RNA stabilizing proteins as molecular targets in cardiovascular pathologies

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Abstract

The stability of mRNA has emerged as a key step in the regulation of eukaryotic gene expression and function. RNA stabilizing proteins (RSPs) contain several RNA recognition motifs, and selectively bind to Adenylate- and uridylate- Rich Elements in the 3' untranslated region of several mRNAs leading to altered processing, stability and translation. These post-transcriptional gene regulations play a critical role in cellular homeostasis; therefore act as molecular switch between 'normal cell' and 'disease state'. Many mRNA binding proteins have been discovered to date, which either stabilize (HuR/HuA, HuB, HuC, HuD) or destabilize (AUF1, Tristetraprolin, KSRP) the target transcripts. Although the function of RSPs has been widely studied in cancer biology, its role in cardiovascular pathologies is only beginning to evolve. The current review provides an overall understanding of the potential role of RSP, specifically HuR-mediated mRNA stability in myocardial infarction, hypertension and hypertrophy. Also, the effect of RSPs on various cellular processes including inflammation, fibrosis, angiogenesis, cell-death and proliferation and its relevance to cardiovascular pathophysiological processes is presented. We also discuss the potential clinical implications of RSPs as therapeutic targets in cardiovascular diseases.

Keywords

RNA stabilizing proteins; RSP; RNA binding proteins; RBP; HuR; ELAVL1; cardiovascular diseases

Introduction

Post-transcriptional gene regulation has been implicated in a variety of biological processes including inflammation, cell cycle, angiogenesis, cell survival, and apoptosis [1–6]. Post-transcriptional RNA modifications occur via intricate network of signaling pathways leading to altered gene expression [7]. RNA stabilizing proteins (RSPs) play a major role in post-

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transcriptional control of RNAs, such as splicing, polyadenylation, mRNA stabilization, mRNA localization and translation, therefore regulate tissue homeostasis [8,9]. Evidence from animal models suggests that RSPs expression and function is altered in a variety of conditions including embryonic development, physiology and disease [10].

RNA binding proteins were originally discovered as proteins that present mRNA to the degradation machinery. Adenylate-uridylylate-Rich Elements (ARE)/poly(U)-binding degradation factor (AUF1), tristetraprolin (TTP) and KH Domain RNA Binding Protein (KSRP) are such proteins that promote mRNA degradation [11,12]. AUF1 was the first RNA binding protein identified that has been shown to destabilize polyribosome-associated transcripts [11,13]. However, some studies have reported that AUF1 also stabilizes mRNA and enhance translation [14]. TTP is a ARE-binding protein that belongs to zinc-finger family of proteins and promotes degradation of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukins (IL-3 and IL-6) mRNA [12]. KSRP promotes ARE-directed mRNA degradation by interacting with the exosome and polyAribonuclease (PARN) and recruiting the degradation machinery [15].

On the contrary, RSPs that bind to mRNA and lead to their stabilization include Polyadenylate-binding protein-interacting protein-2 (PAIP2), AUF1 and a family of embryonic lethal abnormal vision (ELAV) Hu proteins, HuA/HuR (Human antigen-R), HuB, HuC and HuD. PAIP2 stabilizes mRNA by interfering with the binding of Poly-A binding protein (PABP) to the 3' untranslated region (3'-UTR) of mRNA by enhancing the translation initiation [16]. Hu proteins selectively bind to ARE in the 3' untranslated region of mRNAs resulting in their stabilization [17]. Hu proteins, HuB, HuC and HuD are predominantly expressed in nervous system and gonad [18–20]. However, human antigen R (HuR) is ubiquitously expressed and is the best characterized member of the Hu protein family.

In the current review, we discuss the mechanism of RSP-induced stabilization of mRNA, role of RSP in cardiovascular pathophysiological processes including inflammation, angiogenesis, fibrosis, cell death, proliferation. Also, we discuss the potential use of RSPs as molecular targets in diseases with a special interest in HuR protein.

Mechanisms of HuR-mediated mRNA stability

Adenylate-uridylylate-rich elements (AU-rich elements; AREs) are found in the 3'-UTR of many messenger RNAs (mRNAs) that code for nuclear transcription factors, proto-oncogenes, and cytokines [21]. They usually target the mRNA for rapid degradation. RNA binding proteins, through their RNA recognition motifs (RRMs), compete for the ARE sites on the mRNA [22]. The fate of the mRNA depends on the signal that the different RNA binding protein receives from the associated signaling pathway and is accordingly stabilized or destabilized [22,23,5]. For example, proteins like AUF1, TTP, TIA-1, TIAR, and KSRP bind to these elements and destabilize the mRNA, while others (e.g. HuA, HuB, HuC, HuD, HuR) stabilize the mRNA. In this section, we will focus on the mechanism of HuR-mediated mRNA stabilization, which is depicted in Figure 1. The most commonly accepted mechanism is that HuR binds directly to several classes of ARE elements (tandem repeats of

AUUUA; A+U regions with interspersed AUUUA and U-rich sequence with no AUUUA pentamers) [24] and thereby delaying onset of decay [25].

Alternatively, HuR competes with miRNAs (short; 20–23 nucleotide sequences) that bind to the same mRNA, therefore act as modifiers that alter the potential of miRNAs to repress or activate the specific gene expression [26,27]. Competition between HuR and microRNAs results in enhanced gene expression in the presence of HuR-mRNA interaction, and in repression if the microRNA remains associated. Cooperation between HuR and microRNAs leads to lower expression of the shared mRNA [28]. For instance, competitive interactions between HuR and miR-200b post-transcriptionally controls VEGF-A, a pro-angiogenic cytokine mRNA expression [29].

Also, HuR-mediated mRNA stability is regulated by its nuclear-cytoplasmic shuttling that in-turn influences the target mRNA stability. Assisted by its structural motifs containing RNA recognition motifs, hinge region with a nuclear shuttling sequence (HNS), HuR shuttles between nuclear and cytoplasmic compartments via interactions with nuclear export/import adaptor proteins [30]. HuR binds to target mRNA in the nucleus, exports and protects them during cytoplasmic transit and facilitates their recruitment to the translational machinery leading to translation initiation. Alternatively, depending on the stimuli, it may dissociate from the mRNA and shuttle back to the nucleus leading to decay of mRNA [10]. Phosphorylation of HuR by Protein kinase C (PKC) leads to increased translocation to the cytoplasm, resulting in altered cellular processes [31]. Therefore, presence of HuR in the nucleus or cytoplasm determines the normal or disease state of a cell under various physiological and pathological stimuli.

Furthermore, recent reports have shown that HuR also leads to target mRNA stabilization in association with epigenetic changes such as N6-Methyladenosine (m6A) modification [32]. In embryonic stem cells (ESC), HuR preferentially binds mRNAs that are not methylated by N6-methyladenosine (e.g. insulin-like growth factor-binding protein 3, IGFBP3 mRNA); therefore stabilizing IGFBP3 mRNA leading to increase ESCs differentiation [8]. Interestingly, post-translational modification of HuR by methylation (besides phosphorylation) affects its cytoplasmic translocation and function [33]. The co-activator associated arginine methyltransferase 1 (CARM1) catalyzes the methylation of HuR at Arginine 217 (R217K). Methylation by CARM1 has been shown to enhance the function of HuR in stabilizing SIRT1, NAD-dependent protein deacetylase sirtuin-1 mRNAs [34].

Role of RSPs in cardiovascular pathologies

Previous reports indicate that the 3'-UTR can affect gene expression by influencing mRNA stability and translation [3,5]. Several proteins that bind to 3'-UTR of target mRNA involved in cardiovascular pathophysiology have been identified. The role of 3'-UTR mediated mRNA stability that was developed initially with oncogenes and cytokines has enhanced our enthusiasm to understand its applicability to a large number of mRNAs involved in cardiac pathophysiology. The role of RSPs in a diverse range of biological processes including that occurring in other organs have been reviewed here and discussed in the context of cardiovascular diseases (summarized in Table 1).

Myocardial infarction (MI)

Chronic activation of inflammatory response is associated with left ventricular (LV) dysfunction and adverse remodeling following MI. Our previous reports demonstrate that HuR expression increases in the myocardium following ischemic injury [3,23]. IL-10, a potent anti-inflammatory cytokine, blocks mRNA expression of proinflammatory cytokine/chemokine in both human monocyte cell line and mouse macrophages by suppressing the cytokine mRNA-stabilizing protein HuR and inhibition of p38 mitogen-activated protein kinase (MAPK) [21,5]. Furthermore, IL-10 knockout mice showed increased myocardial inflammatory response with exacerbated LV dysfunction, fibrosis and cell death. These adverse changes were associated with increased HuR expression in the myocardium [3]. Intriguingly, HuR knockdown in the myocardium attenuated post-MI inflammatory response, reduced cardiomyocyte cell death and myocardial infarct size resulting in improved LV dysfunction [3]. These responses therefore mimic the beneficial effects of IL-10 therapy for cardiac dysfunction [23].

β -adrenergic receptors are a class of G protein-coupled receptors, which on stimulation with isoproterenol, catecholamines, norepinephrine and other vasoactive agents, contribute to the pathogenesis of various diseases including defects in cardiovascular function [35]. Down-regulation of β -adrenergic receptors in the heart results in reduced contraction in congestive heart failure and MI [36]. Interestingly, the transacting factors AUF1, HuR, and hnRNP-A1 have been shown to mediate mRNA stability of β 1-adrenergic receptor [10,37]. Also, individuals with myocardial failure showed higher AUF1 protein levels corresponding to their elevated cardiac norepinephrine levels [37]. β -adrenergic receptor mRNA decay may be under both positive and negative regulation as HuR and hnRNP-A1 have been suggested to be stabilizing and AUF1 to be destabilizing [10].

The sarcoendoplasmic reticulum (SR) calcium transport ATPase (SERCA) pump transports calcium ions from the cytoplasm into the SR therefore maintaining cardiomyocyte contractile function. Impairment in SERCA2a (cardiac isoform) activity is a key abnormality in heart failure patients with reduced ejection fraction [38]. It is not known if SERCA2 mRNA stability is mediated through RSPs. However, in primary cultured neonatal rat heart cells, the half-life of SERCA2 mRNA is controlled by PKC [39], which has been shown to promote HuR translocation from nucleus to cytoplasm [1]. It might be interesting to determine the direct role of HuR on SERCA2 mRNA stability and the resulting heart failure.

Hypertension

Patients with hypertension are predisposed to cardiovascular diseases. Hypertension is associated with dysfunctional vascular endothelium and thickening of the smooth muscle layer around the vessel [40,41]. Endothelial Nitric Oxide Synthase (eNOS) expressed in endothelium of blood vessels and heart, plays a role in cardiovascular homeostasis, both under physiological condition and in response to stress [42]. NO (Nitric oxide) generated by eNOS causes relaxation in the vasculature and prevents smooth muscle proliferation and also exerts a negative inotropic effect on cardiac muscle [10,42]. The eNOS mRNA decay/stability and expression has been shown to alter in response to cell proliferation, hypoxia, or

sheer stress [43]. Previous study has shown that HuR was down regulated in an aged genetic model of hypertension and was associated with reduced expression of soluble guanylyl cyclase (sGC), a vital receptor of NO which is a key regulator of vascular smooth muscle force and growth through its production of cGMP [44]. NO acts in a cGMP-dependent mechanism to inhibit the expression level of HuR, thereby reducing the stability of MMP-9 mRNA leading to altered proliferation, hypertrophic remodeling, angiogenesis, and apoptosis [44]. Furthermore, HuR has been shown to stabilize sGC mRNA. Thus, decreased expression of HuR seems to control processes potentially involved in the progression of hypertension [45]. HuR and AUF1 plays a role in the stability of β 2-adrenergic receptor mRNA in smooth muscle that may also contribute to the long-term β 2-adrenergic receptor desensitization in hypertension [10].

Hypertrophy

Cardiac hypertrophy is an adaptive response to both hemodynamic and non-hemodynamic stimuli, such as hypertension and MI, and is a major risk factor for heart failure and death [46,40]. Cardiac hypertrophy is often accompanied by structural remodeling characterized by activation of proinflammatory response, fibrogenesis, cardiac cell death and enlargement of existing cardiomyocytes, leading to decreased compliance and increased risk for heart failure [35,47]. Hypertrophy leads to increased expression of several transcripts during the remodeling process, which might be protective initially and might result in congestive heart failure as the disease progresses. For instance, increased glucose transporter 1 (GLUT1) expression and glucose utilization that accompany pressure overload-induced hypertrophy are believed to be cardio-protective [48]. Studies have suggested that HuR post-transcriptionally regulates GLUT1 expression [2]. However, its implication on cardiac hypertrophy has not been explored and is of potential interest in cardiovascular pathology.

Angiotensin II (Ang II) receptors have a pathophysiological role in hypertension, cardiac hypertrophy and heart failure [49]. Ang II type 1 receptor (AT1R) is responsible for the majority of the effects of Ang II on the heart, including stimulated increases in heart rate, contractility, and cardiomyocyte growth [50]. Overexpression of HuR leads to increased AT1R expression in a 3'-UTR-dependent manner and stabilize AT1R mRNA in coronary artery vascular smooth muscle cells [4]. This effect is enhanced with the treatment of insulin accompanied by the translocation of HuR to the cytoplasm [4]. Thus, HuR stabilizes the hypertrophic gene, AT1R suggesting a potential role in hypertrophic response. Specific studies related to HuR-mediated hypertrophic gene stability and target transcripts will establish the role of HuR in cardiac hypertrophy.

Furthermore, HuR increases TLR4 mRNA stability by binding to its 3'UTR, which is correlated with increased vascular smooth muscle cell (VSMC) proliferation in lungs of rats with left ventricular hypertrophy [51,52]. These studies suggest that HuR might possibly contribute to the regulation of VSMC homeostasis in pathophysiological conditions, including cardiac hypertrophy and atherosclerosis.

Inflammation

Prolonged inflammatory response has been implicated in a number of cardiovascular diseases including MI, hypertrophy, hypertension and diabetes-induced cardiovascular complications. Macrophages participate in these conditions via the secretion of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF α) and interleukin-1 (IL-1), in response to various stimuli [53]. Further, HuR also stabilizes the cyclooxygenase-2 (COX-2) gene that encodes the inducible prostaglandin synthase enzyme implicated in inflammation, cell growth, and proliferation [1]. Interestingly chronic ethanol exposure increases the binding of HuR to the TNF- α 3'UTR in macrophages contributing to increased TNF expression [54]. RSP also plays a critical role in inflammation-induced vascular endothelial dysfunction. In human pulmonary microvascular endothelial cells, HuR increases TNF-induced IL-6 expression by binding to ARE elements and thereby stabilizing its mRNA, whereas TTP, an mRNA degrading protein promotes IL-6 mRNA degradation [55]. Also, initiation of TNF- α translation requires HuR and reduced TTP action. Phosphorylation of TTP decreases its affinity towards TNF α , which in-turn leads to increased HuR binding and stabilization of TNF α [55]. Interestingly, systemic inflammation induced by Lipopolysaccharide (LPS) caused intimal hyperplasia and was associated with increased HuR and Toll like receptor-4 (TLR4) expression in the balloon injured rabbit aorta model [51]. Increases HuR expression has been shown to enhance TLR-4 expression. Thus, HuR induces the stability of primary inflammatory cytokines such as TNF α , COX-2 and interleukins and upregulation of TLR-4 in human aortic smooth muscle cells [56,51] or myocardial cells [57] might accelerate the advancement of hypertension and heart failure. These data suggest that targeting HuR in inflammation-induced pathogenesis might be therapeutically beneficial [1,58].

Endothelial homeostasis and Angiogenesis

Vascular endothelial cells play a critical role in several biological processes like permeability, clotting, inflammation, angiogenesis, and regeneration of the injured tissue [59,41]. Endothelial dysfunction is a hallmark of vascular complications that has been shown to be predictive of future cardiovascular pathological events [41]. Under mechanical and biomechanical stress, HuR has been shown to induce inflammatory response in human umbilical vein endothelial cells by regulating the expression of stress-sensitive genes such as such as Kruppel-like factor 2 (Klf2), eNOS, and bone morphogenic protein 4 (BMP-4) [60]. HuR also promotes endothelial activation by enhancing the stability of ICAM-1 (Intercellular Adhesion Molecule) and VCAM-1 (Vascular Cell Adhesion molecule), thus increasing leukocyte-endothelial cell adhesion [61]. ICAM-1 and VCAM-1 are cell surface glycoproteins that play a critical role in inflammation by stabilizing cell-cell interactions and facilitating leukocyte endothelial transmigration [40,41].

Several RSPs have been previously shown to either stabilize or destabilize the VEGF mRNA, which plays a critical role in angiogenesis. PAIP2 and HuR cooperate to stabilize VEGF mRNA. HuR is upregulated and co-localized with increased expression of VEGF in hypoxic regions and shows a direct binding to the 3' UTR of VEGF [62]. HuR is also required for macrophage production of angiogenic factors, which play critical roles in the neovascular responses to a variety of stimuli, including tissue ischemia [6]. Additionally,

DRBP76/NF90 double-stranded RNA-binding protein, a specific isoform of the DRBP family, binds to VEGF mRNA and facilitates its expression by promoting VEGF mRNA stabilization and translation under hypoxic conditions, thus promoting angiogenesis in vivo [63]. The hypoxia-inducible factor (HIF) functions as a master regulator of angiogenesis in hypoxic conditions. HuR and PTB (polypyrimidine tract-binding Protein) competitively bind to HIF-1 α mRNA and promotes its translation under hypoxia-like conditions [7]. The study using a myeloid-specific HuR knockout mouse model has demonstrated a competitive regulation of VEGF by HuR and miRNA-200b [29]. Thus, HuR stabilizes various genes involved in endothelial function and homeostasis.

Fibrosis

Cardiac fibrosis contributes to pathological scarring, stiffening and contractile dysfunction, which eventually leads to cardiac dysfunction and failure [64]. We have previously demonstrated that IL-10 (anti-inflammatory cytokine) therapy attenuated MI-induced increases in inflammatory response and fibrosis and, therefore decreased LV dysfunction [23]. Interestingly the effects were associated with reduced HuR and MMP-9 activity. Furthermore, we demonstrated that HuR knockdown in macrophages in-vitro significantly reduced stability of TGF- β and MMP-9 mRNA [3].

Studies on fibrogenesis in other organs have corroborated our findings in the heart, for instance, Ang II-induced renal fibrosis is characterized by enhanced expression of profibrotic and proinflammatory genes, including the serine protease inhibitor plasminogen activator inhibitor-1 (PAI-1) and COX-2. The pathological expression of PAI-1 and COX-2 were mediated post-transcriptionally via activation of HuR [65]. HuR also controls TGF- β (transforming growth factor- β)-induced profibrotic activity in the liver [66]. Furthermore, earlier reports have suggested that HuR mediates IL-1 β -induced MMP9 expression in mesangial cells [67]. MMP-9 activation has been associated with increased fibrotic response in the heart [35]. These results suggests that HuR is a critical player in fibrotic response and thus could serve as potential therapeutic target to inhibit fibrosis.

Apoptosis and proliferation

Cardiomyocyte cell death plays a prominent role in the pathophysiology of cardiac remodeling after MI [35]. Ischemia stimulates p53 (a well-known pro-apoptotic factor) leading to apoptosis of cardiac cells including myocytes [68]. In LPS-treated RAW 264.7 cells, endogenous HuR proteins were shown to be associated with p53 mRNA [3]. Furthermore, knockdown of HuR significantly enhanced p53 mRNA decay. Also, myocardial HuR knockdown attenuates cardiomyocyte apoptosis by significantly reducing p53 expression [3].

On the contrary, HuR binds to and stabilizes Mdm2, a critical negative regulator of p53 and keeps p53 levels in check in progenitor cells and there by promotes cell survival [69]. Furthermore, HuR increases the stability of a target mRNA encoding the pro-survival deacetylase SIRT1 and also binds to and promotes the expression of mRNAs encoding Bcl-2 and Mcl-1 [70]. It has been shown that HuR maintains epithelial cell proliferation via delta Np63, a p53-homologue and transcription factor. HuR knockdown in these cells inhibits cell

proliferation and enhances premature senescence [71]. HuR also regulates cyclin A and cyclin B1 cell-cycle related mRNA stability during cell proliferation [72]. Based on these reports, further studies are required to demonstrate its role in cell death and senescence specifically in cardiomyocytes. Cardiomyocyte-specific HuR knockout mice might potentially benefit such studies.

Role of RSPs in other pathophysiological conditions

HuR also has a critical function during skeletal myogenesis linked to its coordinated regulation of muscle differentiation genes encoding myogenin, MyoD, and p21 [73]. Reports have shown that placental branching morphogenesis and embryonic development are affected in HuR knockout embryos leading to embryonic lethality [74]. The transcription and growth factor mRNAs controlled by HuR has been shown to guide morphogenesis, specification and patterning during embryonic development [74]. HuR and AUF1 are synchronously expressed at all the developmental stages analyzed from day 8.5 of embryonic development to adulthood associated with the accumulation of a common target mRNA, c-myc [18]. Thus, HuR in association with several other RSPs might play a critical role in development and disease. However, understanding its role in cardiac development might provide greater insights about its effects on stress-induced cardiomyocyte hypertrophic growth response.

RSP as molecular targets and clinical implications

Due to the central role of RSPs in regulating gene expression at the post-transcriptional level, alterations/mutations in either RSP or their binding sites in target transcripts have been reported to be the cause of several diseases such as cardiovascular pathologies, muscular atrophies, neurological disorders and cancer [3,72]. Perturbations in the regulation of RSP also lead to profound phenotypic alterations in vascular development and homeostasis [61]. As described in the mechanism, RSP stabilize the target transcripts by binding to ARE elements, in association with epigenetic changes, nuclear-cytoplasmic shuttling and cooperative or competitive-dependent association with miRNAs. This intricate network of RSP, miRNAs and epigenetic changes allow robust gene regulation in several cells. Interfering at any stage of the intricate network or regulation of RSP leads to alteration in the disease conditions [24,22]. Due to its role in fine-tuning gene expression, RSP could be used as molecular targets in various diseases.

The vastly studied RNA stabilizing protein, HuR plays a key role in angiogenesis, fibrosis and cardiovascular pathologies by binding to several inflammatory cytokines and growth factors thus leading to stabilization of the target transcripts. Deletion of HuR leads to atrophy of hematopoietic organs, defects in morphogenesis and embryonic lethality [69]. On the contrary, HuR expression has been found to be increased in MI, lung fibrosis and several cancers [67,3]. In our previous study, we found that in a mouse model of MI HuR expression was upregulated and was associated with increased myocardial inflammatory response and cardiomyocyte cell death, leading to cardiac dysfunction and remodeling [23]. These studies suggest that RSP might be potentially used as diagnostic clues to detect the disease processes.

Furthermore, understanding the role of RSP in cardiac development might provide valuable information about its role in cardiomyocyte growth both under physiological and pathological stress. In addition, studies related to its effects on cell proliferation and progenitor cell survival might be useful to understand its role in bone marrow or organ specific stem cell renewal, survival and differentiation, therefore impacting therapeutic strategies to prevent or attenuate cardiovascular diseases.

Conclusions

Current investigations reveal that RSPs play an important regulatory role in various pathophysiological processes including fibrosis, angiogenesis, cell-death, proliferation and cellular metabolism. Therefore, they are key molecules that might decide the normal or diseased state of a cell. Due to their involvement in the above cellular processes, their expression and function is tightly regulated through several mechanisms. Interestingly, these mechanisms could serve as molecular targets for limiting the disease or for therapeutic purposes. Several studies have been performed to establish the prognostic effects of RSP such as HuR in cancer patients but the regulation and prognostic value of HuR in the cardiovascular pathologies are under explored. Therefore, further studies in cardiovascular pathologies will lead to better understanding of the role of RSPs as targets in cardiovascular diseases. However, the current data suggests that RSP such as HuR might be a novel and promising therapeutic target.

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Figure 1. Mechanisms of HuR-mediated mRNA stabilization

HuR increases mRNA stability by either (i) directly binding to ARE region or (ii) co-operative or competitive association with miRNAs or (iii) in association with m6A modification. (iv) Also, nuclear-cytoplasm shuttling regulates HuR-mediated activity. These changes increase the target mRNA stabilization and therefore protein expression leading to altered cellular processes in cardiovascular pathologies.

Table 1

RNA stabilizing proteins function in cardiovascular disease processes and other pathophysiological conditions. Arrow marks indicate upregulation (↑), downregulation (↓) or stabilization (no arrow mark)

Disease processes and target genes	RSPs	Mechanism of action	Ref
<i>Myocardial infarction</i>			
Proinflammatory cytokines (TNF α , IL-1 β , IL-6 etc.)	HuR	HuR mediated mRNA stabilization of proinflammatory cytokines is inhibited by IL-10; results in reduced infarct size.	[21,3,5]
β -adrenergic receptors	HuR, AUF1, hnRNP-A1	β -adrenergic mRNA decay is regulated by HuR, AUF1 and hnRNP-A1.	[10]
SERCA	HuR	Protein kinase C regulates HuR translocation and therefore half-life of SERCA2 mRNA.	[1]
<i>Hypertension</i>			
Soluble Guanylate Cyclase (sGC)	HuR	Decreased expression of HuR in aged hypertension model leading to reduced sGC	[45]
<i>Hypertrophy</i>			
Glucose transporter-1 (Glut1)	HuR	HuR bind and stabilizes Glut1 mRNA	[2]
Toll like receptor (TLR4)	HuR	HuR increases TLR4 mRNA stability during pressure induced hypertrophy.	[51,52]
<i>Inflammation</i>			
TNF α , IL-6	HuR, TTP	HuR in association with TTP controls TNF α and IL-6 mRNA	[55]
<i>Endothelial homeostasis</i>			
eNOS, ICAM-1, VCAM-1	HuR	HuR suppresses eNOS and induces the stability of ICAM-1, VCAM-1 and increases leukocyte-endothelial adhesion	[61]
<i>Angiogenesis</i>			
VEGF	PAIP2 HuR	PAIP2 and HuR cooperate to stabilize VEGF mRNA	[62]
	76/NF90 (DRBP76)	Binds to 3' UTR of VEGF inducing mRNA stabilization in hypoxic conditions.	[63]
HIF1 α	HuR PTB	HuR and PTB competitively bind and stabilize HIF1 α in hypoxic conditions	[7]
Fibrosis			
TGF β , MMP9	HuR	Controls TGF β (Transforming growth factor) and MMP-9 induced profibrotic action	[3,23,66]
Apoptosis and proliferation			
p53, mdm2, Bcl-2, Mcl-1	HuR	HuR binds to and stabilizes mdm2, Bcl-2 and Mcl-1 promoting cell survival	[70,69,3]