replicative Senescence. *Nucleic Acids Res.* **2010**, *38*, 1547–1558. [[CrossRef](#)] [[PubMed](#)]
26. Rebane, A.; Aab, A.; Steitz, J.A. Transportins 1 and 2 Are Redundant Nuclear Import Factors for HnRNP A1 and HuR. *RNA* **2004**, *10*, 590–599. [[CrossRef](#)]
27. Gallouzi, I.E.; Brennan, C.M.; Steitz, J.A. Protein Ligands Mediate the CRM1-Dependent Export of HuR in Response to Heat Shock. *RNA* **2001**, *7*, 1348–1361. [[CrossRef](#)]
28. Abdelmohsen, K.; Gorospe, M. Posttranscriptional Regulation of Cancer Traits by HuR. *Wiley Interdiscip. Rev. RNA* **2010**, *1*, 214–229. [[CrossRef](#)]
29. Srikantan, S.; Gorospe, M. HuR Function in Disease. *Front. Biosci. Landmark Ed.* **2012**, *17*, 189–205. [[CrossRef](#)]
30. Kakuguchi, W.; Kitamura, T.; Kuroshima, T.; Ishikawa, M.; Kitagawa, Y.; Totsuka, Y.; Shindoh, M.; Higashino, F. HuR Knockdown Changes the Oncogenic Potential of Oral Cancer Cells. *Mol. Cancer Res.* **2010**, *8*, 520–528. [[CrossRef](#)]
31. Giles, K.M.; Daly, J.M.; Beveridge, D.J.; Thomson, A.M.; Voon, D.C.; Furneaux, H.M.; Jazayeri, J.A.; Leedman, P.J. The 3'-Untranslated Region of P21WAF1 mRNA Is a Composite Cis-Acting Sequence Bound by RNA-Binding Proteins from Breast Cancer Cells, Including HuR and Poly(C)-Binding Protein. *J. Biol. Chem.* **2003**, *278*, 2937–2946. [[CrossRef](#)] [[PubMed](#)]

32. Wang, W.; Furneaux, H.; Cheng, H.; Caldwell, M.C.; Hutter, D.; Liu, Y.; Holbrook, N.; Gorospe, M. HuR Regulates P21 mRNA Stabilization by UV Light. *Mol. Cell. Biol.* **2000**, *20*, 760–769. [[CrossRef](#)] [[PubMed](#)]
33. Lafarga, V.; Cuadrado, A.; Lopez de Silanes, I.; Bengoechea, R.; Fernandez-Capetillo, O.; Nebreda, A.R. P38 Mitogen-Activated Protein Kinase- and HuR-Dependent Stabilization of P21(Cip1) mRNA Mediates the G(1)/S Checkpoint. *Mol. Cell. Biol.* **2009**, *29*, 4341–4351. [[CrossRef](#)] [[PubMed](#)]
34. Wang, W.; Caldwell, M.C.; Lin, S.; Furneaux, H.; Gorospe, M. HuR Regulates Cyclin A and Cyclin B1 mRNA Stability during Cell Proliferation. *EMBO J.* **2000**, *19*, 2340–2350. [[CrossRef](#)] [[PubMed](#)]
35. Guo, X.; Hartley, R.S. HuR Contributes to Cyclin E1 Dereglulation in MCF-7 Breast Cancer Cells. *Cancer Res.* **2006**, *66*, 7948–7956. [[CrossRef](#)] [[PubMed](#)]
36. Guo, X.; Wu, Y.; Hartley, R.S. Cold-Inducible RNA-Binding Protein Contributes to Human Antigen R and Cyclin E1 Dereglulation in Breast Cancer. *Mol. Carcinog.* **2010**, *49*, 130–140. [[CrossRef](#)] [[PubMed](#)]
37. Durie, D.; Lewis, S.M.; Liwak, U.; Kisilewicz, M.; Gorospe, M.; Holcik, M. RNA-Binding Protein HuR Mediates Cytoprotection through Stimulation of XIAP Translation. *Oncogene* **2011**, *30*, 1460–1469. [[CrossRef](#)]
38. Cok, S.J.; Acton, S.J.; Morrison, A.R. The Proximal Region of the 3'-Untranslated Region of Cyclooxygenase-2 Is Recognized by a Multimeric Protein Complex Containing HuR, TIA-1, TIAR, and the Heterogeneous Nuclear Ribonucleoprotein U. *J. Biol. Chem.* **2003**, *278*, 36157–36162. [[CrossRef](#)]
39. Linker, K.; Pautz, A.; Fechir, M.; Hubrich, T.; Greeve, J.; Kleinert, H. Involvement of KSRP in the Post-Transcriptional Regulation of Human INOS Expression-Complex Interplay of KSRP with TTP and HuR. *Nucleic Acids Res.* **2005**, *33*, 4813–4827. [[CrossRef](#)]
40. Tschernatsch, M.M.O.; Mlecnik, B.; Trajanoski, Z.; Zechner, R.; Zimmermann, R. LPL-Mediated Lipolysis of VLDL Induces an Upregulation of AU-Rich MRNAs and an Activation of HuR in Endothelial Cells. *Atherosclerosis* **2006**, *189*, 310–317. [[CrossRef](#)]
41. Esnault, S.; Malter, J.S. Hyaluronic Acid or TNF-Alpha plus Fibronectin Triggers Granulocyte Macrophage-Colony-Stimulating Factor mRNA Stabilization in Eosinophils yet Engages Differential Intracellular Pathways and mRNA Binding Proteins. *J. Immunol.* **2003**, *171*, 6780–6787. [[CrossRef](#)] [[PubMed](#)]
42. Topisirovic, I.; Siddiqui, N.; Orolicki, S.; Skrabanek, L.A.; Tremblay, M.; Hoang, T.; Borden, K.L.B. Stability of Eukaryotic Translation Initiation Factor 4E mRNA Is Regulated by HuR, and This Activity Is Dysregulated in Cancer. *Mol. Cell. Biol.* **2009**, *29*, 1152–1162. [[CrossRef](#)] [[PubMed](#)]
43. Ghosh, M.; Aguila, H.L.; Michaud, J.; Ai, Y.; Wu, M.-T.; Hemmes, A.; Ristimaki, A.; Guo, C.; Furneaux, H.; Hla, T. Essential Role of the RNA-Binding Protein HuR in Progenitor Cell Survival in Mice. *J. Clin. Investig.* **2009**, *119*, 3530–3543. [[CrossRef](#)] [[PubMed](#)]
44. Masuda, K.; Abdelmohsen, K.; Kim, M.M.; Srikantan, S.; Lee, E.K.; Tominaga, K.; Selimyan, R.; Martindale, J.L.; Yang, X.; Lehmann, E.; et al. Global Dissociation of HuR-MRNA Complexes Promotes Cell Survival after Ionizing Radiation. *EMBO J.* **2011**, *30*, 1040–1053. [[CrossRef](#)] [[PubMed](#)]
45. Nabors, L.B.; Gillespie, G.Y.; Harkins, L.; King, P.H. HuR, a RNA Stability Factor, Is Expressed in Malignant Brain Tumors and Binds to Adenine- and Uridine-Rich Elements within the 3' Untranslated Regions of Cytokine and Angiogenic Factor MRNAs. *Cancer Res.* **2001**, *61*, 2154–2161. [[PubMed](#)]
46. Amadio, M.; Bucolo, C.; Leggio, G.M.; Drago, F.; Govoni, S.; Pascale, A. The PKCbeta/HuR/VEGF Pathway in Diabetic Retinopathy. *Biochem. Pharmacol.* **2010**, *80*, 1230–1237. [[CrossRef](#)] [[PubMed](#)]
47. Avivi, A.; Shams, I.; Joel, A.; Lache, O.; Levy, A.P.; Nevo, E. Increased Blood Vessel Density Provides the Mole Rat Physiological Tolerance to Its Hypoxic Subterranean Habitat. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2005**, *19*, 1314–1316. [[CrossRef](#)]
48. Li, X.; Lu, L.; Bush, D.J.; Zhang, X.; Zheng, L.; Suswam, E.A.; King, P.H. Mutant Copper-Zinc Superoxide Dismutase Associated with Amyotrophic Lateral Sclerosis Binds to Adenine/Uridine-Rich Stability Elements in the Vascular Endothelial Growth Factor 3'-Untranslated Region. *J. Neurochem.* **2009**, *108*, 1032–1044. [[CrossRef](#)]
49. Lu, L.; Zheng, L.; Viera, L.; Suswam, E.; Li, Y.; Li, X.; Estévez, A.G.; King, P.H. Mutant Cu/Zn-Superoxide Dismutase Associated with Amyotrophic Lateral Sclerosis Destabilizes Vascular Endothelial Growth Factor mRNA and Downregulates Its Expression. *J. Neurosci.* **2007**, *27*, 7929–7938. [[CrossRef](#)]
50. Basu, A.; Datta, D.; Zurakowski, D.; Pal, S. Altered VEGF mRNA Stability Following Treatments with Immunosuppressive Agents: Implications for Cancer Development. *J. Biol. Chem.* **2010**, *285*, 25196–25202. [[CrossRef](#)]
51. Abdelmohsen, K.; Pullmann, R.J.; Lal, A.; Kim, H.H.; Galban, S.; Yang, X.; Blethrow, J.D.; Walker, M.; Shubert, J.; Gillespie, D.A.; et al. Phosphorylation of HuR by Chk2 Regulates SIRT1 Expression. *Mol. Cell* **2007**, *25*, 543–557. [[CrossRef](#)] [[PubMed](#)]
52. Niesporek, S.; Kristiansen, G.; Thoma, A.; Weichert, W.; Noske, A.; Buckendahl, A.-C.; Jung, K.; Stephan, C.; Dietel, M.; Denkert, C. Expression of the ELAV-like Protein HuR in Human Prostate Carcinoma Is an Indicator of Disease Relapse and Linked to COX-2 Expression. *Int. J. Oncol.* **2008**, *32*, 341–347. [[CrossRef](#)] [[PubMed](#)]
53. Suzuki, E.; Tsutsumi, A.; Sugihara, M.; Mamura, M.; Goto, D.; Matsumoto, I.; Ito, S.; Ikeda, K.; Ochiai, N.; Sato, Y.; et al. Expression of TNF-Alpha, Tristetraprolin, T-Cell Intracellular Antigen-1 and Hu Antigen R Genes in Synovium of Patients with Rheumatoid Arthritis. *Int. J. Mol. Med.* **2006**, *18*, 273–278. [[PubMed](#)]
54. Abdelmohsen, K.; Lal, A.; Kim, H.H.; Gorospe, M. Posttranscriptional Orchestration of an Anti-Apoptotic Program by HuR. *Cell Cycle* **2007**, *6*, 1288–1292. [[CrossRef](#)] [[PubMed](#)]

55. Ishimaru, D.; Ramalingam, S.; Sengupta, T.K.; Bandyopadhyay, S.; Dellis, S.; Tholanikunnel, B.G.; Fernandes, D.J.; Spicer, E.K. Regulation of Bcl-2 Expression by HuR in HL60 Leukemia Cells and A431 Carcinoma Cells. *Mol. Cancer Res.* **2009**, *7*, 1354–1366. [[CrossRef](#)]
56. Bandyopadhyay, S.; Sengupta, T.K.; Spicer, E.K. PMA Induces Stabilization of Oncostatin M mRNA in Human Lymphoma U937 Cells. *Biochem. J.* **2008**, *410*, 177–186. [[CrossRef](#)]
57. Dixon, D.A.; Tolley, N.D.; King, P.H.; Nabors, L.B.; McIntyre, T.M.; Zimmerman, G.A.; Prescott, S.M. Altered Expression of the mRNA Stability Factor HuR Promotes Cyclooxygenase-2 Expression in Colon Cancer Cells. *J. Clin. Investig.* **2001**, *108*, 1657–1665. [[CrossRef](#)]
58. Lu, Z.; Luo, R.Z.; Peng, H.; Rosen, D.G.; Atkinson, E.N.; Warneke, C.; Huang, M.; Nishimoto, A.; Liu, J.; Liao, W.S.-L.; et al. Transcriptional and Posttranscriptional Down-Regulation of the Imprinted Tumor Suppressor Gene ARHI (DRAS3) in Ovarian Cancer. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2006**, *12*, 2404–2413. [[CrossRef](#)]
59. Young, L.E.; Sanduja, S.; Bemis-Standoli, K.; Pena, E.A.; Price, R.L.; Dixon, D.A. The mRNA Binding Proteins HuR and Tristetraprolin Regulate Cyclooxygenase 2 Expression during Colon Carcinogenesis. *Gastroenterology* **2009**, *136*, 1669–1679. [[CrossRef](#)]
60. Erkinheimo, T.-L.; Lassus, H.; Sivula, A.; Sengupta, S.; Furneaux, H.; Hla, T.; Haglund, C.; Butzow, R.; Ristimäki, A. Cytoplasmic HuR Expression Correlates with Poor Outcome and with Cyclooxygenase 2 Expression in Serous Ovarian Carcinoma. *Cancer Res.* **2003**, *63*, 7591–7594.
61. Barbisan, F.; Mazzucchelli, R.; Santinelli, A.; Lopez-Beltran, A.; Cheng, L.; Scarpelli, M.; Montorsi, F.; Montironi, R. Overexpression of ELAV-like Protein HuR Is Associated with Increased COX-2 Expression in Atrophy, High-Grade Prostatic Intraepithelial Neoplasia, and Incidental Prostate Cancer in Cystoprostatectomies. *Eur. Urol.* **2009**, *56*, 105–112. [[CrossRef](#)]
62. Mrena, J.; Wiksten, J.-P.; Thiel, A.; Kokkola, A.; Pohjola, L.; Lundin, J.; Nordling, S.; Ristimäki, A.; Haglund, C. Cyclooxygenase-2 Is an Independent Prognostic Factor in Gastric Cancer and Its Expression Is Regulated by the Messenger RNA Stability Factor HuR. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2005**, *11*, 7362–7368. [[CrossRef](#)] [[PubMed](#)]
63. Song, I.-S.; Tatebe, S.; Dai, W.; Kuo, M.T. Delayed Mechanism for Induction of Gamma-Glutamylcysteine Synthetase Heavy Subunit mRNA Stability by Oxidative Stress Involving P38 Mitogen-Activated Protein Kinase Signaling. *J. Biol. Chem.* **2005**, *280*, 28230–28240. [[CrossRef](#)] [[PubMed](#)]
64. Farooq, F.; Balabanian, S.; Liu, X.; Holcik, M.; MacKenzie, A. P38 Mitogen-Activated Protein Kinase Stabilizes SMN mRNA through RNA Binding Protein HuR. *Hum. Mol. Genet.* **2009**, *18*, 4035–4045. [[CrossRef](#)] [[PubMed](#)]
65. Okamoto, S.; Ji, H.; Howie, D.; Clarke, K.; Gullo, C.; Manning, S.; Coyle, A.J.; Terhorst, C. Expression of the SH2D1A Gene Is Regulated by a Combination of Transcriptional and Post-Transcriptional Mechanisms. *Eur. J. Immunol.* **2004**, *34*, 3176–3186. [[CrossRef](#)]
66. Li, F.; Hu, D.Y.; Liu, S.; Mahavadi, S.; Yen, W.; Murthy, K.S.; Khalili, K.; Hu, W. RNA-Binding Protein HuR Regulates RGS4 mRNA Stability in Rabbit Colonic Smooth Muscle Cells. *Am. J. Physiol. Cell Physiol.* **2010**, *299*, C1418–C1429. [[CrossRef](#)]
67. Danilin, S.; Sourbier, C.; Thomas, L.; Rothhut, S.; Lindner, V.; Helwig, J.-J.; Jacqmin, D.; Lang, H.; Massfelder, T. Von Hippel-Lindau Tumor Suppressor Gene-Dependent mRNA Stabilization of the Survival Factor Parathyroid Hormone-Related Protein in Human Renal Cell Carcinoma by the RNA-Binding Protein HuR. *Carcinogenesis* **2009**, *30*, 387–396. [[CrossRef](#)]
68. Drury, G.L.; Di Marco, S.; Dormoy-Raclet, V.; Desbarats, J.; Gallouzi, I.-E. FasL Expression in Activated T Lymphocytes Involves HuR-Mediated Stabilization. *J. Biol. Chem.* **2010**, *285*, 31130–31138. [[CrossRef](#)]
69. Figueroa, A.; Cuadrado, A.; Fan, J.; Atasoy, U.; Muscat, G.E.; Muñoz-Canoves, P.; Gorospe, M.; Muñoz, A. Role of HuR in Skeletal Myogenesis through Coordinate Regulation of Muscle Differentiation Genes. *Mol. Cell. Biol.* **2003**, *23*, 4991–5004. [[CrossRef](#)]
70. van der Giessen, K.; Di-Marco, S.; Clair, E.; Gallouzi, I.E. RNAi-Mediated HuR Depletion Leads to the Inhibition of Muscle Cell Differentiation. *J. Biol. Chem.* **2003**, *278*, 47119–47128. [[CrossRef](#)]
71. Deschênes-Furry, J.; Bélanger, G.; Mwanjewe, J.; Lunde, J.A.; Parks, R.J.; Perrone-Bizzozero, N.; Jasmin, B.J. The RNA-Binding Protein HuR Binds to Acetylcholinesterase Transcripts and Regulates Their Expression in Differentiating Skeletal Muscle Cells. *J. Biol. Chem.* **2005**, *280*, 25361–25368. [[CrossRef](#)]
72. Bronicki, L.M.; Jasmin, B.J. Trans-Acting Factors Governing Acetylcholinesterase mRNA Metabolism in Neurons. *Front. Mol. Neurosci.* **2012**, *5*, 36. [[CrossRef](#)] [[PubMed](#)]
73. Mazan-Mamczarz, K.; Galbán, S.; López de Silanes, I.; Martindale, J.L.; Atasoy, U.; Keene, J.D.; Gorospe, M. RNA-Binding Protein HuR Enhances P53 Translation in Response to Ultraviolet Light Irradiation. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 8354–8359. [[CrossRef](#)] [[PubMed](#)]
74. Zou, T.; Mazan-Mamczarz, K.; Rao, J.N.; Liu, L.; Marasa, B.S.; Zhang, A.-H.; Xiao, L.; Pullmann, R.; Gorospe, M.; Wang, J.-Y. Polyamine Depletion Increases Cytoplasmic Levels of RNA-Binding Protein HuR Leading to Stabilization of Nucleophosmin and P53 MRNAs. *J. Biol. Chem.* **2006**, *281*, 19387–19394. [[CrossRef](#)] [[PubMed](#)]
75. de Frutos, S.; Nitta, C.H.; Caldwell, E.; Friedman, J.; González Bosc, L.V. Regulation of Soluble Guanylyl Cyclase-Alpha1 Expression in Chronic Hypoxia-Induced Pulmonary Hypertension: Role of NFATc3 and HuR. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2009**, *297*, L475–L486. [[CrossRef](#)]
76. Tran, H.; Maurer, F.; Nagamine, Y. Stabilization of Urokinase and Urokinase Receptor MRNAs by HuR Is Linked to Its Cytoplasmic Accumulation Induced by Activated Mitogen-Activated Protein Kinase-Activated Protein Kinase 2. *Mol. Cell. Biol.* **2003**, *23*, 7177–7188. [[CrossRef](#)]

77. Haeussler, J.; Haeusler, J.; Striebel, A.M.; Assum, G.; Vogel, W.; Furneaux, H.; Krone, W. Tumor Antigen HuR Binds Specifically to One of Five Protein-Binding Segments in the 3'-Untranslated Region of the Neurofibromin Messenger RNA. *Biochem. Biophys. Res. Commun.* **2000**, *267*, 726–732. [[CrossRef](#)]
78. Abdelmohsen, K.; Srikantan, S.; Yang, X.; Lal, A.; Kim, H.H.; Kuwano, Y.; Galban, S.; Becker, K.G.; Kamara, D.; de Cabo, R.; et al. Ubiquitin-Mediated Proteolysis of HuR by Heat Shock. *EMBO J.* **2009**, *28*, 1271–1282. [[CrossRef](#)]
79. Lin, F.-Y.; Chen, Y.-H.; Lin, Y.-W.; Tsai, J.-S.; Chen, J.-W.; Wang, H.-J.; Chen, Y.-L.; Li, C.-Y.; Lin, S.-J. The Role of Human Antigen R, an RNA-Binding Protein, in Mediating the Stabilization of Toll-like Receptor 4 mRNA Induced by Endotoxin: A Novel Mechanism Involved in Vascular Inflammation. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 2622–2629. [[CrossRef](#)]
80. Dong, R.; Lu, J.-G.; Wang, Q.; He, X.-L.; Chu, Y.-K.; Ma, Q.-J. Stabilization of Snail by HuR in the Process of Hydrogen Peroxide Induced Cell Migration. *Biochem. Biophys. Res. Commun.* **2007**, *356*, 318–321. [[CrossRef](#)]
81. Annabi, B.; Bouzeghrane, M.; Currie, J.-C.; Dulude, H.; Daigneault, L.; Garde, S.; Rabbani, S.A.; Panchal, C.; Wu, J.J.; Béliveau, R. Inhibition of MMP-9 Secretion by the Anti-Metastatic PSP94-Derived Peptide PCK3145 Requires Cell Surface Laminin Receptor Signaling. *Anticancer. Drugs* **2006**, *17*, 429–438. [[CrossRef](#)] [[PubMed](#)]
82. Annabi, B.; Currie, J.-C.; Moghrabi, A.; Béliveau, R. Inhibition of HuR and MMP-9 Expression in Macrophage-Differentiated HL-60 Myeloid Leukemia Cells by Green Tea Polyphenol EGCG. *Leuk. Res.* **2007**, *31*, 1277–1284. [[CrossRef](#)] [[PubMed](#)]
83. Krishnamurthy, P.; Rajasingh, J.; Lambers, E.; Qin, G.; Losordo, D.W.; Kishore, R. IL-10 Inhibits Inflammation and Attenuates Left Ventricular Remodeling after Myocardial Infarction via Activation of STAT3 and Suppression of HuR. *Circ. Res.* **2009**, *104*, e9–e18. [[CrossRef](#)] [[PubMed](#)]
84. Akool, E.-S.; Kleinert, H.; Hamada, F.M.A.; Abdelwahab, M.H.; Förstermann, U.; Pfeilschifter, J.; Eberhardt, W. Nitric Oxide Increases the Decay of Matrix Metalloproteinase 9 mRNA by Inhibiting the Expression of mRNA-Stabilizing Factor HuR. *Mol. Cell. Biol.* **2003**, *23*, 4901–4916. [[CrossRef](#)]
85. Huwiler, A.; Akool, e.-S.; Aschrafi, A.; Hamada, F.M.A.; Pfeilschifter, J.; Eberhardt, W. ATP Potentiates Interleukin-1 Beta-Induced MMP-9 Expression in Mesangial Cells via Recruitment of the ELAV Protein HuR. *J. Biol. Chem.* **2003**, *278*, 51758–51769. [[CrossRef](#)]
86. Woo, H.-H.; Zhou, Y.; Yi, X.; David, C.L.; Zheng, W.; Gilmore-Hebert, M.; Kluger, H.M.; Ulukus, E.C.; Baker, T.; Stoffer, J.B.; et al. Regulation of Non-AU-Rich Element Containing c-Fms Proto-Oncogene Expression by HuR in Breast Cancer. *Oncogene* **2009**, *28*, 1176–1186. [[CrossRef](#)]
87. Kuwano, Y.; Kim, H.H.; Abdelmohsen, K.; Pullmann, R.J.; Martindale, J.L.; Yang, X.; Gorospe, M. MKP-1 mRNA Stabilization and Translational Control by RNA-Binding Proteins HuR and NF90. *Mol. Cell. Biol.* **2008**, *28*, 4562–4575. [[CrossRef](#)]
88. Wang, J.G.; Collinge, M.; Ramgolam, V.; Ayalon, O.; Fan, X.C.; Pardi, R.; Bender, J.R. LFA-1-Dependent HuR Nuclear Export and Cytokine mRNA Stabilization in T Cell Activation. *J. Immunol.* **2006**, *176*, 2105–2113. [[CrossRef](#)]
89. Ming, X.F.; Stoecklin, G.; Lu, M.; Looser, R.; Moroni, C. Parallel and Independent Regulation of Interleukin-3 mRNA Turnover by Phosphatidylinositol 3-Kinase and P38 Mitogen-Activated Protein Kinase. *Mol. Cell. Biol.* **2001**, *21*, 5778–5789. [[CrossRef](#)]
90. Yarovinsky, T.O.; Butler, N.S.; Monick, M.M.; Hunninghake, G.W. Early Exposure to IL-4 Stabilizes IL-4 mRNA in CD4+ T Cells via RNA-Binding Protein HuR. *J. Immunol.* **2006**, *177*, 4426–4435. [[CrossRef](#)]
91. Gealy, C.; Denson, M.; Humphreys, C.; McSharry, B.; Wilkinson, G.; Caswell, R. Posttranscriptional Suppression of Interleukin-6 Production by Human Cytomegalovirus. *J. Virol.* **2005**, *79*, 472–485. [[CrossRef](#)] [[PubMed](#)]
92. Zhou, H.; Jarujaron, S.; Gurley, E.C.; Chen, L.; Ding, H.; Studer, E.; Pandak, W.M.J.; Hu, W.; Zou, T.; Wang, J.-Y.; et al. HIV Protease Inhibitors Increase TNF-Alpha and IL-6 Expression in Macrophages: Involvement of the RNA-Binding Protein HuR. *Atherosclerosis* **2007**, *195*, e134–e143. [[CrossRef](#)] [[PubMed](#)]
93. Suswam, E.A.; Nabors, L.B.; Huang, Y.; Yang, X.; King, P.H. IL-1beta Induces Stabilization of IL-8 mRNA in Malignant Breast Cancer Cells via the 3' Untranslated Region: Involvement of Divergent RNA-Binding Factors HuR, KSRP and TIAR. *Int. J. Cancer* **2005**, *113*, 911–919. [[CrossRef](#)] [[PubMed](#)]
94. Pullmann Jr, R.; Kim, H.H.; Abdelmohsen, K.; Lal, A.; Martindale, J.L.; Yang, X.; Gorospe, M. Analysis of Turnover and Translation Regulatory RNA-Binding Protein Expression through Binding to Cognate MRNAs. *Mol. Cell. Biol.* **2007**, *27*, 6265–6278. [[CrossRef](#)]
95. Al-Ahmadi, W.; Al-Ghamdi, M.; Al-Haj, L.; Al-Saif, M.; Khabar, K.S.A. Alternative Polyadenylation Variants of the RNA Binding Protein, HuR: Abundance, Role of AU-Rich Elements and Auto-Regulation. *Nucleic Acids Res.* **2009**, *37*, 3612–3624. [[CrossRef](#)] [[PubMed](#)]
96. Mrena, J.; Wiksten, J.-P.; Kokkola, A.; Nordling, S.; Haglund, C.; Ristimäki, A. Prognostic Significance of Cyclin A in Gastric Cancer. *Int. J. Cancer* **2006**, *119*, 1897–1901. [[CrossRef](#)]
97. Lal, A.; Kawai, T.; Yang, X.; Mazan-Mamczarz, K.; Gorospe, M. Antiapoptotic Function of RNA-Binding Protein HuR Effected through Prothymosin Alpha. *EMBO J.* **2005**, *24*, 1852–1862. [[CrossRef](#)]
98. Galbán, S.; Kuwano, Y.; Pullmann, R.J.; Martindale, J.L.; Kim, H.H.; Lal, A.; Abdelmohsen, K.; Yang, X.; Dang, Y.; Liu, J.O.; et al. RNA-Binding Proteins HuR and PTB Promote the Translation of Hypoxia-Inducible Factor 1alpha. *Mol. Cell. Biol.* **2008**, *28*, 93–107. [[CrossRef](#)]
99. Ayupova, D.A.; Singh, M.; Leonard, E.C.; Basile, D.P.; Lee, B.S. Expression of the RNA-Stabilizing Protein HuR in Ischemia-Reperfusion Injury of Rat Kidney. *Am. J. Physiol. Renal Physiol.* **2009**, *297*, F95–F105. [[CrossRef](#)]
100. Wang, J.; Zhao, W.; Guo, Y.; Zhang, B.; Xie, Q.; Xiang, D.; Gao, J.; Wang, B.; Chen, Z. The Expression of RNA-Binding Protein HuR in Non-Small Cell Lung Cancer Correlates with Vascular Endothelial Growth Factor-C Expression and Lymph Node Metastasis. *Oncology* **2009**, *76*, 420–429. [[CrossRef](#)]

101. Ido, K.; Nakagawa, T.; Sakuma, T.; Takeuchi, H.; Sato, K.; Kubota, T. Expression of Vascular Endothelial Growth Factor-A and mRNA Stability Factor HuR in Human Astrocytic Tumors. *Neuropathology* **2008**, *28*, 604–611. [[CrossRef](#)] [[PubMed](#)]
102. Sakuma, T.; Nakagawa, T.; Ido, K.; Takeuchi, H.; Sato, K.; Kubota, T. Expression of Vascular Endothelial Growth Factor-A and mRNA Stability Factor HuR in Human Meningiomas. *J. Neurooncol.* **2008**, *88*, 143–155. [[CrossRef](#)] [[PubMed](#)]
103. Mazan-Mamczarz, K.; Hagner, P.R.; Corl, S.; Srikantan, S.; Wood, W.H.; Becker, K.G.; Gorospe, M.; Keene, J.D.; Levenson, A.S.; Gartenhaus, R.B. Post-Transcriptional Gene Regulation by HuR Promotes a More Tumorigenic Phenotype. *Oncogene* **2008**, *27*, 6151–6163. [[CrossRef](#)] [[PubMed](#)]
104. Bhattacharyya, S.N.; Habermacher, R.; Martine, U.; Closs, E.I.; Filipowicz, W. Relief of MicroRNA-Mediated Translational Repression in Human Cells Subjected to Stress. *Cell* **2006**, *125*, 1111–1124. [[CrossRef](#)]
105. Kawai, T.; Lal, A.; Yang, X.; Galban, S.; Mazan-Mamczarz, K.; Gorospe, M. Translational Control of Cytochrome c by RNA-Binding Proteins TIA-1 and HuR. *Mol. Cell. Biol.* **2006**, *26*, 3295–3307. [[CrossRef](#)] [[PubMed](#)]
106. Kullmann, M.; Göpfert, U.; Siewe, B.; Hengst, L. ELAV/Hu Proteins Inhibit P27 Translation via an IRES Element in the P27 5'UTR. *Genes Dev.* **2002**, *16*, 3087–3099. [[CrossRef](#)]
107. Meng, Z.; King, P.H.; Nabors, L.B.; Jackson, N.L.; Chen, C.-Y.; Emanuel, P.D.; Blume, S.W. The ELAV RNA-Stability Factor HuR Binds the 5'-Untranslated Region of the Human IGF-IR Transcript and Differentially Represses Cap-Dependent and IRES-Mediated Translation. *Nucleic Acids Res.* **2005**, *33*, 2962–2979. [[CrossRef](#)]
108. Yeh, C.-H.; Hung, L.-Y.; Hsu, C.; Le, S.-Y.; Lee, P.-T.; Liao, W.-L.; Lin, Y.-T.; Chang, W.-C.; Tseng, J.T. RNA-Binding Protein HuR Interacts with Thrombomodulin 5'untranslated Region and Represses Internal Ribosome Entry Site-Mediated Translation under IL-1 Beta Treatment. *Mol. Biol. Cell* **2008**, *19*, 3812–3822. [[CrossRef](#)]
109. Leandersson, K.; Riesbeck, K.; Andersson, T. Wnt-5a mRNA Translation Is Suppressed by the Elav-like Protein HuR in Human Breast Epithelial Cells. *Nucleic Acids Res.* **2006**, *34*, 3988–3999. [[CrossRef](#)]
110. Kim, H.H.; Kuwano, Y.; Srikantan, S.; Lee, E.K.; Martindale, J.L.; Gorospe, M. HuR Recruits Let-7/RISC to Repress c-Myc Expression. *Genes Dev.* **2009**, *23*, 1743–1748. [[CrossRef](#)]
111. Yoon, J.-H.; Abdelmohsen, K.; Kim, J.; Yang, X.; Martindale, J.L.; Tominaga-Yamanaka, K.; White, E.J.; Orjalo, A.V.; Rinn, J.L.; Kreft, S.G.; et al. Scaffold Function of Long Non-Coding RNA HOTAIR in Protein Ubiquitination. *Nat. Commun.* **2013**, *4*, 2939. [[CrossRef](#)] [[PubMed](#)]
112. Lu, Y.-C.; Chang, S.-H.; Hafner, M.; Li, X.; Tuschl, T.; Elemento, O.; Hla, T. ELAVL1 Modulates Transcriptome-Wide MiRNA Binding in Murine Macrophages. *Cell Rep.* **2014**, *9*, 2330–2343. [[CrossRef](#)] [[PubMed](#)]
113. Poria, D.K.; Guha, A.; Nandi, I.; Ray, P.S. RNA-Binding Protein HuR Sequesters MicroRNA-21 to Prevent Translation Repression of Proinflammatory Tumor Suppressor Gene Programmed Cell Death 4. *Oncogene* **2016**, *35*, 1703–1715. [[CrossRef](#)] [[PubMed](#)]
114. Mukherjee, K.; Ghoshal, B.; Ghosh, S.; Chakrabarty, Y.; Shwetha, S.; Das, S.; Bhattacharyya, S.N. Reversible HuR-MicroRNA Binding Controls Extracellular Export of MiR-122 and Augments Stress Response. *EMBO Rep.* **2016**, *17*, 1184–1203. [[CrossRef](#)] [[PubMed](#)]
115. Yoon, J.-H.; Abdelmohsen, K.; Srikantan, S.; Yang, X.; Martindale, J.L.; De, S.; Huarte, M.; Zhan, M.; Becker, K.G.; Gorospe, M. LincRNA-P21 Suppresses Target mRNA Translation. *Mol. Cell* **2012**, *47*, 648–655. [[CrossRef](#)]
116. Chai, Y.; Liu, J.; Zhang, Z.; Liu, L. HuR-Regulated LncRNA NEAT1 Stability in Tumorigenesis and Progression of Ovarian Cancer. *Cancer Med.* **2016**, *5*, 1588–1598. [[CrossRef](#)]
117. Zou, T.; Jaladanki, S.K.; Liu, L.; Xiao, L.; Chung, H.K.; Wang, J.-Y.; Xu, Y.; Gorospe, M.; Wang, J.-Y. H19 Long Noncoding RNA Regulates Intestinal Epithelial Barrier Function via MicroRNA 675 by Interacting with RNA-Binding Protein HuR. *Mol. Cell. Biol.* **2016**, *36*, 1332–1341. [[CrossRef](#)]
118. Jeyaraj, S.C.; Singh, M.; Ayupova, D.A.; Govindaraju, S.; Lee, B.S. Transcriptional Control of Human Antigen R by Bone Morphogenetic Protein. *J. Biol. Chem.* **2010**, *285*, 4432–4440. [[CrossRef](#)]
119. Kang, M.-J.; Ryu, B.-K.; Lee, M.-G.; Han, J.; Lee, J.-H.; Ha, T.-K.; Byun, D.-S.; Chae, K.-S.; Lee, B.-H.; Chun, H.S.; et al. NF-KappaB Activates Transcription of the RNA-Binding Factor HuR, via PI3K-AKT Signaling, to Promote Gastric Tumorigenesis. *Gastroenterology* **2008**, *135*, 2030–2042.e3. [[CrossRef](#)]
120. Dai, W.; Zhang, G.; Makeyev, E.V. RNA-Binding Protein HuR Autoregulates Its Expression by Promoting Alternative Polyadenylation Site Usage. *Nucleic Acids Res.* **2012**, *40*, 787–800. [[CrossRef](#)]
121. Singh, M.; Martinez, A.R.; Govindaraju, S.; Lee, B.S. HuR Inhibits Apoptosis by Amplifying Akt Signaling through a Positive Feedback Loop. *J. Cell. Physiol.* **2013**, *228*, 182–189. [[CrossRef](#)] [[PubMed](#)]
122. Chang, N.; Ge, J.; Xiu, L.; Zhao, Z.; Duan, X.; Tian, L.; Xie, J.; Yang, L.; Li, L. HuR Mediates Motility of Human Bone Marrow-Derived Mesenchymal Stem Cells Triggered by Sphingosine 1-Phosphate in Liver Fibrosis. *J. Mol. Med.* **2017**, *95*, 69–82. [[CrossRef](#)] [[PubMed](#)]
123. Bai, D.; Gao, Q.; Li, C.; Ge, L.; Gao, Y.; Wang, H. A Conserved TGFβ1/HuR Feedback Circuit Regulates the Fibrogenic Response in Fibroblasts. *Cell. Signal.* **2012**, *24*, 1426–1432. [[CrossRef](#)] [[PubMed](#)]
124. Guha, A.; Nag, S.; Ray, P.S. Negative Feedback Regulation by HuR Controls TRIM21 Expression and Function in Response to UV Radiation. *Sci. Rep.* **2020**, *10*, 11753. [[CrossRef](#)]
125. Guo, X.; Wu, Y.; Hartley, R.S. MicroRNA-125a Represses Cell Growth by Targeting HuR in Breast Cancer. *RNA Biol.* **2009**, *6*, 575–583. [[CrossRef](#)]

126. Abdelmohsen, K.; Kim, M.M.; Srikantan, S.; Mercken, E.M.; Brennan, S.E.; Wilson, G.M.; de Cabo, R.; Gorospe, M. MiR-519 Suppresses Tumor Growth by Reducing HuR Levels. *Cell Cycle* **2010**, *9*, 1354–1359. [[CrossRef](#)]
127. Leucci, E.; Zriwil, A.; Gregersen, L.H.; Jensen, K.T.; Obad, S.; Bellan, C.; Leoncini, L.; Kauppinen, S.; Lund, A.H. Inhibition of MiR-9 de-Represses HuR and DICER1 and Impairs Hodgkin Lymphoma Tumour Outgrowth in Vivo. *Oncogene* **2012**, *31*, 5081–5089. [[CrossRef](#)]
128. Guo, J.; Li, M.; Meng, X.; Sui, J.; Dou, L.; Tang, W.; Huang, X.; Man, Y.; Wang, S.; Li, J. MiR-291b-3p Induces Apoptosis in Liver Cell Line NCTC1469 by Reducing the Level of RNA-Binding Protein HuR. *Cell. Physiol. Biochem. Int. J. Exp. Cell. Physiol. Biochem. Pharmacol.* **2014**, *33*, 810–822. [[CrossRef](#)]
129. Roff, A.N.; Craig, T.J.; August, A.; Stellato, C.; Ishmael, F.T. MicroRNA-570-3p Regulates HuR and Cytokine Expression in Airway Epithelial Cells. *Am. J. Clin. Exp. Immunol.* **2014**, *3*, 68–83.
130. Guo, X.; Connick, M.C.; Vanderhoof, J.; Ishak, M.-A.; Hartley, R.S. MicroRNA-16 Modulates HuR Regulation of Cyclin E1 in Breast Cancer Cells. *Int. J. Mol. Sci.* **2015**, *16*, 7112–7132. [[CrossRef](#)]
131. Liu, Y.; Chen, X.; Cheng, R.; Yang, F.; Yu, M.; Wang, C.; Cui, S.; Hong, Y.; Liang, H.; Liu, M.; et al. The Jun/MiR-22/HuR Regulatory Axis Contributes to Tumourigenesis in Colorectal Cancer. *Mol. Cancer* **2018**, *17*, 11. [[CrossRef](#)] [[PubMed](#)]
132. Al-Haidari, A.; Algaber, A.; Madhi, R.; Syk, I.; Thorlacius, H. MiR-155-5p Controls Colon Cancer Cell Migration via Post-Transcriptional Regulation of Human Antigen R (HuR). *Cancer Lett.* **2018**, *421*, 145–151. [[CrossRef](#)] [[PubMed](#)]
133. Li, H.; Park, S.; Kilburn, B.; Jelinek, M.A.; Henschen-Edman, A.; Aswad, D.W.; Stallcup, M.R.; Laird-Offringa, I.A. Lipopolysaccharide-Induced Methylation of HuR, an mRNA-Stabilizing Protein, by CARM1. Coactivator-Associated Arginine Methyltransferase. *J. Biol. Chem.* **2002**, *277*, 44623–44630. [[CrossRef](#)]
134. Calvanese, V.; Lara, E.; Suárez-Alvarez, B.; Abu Dawud, R.; Vázquez-Chantada, M.; Martínez-Chantar, M.L.; Embade, N.; López-Nieva, P.; Horrillo, A.; Hmadcha, A.; et al. Sirtuin 1 Regulation of Developmental Genes during Differentiation of Stem Cells. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 13736–13741. [[CrossRef](#)]
135. Pang, L.; Tian, H.; Chang, N.; Yi, J.; Xue, L.; Jiang, B.; Gorospe, M.; Zhang, X.; Wang, W. Loss of CARM1 Is Linked to Reduced HuR Function in Replicative Senescence. *BMC Mol. Biol.* **2013**, *14*, 15. [[CrossRef](#)] [[PubMed](#)]
136. Vigouroux, C.; Casse, J.-M.; Battaglia-Hsu, S.-F.; Brochin, L.; Luc, A.; Paris, C.; Lacomme, S.; Gueant, J.-L.; Vignaud, J.-M.; Gauchotte, G. Methyl(R217)HuR and MCM6 Are Inversely Correlated and Are Prognostic Markers in Non Small Cell Lung Carcinoma. *Lung Cancer* **2015**, *89*, 189–196. [[CrossRef](#)] [[PubMed](#)]
137. Filippova, N.; Yang, X.; Nabors, L.B. Growth Factor Dependent Regulation of Centrosome Function and Genomic Instability by HuR. *Biomolecules* **2015**, *5*, 263–281. [[CrossRef](#)]
138. Yoon, J.-H.; Abdelmohsen, K.; Srikantan, S.; Guo, R.; Yang, X.; Martindale, J.L.; Gorospe, M. Tyrosine Phosphorylation of HuR by JAK3 Triggers Dissociation and Degradation of HuR Target MRNAs. *Nucleic Acids Res.* **2014**, *42*, 1196–1208. [[CrossRef](#)]
139. Yu, T.-X.; Wang, P.-Y.; Rao, J.N.; Zou, T.; Liu, L.; Xiao, L.; Gorospe, M.; Wang, J.-Y. Chk2-Dependent HuR Phosphorylation Regulates Occludin mRNA Translation and Epithelial Barrier Function. *Nucleic Acids Res.* **2011**, *39*, 8472–8487. [[CrossRef](#)]
140. Akaike, Y.; Masuda, K.; Kuwano, Y.; Nishida, K.; Kajita, K.; Kurokawa, K.; Satake, Y.; Shoda, K.; Imoto, I.; Rokutan, K. HuR Regulates Alternative Splicing of the TRA2 β Gene in Human Colon Cancer Cells under Oxidative Stress. *Mol. Cell. Biol.* **2014**, *34*, 2857–2873. [[CrossRef](#)]
141. Liu, L.; Rao, J.N.; Zou, T.; Xiao, L.; Wang, P.-Y.; Turner, D.J.; Gorospe, M.; Wang, J.-Y. Polyamines Regulate C-Myc Translation through Chk2-Dependent HuR Phosphorylation. *Mol. Biol. Cell* **2009**, *20*, 4885–4898. [[CrossRef](#)] [[PubMed](#)]
142. Liao, W.-L.; Wang, W.-C.; Chang, W.-C.; Tseng, J.T. The RNA-Binding Protein HuR Stabilizes Cytosolic Phospholipase A2 α mRNA under Interleukin-1 β Treatment in Non-Small Cell Lung Cancer A549 Cells. *J. Biol. Chem.* **2011**, *286*, 35499–35508. [[CrossRef](#)] [[PubMed](#)]
143. Doller, A.; Huwiler, A.; Müller, R.; Radeke, H.H.; Pfeilschifter, J.; Eberhardt, W. Protein Kinase C Alpha-Dependent Phosphorylation of the mRNA-Stabilizing Factor HuR: Implications for Posttranscriptional Regulation of Cyclooxygenase-2. *Mol. Biol. Cell* **2007**, *18*, 2137–2148. [[CrossRef](#)] [[PubMed](#)]
144. Kim, H.H.; Abdelmohsen, K.; Lal, A.; Pullmann, R.J.; Yang, X.; Galban, S.; Srikantan, S.; Martindale, J.L.; Blethrow, J.; Shokat, K.M.; et al. Nuclear HuR Accumulation through Phosphorylation by Cdk1. *Genes Dev.* **2008**, *22*, 1804–1815. [[CrossRef](#)]
145. Filippova, N.; Yang, X.; King, P.; Nabors, L.B. Phosphoregulation of the RNA-Binding Protein Hu Antigen R (HuR) by Cdk5 Affects Centrosome Function. *J. Biol. Chem.* **2012**, *287*, 32277–32287. [[CrossRef](#)]
146. Kim, H.H.; Yang, X.; Kuwano, Y.; Gorospe, M. Modification at HuR(S242) Alters HuR Localization and Proliferative Influence. *Cell Cycle* **2008**, *7*, 3371–3377. [[CrossRef](#)]
147. Chu, P.-C.; Chuang, H.-C.; Kulp, S.K.; Chen, C.-S. The mRNA-Stabilizing Factor HuR Protein Is Targeted by β -TrCP Protein for Degradation in Response to Glycolysis Inhibition. *J. Biol. Chem.* **2012**, *287*, 43639–43650. [[CrossRef](#)]
148. Doller, A.; Winkler, C.; Azrilian, I.; Schulz, S.; Hartmann, S.; Pfeilschifter, J.; Eberhardt, W. High-Constitutive HuR Phosphorylation at Ser 318 by PKC δ Propagates Tumor Relevant Functions in Colon Carcinoma Cells. *Carcinogenesis* **2011**, *32*, 676–685. [[CrossRef](#)]
149. Latorre, E.; Castiglioni, I.; Gatto, P.; Carelli, S.; Quattrone, A.; Provenzani, A. Loss of Protein Kinase C δ /HuR Interaction Is Necessary to Doxorubicin Resistance in Breast Cancer Cell Lines. *J. Pharmacol. Exp. Ther.* **2014**, *349*, 99–106. [[CrossRef](#)]
150. Ubersax, J.A.; Woodbury, E.L.; Quang, P.N.; Paraz, M.; Blethrow, J.D.; Shah, K.; Shokat, K.M.; Morgan, D.O. Targets of the Cyclin-Dependent Kinase Cdk1. *Nature* **2003**, *425*, 859–864. [[CrossRef](#)]

151. Degese, M.S.; Tanos, T.; Naipauer, J.; Gingerich, T.; Chiappe, D.; Echeverria, P.; LaMarre, J.; Gutkind, J.S.; Coso, O.A. An Interplay between the P38 MAPK Pathway and AUBPs Regulates C-Fos mRNA Stability during Mitogenic Stimulation. *Biochem. J.* **2015**, *467*, 77–90. [[CrossRef](#)] [[PubMed](#)]
152. Doller, A.; Schlepckow, K.; Schwalbe, H.; Pfeilschifter, J.; Eberhardt, W. Tandem Phosphorylation of Serines 221 and 318 by Protein Kinase Cdelta Coordinates mRNA Binding and Nucleocytoplasmic Shuttling of HuR. *Mol. Cell. Biol.* **2010**, *30*, 1397–1410. [[CrossRef](#)] [[PubMed](#)]
153. Fialcowitz-White, E.J.; Brewer, B.Y.; Ballin, J.D.; Willis, C.D.; Toth, E.A.; Wilson, G.M. Specific Protein Domains Mediate Cooperative Assembly of HuR Oligomers on AU-Rich MRNA-Destabilizing Sequences. *J. Biol. Chem.* **2007**, *282*, 20948–20959. [[CrossRef](#)] [[PubMed](#)]
154. Liwak-Muir, U.; Dobson, C.C.; Naing, T.; Wylie, Q.; Chehade, L.; Baird, S.D.; Chakraborty, P.K.; Holcik, M. ERK8 Is a Novel HuR Kinase That Regulates Tumour Suppressor PDCD4 through a MiR-21 Dependent Mechanism. *Oncotarget* **2016**, *7*, 1439–1450. [[CrossRef](#)]
155. Bergalet, J.; Fawal, M.; Lopez, C.; Desjobert, C.; Lamant, L.; Delsol, G.; Morello, D.; Espinos, E. HuR-Mediated Control of C/EBPbeta mRNA Stability and Translation in ALK-Positive Anaplastic Large Cell Lymphomas. *Mol. Cancer Res.* **2011**, *9*, 485–496. [[CrossRef](#)]
156. Gummadi, L.; Taylor, L.; Curthoys, N.P. Concurrent Binding and Modifications of AUF1 and HuR Mediate the PH-Responsive Stabilization of Phosphoenolpyruvate Carboxykinase mRNA in Kidney Cells. *Am. J. Physiol. Renal Physiol.* **2012**, *303*, F1545–F1554. [[CrossRef](#)]
157. Dickson, A.M.; Anderson, J.R.; Barnhart, M.D.; Sokoloski, K.J.; Oko, L.; Opyrchal, M.; Galanis, E.; Wilusz, C.J.; Morrison, T.E.; Wilusz, J. Dephosphorylation of HuR Protein during Alphavirus Infection Is Associated with HuR Relocalization to the Cytoplasm. *J. Biol. Chem.* **2012**, *287*, 36229–36238. [[CrossRef](#)]
158. Mazroui, R.; Di Marco, S.; Clair, E.; von Roretz, C.; Tenenbaum, S.A.; Keene, J.D.; Saleh, M.; Gallouzi, I.-E. Caspase-Mediated Cleavage of HuR in the Cytoplasm Contributes to Pp32/PHAP-I Regulation of Apoptosis. *J. Cell Biol.* **2008**, *180*, 113–127. [[CrossRef](#)]
159. von Roretz, C.; Gallouzi, I.-E. Protein Kinase RNA/FADD/Caspase-8 Pathway Mediates the Proapoptotic Activity of the RNA-Binding Protein Human Antigen R (HuR). *J. Biol. Chem.* **2010**, *285*, 16806–16813. [[CrossRef](#)]
160. Beauchamp, P.; Nassif, C.; Hillock, S.; van der Giessen, K.; von Roretz, C.; Jasmin, B.J.; Gallouzi, I.-E. The Cleavage of HuR Interferes with Its Transportin-2-Mediated Nuclear Import and Promotes Muscle Fiber Formation. *Cell Death Differ.* **2010**, *17*, 1588–1599. [[CrossRef](#)]
161. Zhou, H.-L.; Geng, C.; Luo, G.; Lou, H. The P97-UBXD8 Complex Destabilizes MRNA by Promoting Release of Ubiquitinated HuR from MRNP. *Genes Dev.* **2013**, *27*, 1046–1058. [[CrossRef](#)] [[PubMed](#)]
162. Lucchesi, C.; Sheikh, M.S.; Huang, Y. Negative Regulation of RNA-Binding Protein HuR by Tumor-Suppressor ECRG2. *Oncogene* **2016**, *35*, 2565–2573. [[CrossRef](#)] [[PubMed](#)]
163. Ke, Y.; Han, Y.; Guo, X.; Wen, J.; Wang, K.; Jiang, X.; Tian, X.; Ba, X.; Boldogh, I.; Zeng, X. PARP1 Promotes Gene Expression at the Post-Transcriptional Level by Modulating the RNA-Binding Protein HuR. *Nat. Commun.* **2017**, *8*, 14632. [[CrossRef](#)] [[PubMed](#)]
164. Ke, Y.; Lv, X.; Fu, X.; Zhang, J.; Bohio, A.A.; Zeng, X.; Hao, W.; Wang, R.; Boldogh, I.; Ba, X. Poly(ADP-Ribosyl)ation Enhances HuR Oligomerization and Contributes to pro-Inflammatory Gene MRNA Stabilization. *Cell. Mol. Life Sci.* **2021**, *78*, 1817–1835. [[CrossRef](#)]
165. Bibli, S.-I.; Hu, J.; Sigala, F.; Wittig, I.; Heidler, J.; Zukunft, S.; Tsilimigras, D.I.; Randriamboavonjy, V.; Wittig, J.; Kojonazarov, B.; et al. Cystathionine γ Lyase Sulfhydrates the RNA Binding Protein Human Antigen R to Preserve Endothelial Cell Function and Delay Atherogenesis. *Circulation* **2019**, *139*, 101–114. [[CrossRef](#)]
166. Deka, K.; Saha, S. Heat Stress Induced Arginylation of HuR Promotes Alternative Polyadenylation of Hsp70.3 by Regulating HuR Stability and RNA Binding. *Cell Death Differ.* **2021**, *28*, 730–747. [[CrossRef](#)]
167. Kristensen, L.S.; Hansen, T.B.; Venø, M.T.; Kjems, J. Circular RNAs in Cancer: Opportunities and Challenges in the Field. *Oncogene* **2017**, *37*, 555–565. [[CrossRef](#)]
168. Abdelmohsen, K.; Panda, A.C.; Munk, R.; Grammatikakis, I.; Dudekula, D.B.; De, S.; Kim, J.; Noh, J.H.; Kim, K.M.; Martindale, J.L.; et al. Identification of HuR Target Circular RNAs Uncovers Suppression of PABPN1 Translation by CircPABPN1. *RNA Biol.* **2017**, *14*, 361–369. [[CrossRef](#)]
169. David, P.S.; Tanveer, R.; Port, J.D. FRET-Detectable Interactions between the ARE Binding Proteins, HuR and P37AUF1. *RNA* **2007**, *13*, 1453–1468. [[CrossRef](#)]
170. Ripin, N.; Boudet, J.; Duszczczyk, M.M.; Hinniger, A.; Faller, M.; Krepl, M.; Gadi, A.; Schneider, R.J.; Šponer, J.; Meisner-Kober, N.C.; et al. Molecular Basis for AU-Rich Element Recognition and Dimerization by the HuR C-Terminal RRM. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 2935–2944. [[CrossRef](#)]
171. Soller, M.; White, K. ELAV Multimerizes on Conserved AU4-6 Motifs Important for Ewg Splicing Regulation. *Mol. Cell. Biol.* **2005**, *25*, 7580–7591. [[CrossRef](#)] [[PubMed](#)]
172. Meisner, N.-C.; Hintersteiner, M.; Mueller, K.; Bauer, R.; Seifert, J.-M.; Naegeli, H.-U.; Ottl, J.; Oberer, L.; Guenat, C.; Moss, S.; et al. Identification and Mechanistic Characterization of Low-Molecular-Weight Inhibitors for HuR. *Nat. Chem. Biol.* **2007**, *3*, 508–515. [[CrossRef](#)] [[PubMed](#)]

173. Filippova, N.; Yang, X.; Ananthan, S.; Sorochinsky, A.; Hackney, J.R.; Gentry, Z.; Bae, S.; King, P.; Nabors, L.B. Hu Antigen R (HuR) Multimerization Contributes to Glioma Disease Progression. *J. Biol. Chem.* **2017**, *292*, 16999–17010. [[CrossRef](#)] [[PubMed](#)]
174. Gantt, K.; Cherry, J.; Tenney, R.; Karschner, V.; Pekala, P.H. An Early Event in Adipogenesis, the Nuclear Selection of the CCAAT Enhancer-Binding Protein β (C/EBP β) mRNA by HuR and Its Translocation to the Cytosol *. *J. Biol. Chem.* **2005**, *280*, 24768–24774. [[CrossRef](#)]
175. Cherry, J.; Karschner, V.; Jones, H.; Pekala, P.H. HuR, an RNA-Binding Protein, Involved in the Control of Cellular Differentiation. *In Vivo* **2006**, *20*, 17–23.
176. Siang, D.T.C.; Lim, Y.C.; Kyaw, A.M.M.; Win, K.N.; Chia, S.Y.; Degirmenci, U.; Hu, X.; Tan, B.C.; Walet, A.C.E.; Sun, L.; et al. The RNA-Binding Protein HuR Is a Negative Regulator in Adipogenesis. *Nat. Commun.* **2020**, *11*, 213. [[CrossRef](#)]
177. Katsanou, V.; Papadaki, O.; Milatos, S.; Blackshear, P.J.; Anderson, P.; Kollias, G.; Kontoyiannis, D.L. HuR as a Negative Posttranscriptional Modulator in Inflammation. *Mol. Cell* **2005**, *19*, 777–789. [[CrossRef](#)]
178. Gerbes, A.; Zoulim, F.; Tilg, H.; Dufour, J.-F.; Bruix, J.; Paradis, V.; Salem, R.; Peck-Radosavljevic, M.; Galle, P.R.; Greten, T.F.; et al. Gut Roundtable Meeting Paper: Selected Recent Advances in Hepatocellular Carcinoma. *Gut* **2018**, *67*, 380–388. [[CrossRef](#)]
179. Villanueva, A. Hepatocellular Carcinoma. *N. Engl. J. Med.* **2019**, *380*, 1450–1462. [[CrossRef](#)]
180. Rizzo, A.; Ricci, A.D.; Gadaleta-Caldarola, G.; Brandi, G. First-Line Immune Checkpoint Inhibitor-Based Combinations in Unresectable Hepatocellular Carcinoma: Current Management and Future Challenges. *Expert Rev. Gastroenterol. Hepatol.* **2021**, *15*, 1245–1251. [[CrossRef](#)]
181. Rizzo, A.; Ricci, A.D. PD-L1, TMB, and Other Potential Predictors of Response to Immunotherapy for Hepatocellular Carcinoma: How Can They Assist Drug Clinical Trials? *Expert Opin. Investig. Drugs* **2022**, *31*, 415–423. [[CrossRef](#)]
182. Reig, M.; Forner, A.; Rimola, J.; Ferrer-Fàbrega, J.; Burrel, M.; Garcia-Criado, Á.; Kelley, R.K.; Galle, P.R.; Mazzaferro, V.; Salem, R.; et al. BCLC Strategy for Prognosis Prediction and Treatment Recommendation: The 2022 Update. *J. Hepatol.* **2022**, *76*, 681–693. [[CrossRef](#)] [[PubMed](#)]
183. Massarweh, N.N.; El-Serag, H.B. Epidemiology of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. *Cancer Control* **2017**, *24*, 1073274817729245. [[CrossRef](#)] [[PubMed](#)]
184. Zabron, A.; Edwards, R.J.; Khan, S.A. The Challenge of Cholangiocarcinoma: Dissecting the Molecular Mechanisms of an Insidious Cancer. *Dis. Model. Mech.* **2013**, *6*, 281–292. [[CrossRef](#)] [[PubMed](#)]
185. Krenzien, F.; Nevermann, N.; Krombholz, A.; Benzing, C.; Haber, P.; Fehrenbach, U.; Lurje, G.; Pelzer, U.; Pratschke, J.; Schmelzle, M.; et al. Treatment of Intrahepatic Cholangiocarcinoma—A Multidisciplinary Approach. *Cancers* **2022**, *14*, 362. [[CrossRef](#)] [[PubMed](#)]
186. Banales, J.M.; Marin, J.J.G.; Lamarca, A.; Rodrigues, P.M.; Khan, S.A.; Roberts, L.R.; Cardinale, V.; Carpino, G.; Andersen, J.B.; Braconi, C.; et al. Cholangiocarcinoma 2020: The next Horizon in Mechanisms and Management. *Nat. Rev. Gastroenterol. Hepatol.* **2020**, *17*, 557–588. [[CrossRef](#)] [[PubMed](#)]
187. Embade, N.; Fernández-Ramos, D.; Varela-Rey, M.; Beraza, N.; Sini, M.; de Juan, V.G.; Woodhoo, A.; Martínez-López, N.; Rodríguez-Iruretagoyena, B.; Bustamante, F.J.; et al. Mdm2 Regulates HuR Stability in Human Liver and Colon Cancer through Neddylation. *Hepatology* **2012**, *55*, 1237–1248. [[CrossRef](#)]
188. Zhu, H.; Berkova, Z.; Mathur, R.; Sehgal, L.; Khashab, T.; Tao, R.-H.; Ao, X.; Feng, L.; Sabichi, A.L.; Blechacz, B.; et al. HuR Suppresses Fas Expression and Correlates with Patient Outcome in Liver Cancer. *Mol. Cancer Res.* **2015**, *13*, 809–818. [[CrossRef](#)]
189. Vázquez-Chantada, M.; Fernández-Ramos, D.; Embade, N.; Martínez-Lopez, N.; Varela-Rey, M.; Woodhoo, A.; Luka, Z.; Wagner, C.; Anglim, P.P.; Finnell, R.H.; et al. HuR/Methyl-HuR and AUF1 Regulate the MAT Expressed During Liver Proliferation, Differentiation, and Carcinogenesis. *Gastroenterology* **2010**, *138*, 1943–1953.e3. [[CrossRef](#)]
190. Ally, A.; Balasundaram, M.; Carlsen, R.; Chuah, E.; Clarke, A.; Dhalla, N.; Holt, R.A.; Jones, S.J.M.; Lee, D.; Ma, Y.; et al. Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma. *Cell* **2017**, *169*, 1327–1341.e23. [[CrossRef](#)]
191. Toyota, K.; Murakami, Y.; Kondo, N.; Uemura, K.; Nakagawa, N.; Takahashi, S.; Sueda, T. Cytoplasmic Hu-Antigen R (HuR) Expression Is Associated with Poor Survival in Patients with Surgically Resected Cholangiocarcinoma Treated with Adjuvant Gemcitabine-Based Chemotherapy. *Ann. Surg. Oncol.* **2018**, *25*, 1202–1210. [[CrossRef](#)] [[PubMed](#)]
192. Villanueva, A.; Chiang, D.Y.; Newell, P.; Peix, J.; Thung, S.; Alsinet, C.; Tovar, V.; Roayaie, S.; Minguez, B.; Sole, M.; et al. Pivotal Role of MTOR Signaling in Hepatocellular Carcinoma. *Gastroenterology* **2008**, *135*, 1972–1983.e11. [[CrossRef](#)] [[PubMed](#)]
193. Wang, L.; Ding, Q.; Zhao, L.; Pan, Y.; Song, Z.; Qin, Y.; Yan, X. Decreased BMP-7 and p-Smad1/5/8 Expression, and Increased Levels of Gremlin in Hepatocellular Carcinoma. *Oncol. Lett.* **2018**, *16*, 2113–2118. [[CrossRef](#)]
194. Hung, C.-M.; Huang, W.-C.; Pan, H.-L.; Chien, P.-H.; Lin, C.-W.; Chen, L.-C.; Chien, Y.-F.; Lin, C.-C.; Leow, K.-H.; Chen, W.-S.; et al. Hepatitis B Virus X Upregulates HuR Protein Level to Stabilize HER2 Expression in Hepatocellular Carcinoma Cells. *Bio. Res. Int.* **2014**, *2014*, 827415. [[CrossRef](#)] [[PubMed](#)]
195. Martínez-Chantar, M.L.; Vázquez-Chantada, M.; Garnacho, M.; Latasa, M.U.; Varela-Rey, M.; Dotor, J.; Santamaria, M.; Martínez-Cruz, L.A.; Parada, L.A.; Lu, S.C.; et al. S-Adenosylmethionine Regulates Cytoplasmic HuR Via AMP-Activated Kinase. *Gastroenterology* **2006**, *131*, 223–232. [[CrossRef](#)]
196. Lai, K.K.Y.; Kweon, S.-M.; Chi, F.; Hwang, E.; Kabe, Y.; Higashiyama, R.; Qin, L.; Yan, R.; Wu, R.P.; Lai, K.; et al. Stearoyl-CoA Desaturase Promotes Liver Fibrosis and Tumor Development in Mice via a Wnt Positive-Signaling Loop by Stabilization of Low-Density Lipoprotein-Receptor-Related Proteins 5 and 6. *Gastroenterology* **2017**, *152*, 1477–1491. [[CrossRef](#)]

197. Chen, Y.; Peng, C.; Chen, J.; Chen, D.; Yang, B.; He, B.; Hu, W.; Zhang, Y.; Liu, H.; Dai, L.; et al. WTAP Facilitates Progression of Hepatocellular Carcinoma via M6A-HuR-Dependent Epigenetic Silencing of ETS1. *Mol. Cancer* **2019**, *18*, 127. [[CrossRef](#)]
198. Zhang, R.; Wang, J. HuR Stabilizes TFAM mRNA in an ATM/P38-Dependent Manner in Ionizing Irradiated Cancer Cells. *Cancer Sci.* **2018**, *109*, 2446–2457. [[CrossRef](#)]
199. Zhang, L.-F.; Lou, J.-T.; Lu, M.-H.; Gao, C.; Zhao, S.; Li, B.; Liang, S.; Li, Y.; Li, D.; Liu, M.-F. Suppression of MiR-199a Maturation by HuR Is Crucial for Hypoxia-Induced Glycolytic Switch in Hepatocellular Carcinoma. *EMBO J.* **2015**, *34*, 2671–2685. [[CrossRef](#)]
200. Cao, C.; Sun, J.; Zhang, D.; Guo, X.; Xie, L.; Li, X.; Wu, D.; Liu, L. The Long Intergenic Noncoding RNA UFC1, a Target of MicroRNA 34a, Interacts with the mRNA Stabilizing Protein HuR to Increase Levels of β -Catenin in HCC Cells. *Gastroenterology* **2015**, *148*, 415–426.e18. [[CrossRef](#)]
201. Huang, J.-F.; Jiang, H.-Y.; Cai, H.; Liu, Y.; Zhu, Y.-Q.; Lin, S.-S.; Hu, T.-T.; Wang, T.-T.; Yang, W.-J.; Xiao, B.; et al. Genome-Wide Screening Identifies Oncofetal LncRNA Ptn-Dt Promoting the Proliferation of Hepatocellular Carcinoma Cells by Regulating the Ptn Receptor. *Oncogene* **2019**, *38*, 3428–3445. [[CrossRef](#)] [[PubMed](#)]
202. He, X.; Zheng, Y.; Zhang, Y.; Gan, Y.; Zhou, Y.; Liang, H.; Wu, D.; Ge, W.; Deng, J.; Xu, X. Long Non-Coding RNA AK058003, as a Precursor of MiR-15a, Interacts with HuR to Inhibit the Expression of γ -Synuclein in Hepatocellular Carcinoma Cells. *Oncotarget* **2017**, *8*, 9451–9465. [[CrossRef](#)] [[PubMed](#)]
203. Liu, B.; Yang, G.; Wang, X.; Liu, J.; Lu, Z.; Wang, Q.; Xu, B.; Liu, Z.; Li, J. CircBACH1 (Hsa_circ_0061395) Promotes Hepatocellular Carcinoma Growth by Regulating P27 Repression via HuR. *J. Cell. Physiol.* **2020**, *235*, 6929–6941. [[CrossRef](#)] [[PubMed](#)]
204. Liu, H.; Lan, T.; Li, H.; Xu, L.; Chen, X.; Liao, H.; Chen, X.; Du, J.; Cai, Y.; Wang, J.; et al. Circular RNA CircDLC1 Inhibits MMP1-Mediated Liver Cancer Progression via Interaction with HuR. *Theranostics* **2021**, *11*, 1396–1411. [[CrossRef](#)]
205. Wang, Y.; Gao, R.; Li, J.; Tang, S.; Li, S.; Tong, Q.; Li, S. Downregulation of Hsa_circ_0074854 Suppresses the Migration and Invasion in Hepatocellular Carcinoma via Interacting with HuR and via Suppressing Exosomes-Mediated Macrophage M2 Polarization. *Int. J. Nanomed.* **2021**, *16*, 2803–2818. [[CrossRef](#)]
206. Martínez-López, N.; Varela-Rey, M.; Fernández-Ramos, D.; Woodhoo, A.; Vázquez-Chantada, M.; Embade, N.; Espinosa-Hevia, L.; Bustamante, F.J.; Parada, L.A.; Rodríguez, M.S.; et al. Activation of LKB1-Akt Pathway Independent of Phosphoinositide 3-Kinase Plays a Critical Role in the Proliferation of Hepatocellular Carcinoma from Nonalcoholic Steatohepatitis. *Hepatology* **2010**, *52*, 1621–1631. [[CrossRef](#)]
207. Chen, T.; Dai, X.; Dai, J.; Ding, C.; Zhang, Z.; Lin, Z.; Hu, J.; Lu, M.; Wang, Z.; Qi, Y.; et al. AFP Promotes HCC Progression by Suppressing the HuR-Mediated Fas/FADD Apoptotic Pathway. *Cell Death Dis.* **2020**, *11*, 822. [[CrossRef](#)]
208. Ji, E.; Kim, C.; Kang, H.; Ahn, S.; Jung, M.; Hong, Y.; Tak, H.; Lee, S.; Kim, W.; Lee, E.K. RNA Binding Protein HuR Promotes Autophagosome Formation by Regulating Expression of Autophagy-Related Proteins 5, 12, and 16 in Human Hepatocellular Carcinoma Cells. *Mol. Cell. Biol.* **2019**, *39*, e00508-18. [[CrossRef](#)]
209. Papatheofani, V.; Levidou, G.; Sarantis, P.; Koustas, E.; Karamouzis, M.V.; Pergaris, A.; Kouraklis, G.; Theocharis, S. HuR Protein in Hepatocellular Carcinoma: Implications in Development, Prognosis and Treatment. *Biomedicines* **2021**, *9*, 119. [[CrossRef](#)]
210. Mohibi, S.; Chen, X.; Zhang, J. Cancer the 'RBP' eutics-RNA-Binding Proteins as Therapeutic Targets for Cancer. *Pharmacol. Ther.* **2019**, *203*, 107390. [[CrossRef](#)]
211. Blanco, F.F.; Jimbo, M.; Wulfkühle, J.; Gallagher, I.; Deng, J.; Enyenihi, L.; Meisner-Kober, N.; Londin, E.; Rigoutsos, I.; Sawicki, J.A.; et al. The mRNA-Binding Protein HuR Promotes Hypoxia-Induced Chemoresistance through Posttranscriptional Regulation of the Proto-Oncogene PIM1 in Pancreatic Cancer Cells. *Oncogene* **2016**, *35*, 2529–2541. [[CrossRef](#)]
212. Romeo, C.; Weber, M.C.; Zarei, M.; DeCicco, D.; Chand, S.N.; Lobo, A.D.; Winter, J.M.; Sawicki, J.A.; Sachs, J.N.; Meisner-Kober, N.; et al. HuR Contributes to TRAIL Resistance by Restricting Death Receptor 4 Expression in Pancreatic Cancer Cells. *Mol. Cancer Res.* **2016**, *14*, 599–611. [[CrossRef](#)] [[PubMed](#)]
213. Lang, M.; Berry, D.; Passecker, K.; Mesteri, I.; Bhujra, S.; Ebner, F.; Sedlyarov, V.; Evstatiev, R.; Dammann, K.; Loy, A.; et al. HuR Small-Molecule Inhibitor Elicits Differential Effects in Adenomatous Polyposis and Colorectal Carcinogenesis. *Cancer Res.* **2017**, *77*, 2424–2438. [[CrossRef](#)] [[PubMed](#)]
214. D'Agostino, V.G.; Lal, P.; Mantelli, B.; Tiedje, C.; Zucal, C.; Thongon, N.; Gaestel, M.; Latorre, E.; Marinelli, L.; Seneci, P.; et al. Dihydrotanshinone-I Interferes with the RNA-Binding Activity of HuR Affecting Its Post-Transcriptional Function. *Sci. Rep.* **2015**, *5*, 16478. [[CrossRef](#)]
215. Chae, M.-J.; Sung, H.Y.; Kim, E.-H.; Lee, M.; Kwak, H.; Chae, C.H.; Kim, S.; Park, W.-Y. Chemical Inhibitors Destabilize HuR Binding to the AU-Rich Element of TNF-Alpha mRNA. *Exp. Mol. Med.* **2009**, *41*, 824–831. [[CrossRef](#)] [[PubMed](#)]
216. Wu, X.; Lan, L.; Wilson, D.M.; Marquez, R.T.; Tsao, W.-C.; Gao, P.; Roy, A.; Turner, B.A.; McDonald, P.; Tunge, J.A.; et al. Identification and Validation of Novel Small Molecule Disruptors of HuR-MRNA Interaction. *ACS Chem. Biol.* **2015**, *10*, 1476–1484. [[CrossRef](#)] [[PubMed](#)]
217. Muralidharan, R.; Mehta, M.; Ahmed, R.; Roy, S.; Xu, L.; Aubé, J.; Chen, A.; Zhao, Y.D.; Herman, T.; Ramesh, R.; et al. HuR-Targeted Small Molecule Inhibitor Exhibits Cytotoxicity towards Human Lung Cancer Cells. *Sci. Rep.* **2017**, *7*, 9694. [[CrossRef](#)] [[PubMed](#)]
218. Allegri, L.; Baldan, F.; Roy, S.; Aubé, J.; Russo, D.; Filetti, S.; Damante, G. The HuR CMLD-2 Inhibitor Exhibits Antitumor Effects via MAD2 Downregulation in Thyroid Cancer Cells. *Sci. Rep.* **2019**, *9*, 7374. [[CrossRef](#)]

219. Wu, X.; Gardashova, G.; Lan, L.; Han, S.; Zhong, C.; Marquez, R.T.; Wei, L.; Wood, S.; Roy, S.; Gowthaman, R.; et al. Targeting the Interaction between RNA-Binding Protein HuR and FOXQ1 Suppresses Breast Cancer Invasion and Metastasis. *Commun. Biol.* **2020**, *3*, 193. [[CrossRef](#)]
220. Yang, L.-Q.; Yu, S.-P.; Yang, Y.-T.; Zhao, Y.-S.; Wang, F.-Y.; Chen, Y.; Li, Q.-H.; Tian, P.; Zhu, Y.-Y.; Zhang, J.-G.; et al. Muscone Derivative ZM-32 Inhibits Breast Tumor Angiogenesis by Suppressing HuR-Mediated VEGF and MMP9 Expression. *Biomed. Pharmacother.* **2021**, *136*, 111265. [[CrossRef](#)]
221. Yang, H.; Zheng, Y.; Li, T.W.H.; Peng, H.; Fernandez-Ramos, D.; Martínez-Chantar, M.L.; Rojas, A.L.; Mato, J.M.; Lu, S.C. Methionine Adenosyltransferase 2B, HuR, and Sirtuin 1 Protein Cross-Talk Impacts on the Effect of Resveratrol on Apoptosis and Growth in Liver Cancer Cells. *J. Biol. Chem.* **2013**, *288*, 23161–23170. [[CrossRef](#)] [[PubMed](#)]
222. Lee, J.-Y.; Chung, T.-W.; Choi, H.-J.; Lee, C.H.; Eun, J.S.; Han, Y.T.; Choi, J.-Y.; Kim, S.-Y.; Han, C.-W.; Jeong, H.-S.; et al. A Novel Cantharidin Analog N-Benzylcantharidinamide Reduces the Expression of MMP-9 and Invasive Potentials of Hep3B via Inhibiting Cytosolic Translocation of HuR. *Biochem. Biophys. Res. Commun.* **2014**, *447*, 371–377. [[CrossRef](#)] [[PubMed](#)]
223. Doller, A.; Badawi, A.; Schmid, T.; Brauss, T.; Pleli, T.; zu Heringdorf, D.M.; Piiper, A.; Pfeilschifter, J.; Eberhardt, W. The Cytoskeletal Inhibitors Latrunculin A and Blebbistatin Exert Antitumorigenic Properties in Human Hepatocellular Carcinoma Cells by Interfering with Intracellular HuR Trafficking. *Exp. Cell Res.* **2015**, *330*, 66–80. [[CrossRef](#)] [[PubMed](#)]
224. Barbier-torres, L.; Fernández-ramos, D.; Martínez-chantar, M.L. The Levels of the RNA Binding Protein Hu Antigen R Determine the Druggability of the Neddylolation Pathway in Liver Cancer. *RNA Dis.* **2016**, *3*, 1–10. [[CrossRef](#)]
225. Sanna, M.D.; Quattrone, A.; Galeotti, N. Silencing of the RNA-Binding Protein HuR Attenuates Hyperalgesia and Motor Disability in Experimental Autoimmune Encephalomyelitis. *Neuropharmacology* **2017**, *123*, 116–125. [[CrossRef](#)]
226. Muralidharan, R.; Babu, A.; Amreddy, N.; Basalingappa, K.; Mehta, M.; Chen, A.; Zhao, Y.D.; Kompella, U.B.; Munshi, A.; Ramesh, R. Folate Receptor-Targeted Nanoparticle Delivery of HuR-RNAi Suppresses Lung Cancer Cell Proliferation and Migration. *J. Nanobiotechnol.* **2016**, *14*, 47. [[CrossRef](#)]
227. Katsanou, V.; Milatos, S.; Yiakouvaki, A.; Sgantzi, N.; Kotsoni, A.; Alexiou, M.; Harokopos, V.; Aidinis, V.; Hemberger, M.; Kontoyiannis, D.L. The RNA-Binding Protein Elavl1/HuR Is Essential for Placental Branching Morphogenesis and Embryonic Development. *Mol. Cell. Biol.* **2009**, *29*, 2762–2776. [[CrossRef](#)]
228. Sun, D.-Q.; Wang, Y.; Liu, D.-G. Cancer Cell Growth Suppression by a 62nt AU-Rich RNA from C/EBP β 3'UTR through Competitive Binding with HuR. *Biochem. Biophys. Res. Commun.* **2012**, *426*, 122–128. [[CrossRef](#)]
229. Nimjee, S.M.; White, R.R.; Becker, R.C.; Sullenger, B.A. Aptamers as Therapeutics. *Annu. Rev. Pharmacol. Toxicol.* **2017**, *57*, 61–79. [[CrossRef](#)]