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Functional interplay between RNA-binding protein HuR and microRNAs

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Abstract

The mammalian RNA-binding protein (RBP) HuR associates with numerous mRNAs encoding proteins with roles in cell division, cell survival, immune response, and differentiation. HuR was known to stabilize many of these mRNAs and/or modulated their translation, but the molecular processes by which HuR affected the fate of target mRNAs was largely unknown. Evidence accumulated over the past five years has revealed that the influence of HuR on many bound transcripts depends on HuR's interplay with microRNAs which associate with the same mRNAs. Here, we review the interactions of HuR and microRNAs – both competitive and cooperative – that govern expression of shared target mRNAs. *Competition* between HuR and microRNAs typically results in enhanced gene expression if the HuR-mRNA interaction prevails, and in repression if the microRNA remains associated. *Cooperation* between HuR and microRNAs leads to lower expression of the shared mRNA. We also describe the regulation of HuR levels by microRNAs as well as the regulation of microRNA levels by HuR. Finally, we discuss transcriptome-wide analyses of HuR-bound mRNAs with neighboring microRNA sites, and review the emerging mechanisms whereby microRNAs confer versatility and strength to the post-transcriptional outcomes of HuR targets.

1.0. INTRODUCTION

Post-transcriptional gene expression is controlled at multiple levels, including pre-mRNA splicing and maturation, as well as mRNA transport, editing, storage, stability, and translation [1, 2]. The control of mRNA turnover and translation in the cytoplasm is particularly effective in eliciting rapid changes in the patterns of expressed proteins following environmental perturbations. Noncoding RNAs (particularly microRNAs) and turnover and translation regulatory RNA-binding proteins (TTR-RBPs) are major *trans*-binding factors that associate with specific *cis* elements in mRNAs and modulate their stability and translation [3-5].

1.1. MicroRNAs

MicroRNAs (miRNAs) are short (~22-nucleotides) noncoding RNAs that potently influence gene expression patterns [6, 7]. They are synthesized from long primary miRNA (pri-miRNA) transcripts which are processed in the nucleus by ribonucleases (Drosha and DiGeorge critical region 8) to generate precursor (pre-miRNA) transcripts. Following export to the cytoplasm by exportin 5, the pre-miRNA is further processed by the ribonuclease Dicer, yielding ~22-nt duplex RNAs; one strand of the duplex is loaded into the miRNA-containing ribonucleoprotein inhibitory complex (RISC), which contains Argonaute proteins

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[8, 9]. The miRNA-RISC then targets a specific mRNA, typically at the 3'-untranslated region (UTR). The miRNA and mRNA form a partial hybrid that often requires the presence of a 'seed' region (nucleotides 2 to 7 of the miRNA) of strong complementarity with the mRNA. The association of miRNA-RISC with an mRNA lowers the stability of the mRNA, suppresses its translation, or has both of these effects [6, 7]. However, under specific circumstances, like during cellular quiescence, microRNAs can also promote translation [10].

1.1.1. Combinatorial actions of microRNAs—As discussed by Serva and coworkers [11], a single microRNA usually has only partial effect in reducing the stability or translation of a target mRNA; thus, microRNAs often work in concert to inhibit the expression of a shared target mRNA [12]. In addition, given that a single microRNA can target multiple mRNAs, it can simultaneously influence the production of different proteins. In some instances, these coordinate target proteins are related functionally [11].

1.2. HuR

The mammalian Hu/elav (embryonic lethal abnormal vision in *Drosophila*) family of TTR-RBPs comprises the ubiquitous HuR (HuA) and the primarily neuronal proteins HuB, HuC, and HuD [13]. Since its discovery fifteen years ago [14], HuR has been found to interact with numerous mRNAs [15-18]. It was originally described as a stabilizing TTR-RBP [19], but was later found to affect the translation of target mRNAs, generally promoting translation, but sometimes inhibiting it (reviewed in [13, 18, 20]). In keeping with its abundant nuclear presence, HuR can also interact with pre-mRNA and may affect splicing, as revealed in recent high-throughput studies using PAR-CLIP (photoactivatable-ribonucleoside-enhanced crosslinking and immunoprecipitation [15, 16]). However, in this review, we will focus on the actions of HuR in the *cytoplasm*, where it stabilizes target mRNAs and modulates their translation.

1.2.1. Influence of HuR on target mRNAs—Through its three RNA recognition motifs (RRMs), HuR interacts with target mRNA, many of which bear U- and AU-rich elements (AREs) in their 3'UTRs. However, HuR can also bind to sequences in the 5'UTR of some target mRNAs [21-23] and, as mentioned above, also with pre-mRNAs near splice sites [15, 16]. HuR target mRNAs encode proteins implicated in cellular proliferation, angiogenesis, inflammation, differentiation, signaling, genotoxic and oxidative damage, nutrient deprivation, and hypoxia (reviewed in [18]).

HuR stabilizes many of its bound mRNAs [18-20]. The exact mechanisms of stabilization have not been fully elucidated, but binding of HuR to a target mRNA was widely believed to block the association of other TTR-RBPs capable of recruiting the mRNA to sites of decay like the exosome or processing bodies (PBs). However, as we discuss here, HuR also appears to protect mRNAs from degradation through competition with microRNAs (section 2.1.) with affinity for the same mRNAs.

HuR also modulates the translation of several target mRNAs [13, 18]. In some cases, HuR promotes the translation of some target mRNA through its association with 5'UTR internal ribosome entry site (IRESs) [24], although competition of HuR with microRNAs also represents an effective way to enhance translation (section 2.1.) [25]. HuR also inhibits the translation of a small subset of target mRNAs; in some instances, this effect was attributed to the disruption of 5'UTR IRESs [21-23], but for some targets, reduced translation was linked to HuR's recruitment of miRNA-RISC complexes to their 3'UTR [26] (section 2.2.).

1.2.2. Regulation of HuR function—Initial studies identified HuR cytoplasmic export as a critical way to control expression of HuR target mRNAs, but recent work has shown that HuR abundance and post-translational modifications also potentially influence HuR function. These processes are only covered briefly here, since they are reviewed in detail in an excellent piece by Eberhardt and coworkers in this volume [27].

HuR localization: The transport of HuR across the nuclear envelope requires a specific HuR domain (the HuR nucleocytoplasmic shuttling domain or HNS) and several transport machinery components, including transportins 1 and 2, the chromosome region maintenance 1 (CRM1), and importin-1 α [28-31]. HuR nucleocytoplasmic transport is also influenced by kinases [cyclin-dependent kinase 1 (Cdk1), AMP-activated protein kinase (AMPK), protein kinase C (PKC), and the mitogen-activated protein kinase (MAPK) p38] which phosphorylate HuR and proteins that transport HuR [32-36]. In general, modification of residues within or near the HNS alter HuR subcellular localization [27].

HuR abundance: The steady-state levels of HuR protein are regulated transcriptionally by the nuclear factor (NF)- κ B and by Smads [37, 38]. At the post-transcriptional level, HuR binds the *HuR* mRNA, stabilizes it, and enhances its cytoplasmic export [39]. A number of microRNAs negatively regulate HuR production (section 3.0.). The stability of HuR is further controlled by ubiquitination [in response to heat stress] and by cleavage via caspases [40, 41].

HuR binding to target mRNAs: Generally speaking, the phosphorylation of residues within the RRM1s affects HuR binding to target mRNAs. Phosphorylation by the checkpoint kinase Chk2 at HuR residues Ser-88, Ser-100, and Thr-118 (located between and within RRM1 and RRM2) modulates HuR binding to several target mRNAs [42, 43]. Oxidative stress and γ irradiation activated Chk2, which in turn phosphorylated HuR and dissociated it from many mRNAs [42, 43]. Phosphorylation by PKC α at HuR Ser-158 and Ser-221 in response to ATP treatment, and phosphorylation by PKC δ of Ser-221 and Ser-318 in response to angiotensin II (AngII) promoted the binding activity of HuR [32, 33, 44, 45]. In cells exposed to γ irradiation, p38 phosphorylated HuR at Thr-118, increasing its association with p21 mRNA [46]. Finally, HuR methylation at Asp-271 by CARM1 (coactivator-associated arginine methyltransferase 1) in response to lipopolysaccharide stimulation promoted HuR binding to and stabilization of TNF α mRNA [47].

2.0. HuR and microRNAs regulate shared target mRNAs

MicroRNAs and HuR regulate each other's function in many ways, including by mutually influencing their expression (sections 3.0. and 4.0.), and by jointly affecting the expression of shared target mRNAs (below). This combinatorial regulation is supported by the observations that HuR and Argonaute share many interacting mRNAs [48, 49], and that HuR and microRNAs can function competitively (section 2.1.) and cooperatively (section 2.2.). In this section, we concentrate on the joint regulation of shared mRNAs by HuR and microRNAs (Table 1) [50,51].

2.1. Competitive regulation of mRNAs by HuR and miRNAs

Since HuR functions primarily as a positive regulator of mRNA stability and/or translation, whereas microRNAs are typically negative regulators of the same processes, it is easy to envision how these two regulators might antagonize each other's function. Accordingly, their association might result in opposing effects on the localization of mRNAs, either in translationally active polysomes or in repressive cytoplasmic complexes (e.g., PBs) [25, 52, 53].

CAT1 mRNA—In the very first report of functional competition between HuR and microRNA, Bhattacharyya and colleagues found that HuR translocation from nucleus to cytoplasm under stress conditions (amino acid deprivation) relieved the miR-122-elicited repression of the mRNA encoding the cationic amino acid transporter 1 (*CAT1* mRNA) [25]. The authors showed that in human liver cancer cells, the stress-induced de-repression of *CAT1* mRNA was due to relocation of the transcripts from PBs to translationally engaged polysomes.

TOP2A mRNA—Up- or downregulation HuR levels and microRNA levels during normal cellular processes like cell division or differentiation can also change their relative influence on shared transcripts. For example, the increase expression of topoisomerase II alpha (*TOP2A*, an enzyme that relieves tension from supercoiled DNA) by HuR was highest during G2/M phase, when HuR was most abundant [54]. Using a novel strategy based on the tagging of a transcript with MS2 RNA hairpins to identify associated microRNAs, miR-548c was found to interact with the *TOP2A* mRNA 3'UTR [52]. Accordingly, HuR downregulation or miR-548c overexpression increased the interaction of *TOP2A* mRNA with miR-548c-RISC and the recruitment of *TOP2A* transcripts to PBs. In turn, HuR overexpression decreased miR-548c-*TOP2A* mRNA interaction and reversed the miR-548c-mediated repression. Moreover, as miR-548c levels were most abundant during the G1 phase, miR-548c lowered *TOP2A* mRNA translation in G1 [52].

NCL mRNA—A similar competitive regulation was recently found to control the expression of the nucleolar RNA-binding and DNA-binding protein nucleolin (NCL). NCL expression was promoted by HuR and repressed by miR-494 [53]. As seen with *TOP2A*, HuR increase lowered *NCL* mRNA interaction with miR-494-RISC, reduced the recruitment of *NCL* transcripts to PBs and elevated NCL production. Conversely, miR-494 upregulation increased *NCL* mRNA interaction with RISC, diminished the interaction of HuR with *NCL* mRNA, and decreased NCL levels.

COX2 mRNA—Very recently, Young and coworkers reported that in colorectal cancer (CRC) and in cultured CRC lines, expression of the proinflammatory enzyme cyclooxygenase-2 (Cox-2) was controlled by the antagonistic interaction of HuR and miR-16. Cox-2 expression was negatively regulated by miR-16, and this inhibition was reversed when HuR was overexpressed in CRC cells [55] (more details in section 3.3.).

ERBB2 mRNA—ERBB-2 promotes resistance to therapy and malignant progression in prostate cancer. miR-331-3p associates with the *ERBB2* 3'UTR at two different sites and repressed *ERBB2* biosynthesis. A recent study [56] showed that HuR binds to a U-rich element in the *ERBB2* mRNA and competed for association of miR-331-3p, thereby preventing the inhibitory action of miR-331-3p and enhancing ERBB2 biosynthesis.

Transcriptome-wide analysis of antagonism between HuR and microRNAs—

Two groups recently studied transcriptome-wide HuR-mRNA interactions using PAR-CLIP and compared their results with previously known miRNA-mRNA interactions to understand the prevalence of this combinatorial regulation [15, 16]. In one of these studies [16], Lebedeva and colleagues found that microRNA binding sites were preferentially located toward the boundaries of 3'UTR as previously reported [50, 57] whereas HuR binding sites distributed uniformly along the 3'UTR except for regions surrounding the stop codon and the polyadenylation site. Bioinformatic predictions revealed that instead of overlapping with HuR sites, most of the miRNA sites were found in the immediate vicinity of HuR binding sites. With overlapping binding sites, direct competition between microRNA and HuR should be possible, whereas in the context of nonoverlapping sites,

competition could occur by steric hindrance or by non-steric hindrance involving changes in the secondary structure of the RNA. In the second HuR PAR-CLIP study [15], Mukherjee and coworkers broadly confirmed these results and further reported differences in transcript abundance after HuR knockdown or microRNA knockdown. The authors proposed that where microRNA and HuR binding sites overlapped, the transcripts were preferentially regulated by HuR, but when the binding sites are non-overlapping the transcripts were mainly regulated by the microRNA.

Our understanding of the competition between HuR and microRNAs is still preliminary. Given the results with *CAT1*, *TOP2A*, and *NCL* mRNAs, where HuR binds at far distances from microRNAs, it is generally believed that conformational changes of the RNA (which remain challenging to study) could favor HuR-mRNA interactions and exclude miRNA-mRNA interactions, and vice versa (Fig. 1). Competition at distant sites could also result from physical recruitment of the mRNA to different parts of the cell; for example, microRNAs could recruit mRNAs to PBs, while HuR could recruit mRNAs to polysomes or even to the nucleus. Little experimental evidence is available as-yet in support of these models.

2.2. Cooperative regulation of mRNAs by HuR and miRNAs

Although HuR typically stabilizes and/or increases target mRNA translation, there is a handful of examples of HuR's repressive effect on some target mRNAs [21, 22, 26]. In these instances, miRNAs could work co-operatively with HuR to downregulate gene expression. Here, we review the limited examples reported so far of HuR cooperating with microRNAs to repress target mRNAs via destabilization or inhibition of translation.

MYC mRNA—Kim et al. [26] reported that HuR associated with the 3'UTR of the *MYC* mRNA and enhanced production of the proto-oncogene c-Myc. HuR facilitated the interaction of let-7-RISC with the *MYC* 3'UTR, leading to its destabilization and translational repression. As with competition examples, the HuR and let-7 binding sites on the *MYC* 3'UTR were over 100 nt apart, so HuR binding was proposed to trigger a conformational change in the *MYC* 3'UTR which promoted the interaction of let-7-RISC [26].

RhoB mRNA—More recently, Glorian et al [58] reported that the HuR-dependent recruitment of miR-19 to the *RhoB* mRNA was responsible for repressing the production of RhoB (Ras homolog B, a GTP-binding protein) after exposure to ultraviolet light. Accordingly, loss of interaction with HuR and miR-19 led to increased RhoB production and triggered apoptosis. In a manner reminiscent of the HuR/let-7 and *MYC* mRNA, HuR binding to *RhoB* mRNA facilitated the loading of miR-19-RISC at a distal region of *RhoB* mRNA.

p16 mRNA—Chang et al [59] similarly observed that RISC components were recruited to the mRNA encoding the cdk inhibitor, tumor suppressor, and senescence-associated protein p16. This interaction led to the destabilization of p16 mRNA in a manner that was dependent on HuR and another RBP (AUF1), although the specific miRNAs involved were not identified.

2.3. General aspects of the combinatorial gene regulation by HuR and miRNAs

While individual mRNA studies have uncovered different ways in which HuR and microRNAs can compete or cooperate, and transcriptome-wide analyses of HuR and Ago2 sites support the existence of these regulatory mechanisms, our understanding of this combinatorial regulation is still rudimentary. To comprehend this process better, further

analyses of individual mRNAs is needed, including the specific HuR and microRNA sites, the distance between them, and how binding of each factor affects the local secondary structure of the RNA (using technologies like SHAPE (hydroxyl acylation analyzed by primer extension [60]). Second, it is necessary to understand in better molecular detail how HuR and microRNAs modulate the translation and stability of its targets. Third, while HuR and microRNAs preferentially interact with AU-rich elements [50, 57] in the 3'UTR of target mRNAs, high-throughput analyses did not reveal more widespread examples of competitive regulation of target mRNA decay by HuR and microRNAs. Perhaps different experimental designs to identify Ago2 sites in the presence and absence of HuR or after stress or mitogenic signals will be informative. In this regard, perhaps testing mRNA levels is insufficient, since both HuR and microRNAs can also modulate translation; instead, high-throughput changes in translation should be studied using assays like pulsed SILAC, nascent translation assays, and polysome profiling. Finally, care must be taken to differentiate this combinatorial regulation from the direct regulation of HuR abundance by microRNAs (section 3.0.) or the regulation of microRNAs levels by HuR (section 4.0.).

3.0. microRNAs that regulate HuR expression

MicroRNAs are among the few identified regulators of HuR expression levels. Indeed, some of the effects attributed to these microRNAs could in fact be indirect, through their regulation of HuR production. In this section, we will review the microRNAs that modulate HuR levels.

3.1. miR-519

HuR expression was potently lowered by the microRNA miR-519 in several human cancer cell lines, including HeLa (cervical), HCT116 and RKO (colon), and A2780 (ovarian) [61]. This reduction was primarily caused by the repression of HuR translation, not by decreased *HuR* mRNA stability. Interestingly, of the two putative sites of miR-519 interaction on the *HuR* mRNA, one residing in its coding region (CR) and one in its 3'UTR, the CR site repressed HuR translation more potently. In a replicative senescence model, miR-519 levels correlated inversely with HuR, as miR-519 levels rose and HuR levels and cell proliferation declined in senescent cells [62]. The levels of miR-519 and HuR also showed inverse correlation in tissue pairs from cancer patients: cancer tissues displayed high HuR and low miR-519 levels, normal tissues had high miR-519 and low HuR levels. Since HuR promotes cell proliferation and tumorigenesis [61, 63], overexpression of miR-519 inhibited DNA replication and cell division and reduced tumorigenesis, supporting the view that miR-519 could function as a tumor suppressor microRNA [63].

3.2. miR-125a

Although miR-125a and miR-125b differ only by a central diuridine insertion and a U-to-C change, only miR-125a (not miR-125b) suppressed HuR expression by interacting with the 3'UTR of HuR mRNA, as shown in a breast cancer model [64]. As with miR-519, an inverse correlation between HuR of miR-125a was reported in breast cancer cells, where miR-125a levels were low and HuR levels were high [64].

3.3. miR-16

In the human breast carcinoma cell line MDA-MB-231, low miR-16 and high HuR was linked to the interaction of miR-16 to the HuR 3'UTR and its negative influence HuR translation [65]. As miR-16 inhibited the expression of cancer-associated proteins Cox-2, TNF α , Bcl-2, Mcl-1, and Cyclin D1 [66, 67], and these mRNAs are also targets of stabilization and/or translational upregulation by HuR [18], the authors proposed that miR-16 reduced the expression of these target mRNAs both by directly inhibiting them and

by lowering the levels of their positive regulator, HuR. Through an unexpected negative feedback mechanism, HuR protein also associated with miR-16 and this interaction was linked to a reduction in miR-16 levels (section 4.1., [55]).

3.4. miR-34a

A direct transcriptional target of p53, miR-34a triggered apoptosis in HCT116 colon cancer cells and in chronic lymphocytic leukemia cells [68, 69], caused G1 arrest and lowered colony formation in the osteosarcoma cell line U2OS [70], and diminished proliferation and accelerated senescence in the fetal lung cell line IMR90 [71]. Accordingly, miR-34a levels decline in many cancers [68, 72] and is a key mediator of tumor suppression by directly and indirectly controlling the expression of many proteins [73]. Recently, miR-34a levels were found to be low, while HuR levels were high, in paclitaxel-resistant cells generated from hormone refractory prostate cancer cells (PC3PR) [74]. Although it was not shown whether miR-34a directly associated with the HuR mRNA, miR-34a overexpression lowered HuR production in PC3PR cells. Therefore, Kojima and colleagues proposed that miR-34a not only directly lowered the levels of cancer-related genes (e.g., Sirt1, Bcl-2) by directly associating with their 3'UTRs and triggering repression, but miR-34a also indirectly reduced their levels by suppressing the production of HuR, a positive regulator of SIRT1 and Bcl-2 mRNAs. Together, HuR, Sirt1, and Bcl2 played important roles in the development of paclitaxel resistance in PC3PR cells [74].

4.0. Regulation of microRNA expression by HuR

HuR also influences the expression of certain microRNAs, although only a limited number of examples has been reported and the mechanisms are poorly understood at present.

4.1. miR-16

HuR was recently found to interact with miR-16 in colon cancer cells [65]. In this model system miR-16 associated with *COX2* 3'UTR and reduced Cox-2 abundance, as mentioned above (section 3.3). HuR competed for binding to this mRNA and thus promoted *COX2* mRNA stability and Cox-2 expression. Additionally, however, the accumulation of HuR in the cytoplasm led to HuR binding to miR-16 and this interaction was linked to a rapid decline in the steady-state levels of miR-16 [55]. The molecular details of this reduction are unknown, but these results make the provocative case that HuR could promote Cox-2 expression both by direct binding to *COX2* 3'UTR, and by indirectly reducing the abundance of the key *COX2* mRNA repressor miR-16.

4.2. miR-7

The levels of miR-7 increased dramatically after silencing HuR [16]. As miR-7 is contained within the last intron of the *HNRNPK* gene and hnRNP K is a highly expressed housekeeping protein, the authors propose that HuR strongly suppresses the biogenesis of mature miR-7 at the level of processing, perhaps by affecting the fate of the excised intron that contains the miR-7 precursor. The striking rise in miR-7 abundance after silencing HuR prompted the authors to suggest that a number of HuR-elicited actions be the consequence of HuR-mediated lowering of miR-7 production [16].

4.3. Other microRNAs

PAR-CLIP analysis revealed the interaction of HuR with microRNA precursor transcripts (pri-microRNAs) [15, 16]. In addition, this global analysis also found a number of mature microRNAs which are direct targets of HuR, including the oncogenic microRNAs miR-21 and miR-221, and several microRNAs with functional links to HuR activity (e.g., miR-125a and various members of the let-7 family). It is presently unknown whether HuR affects the

expression of bound microRNAs by enhancing their degradation (as described for miR-16) or other aspects of their expression or function.

5.0. Conclusions

HuR is a prominent regulator of the cytoplasmic fate of its target mRNAs, but the mechanism of HuR actions were only partly explained by its functional links to TTR-RBPs which promoted decay and repressed translation. Studies over the past half-decade have revealed that many HuR actions on target mRNAs may be due to HuR's physical and functional interactions with microRNAs. HuR competes with several microRNAs (Section 2.1.), thereby antagonizing their repressive influence on target mRNAs, while HuR can also cooperate (Section 2.2.) with other microRNAs in repressing protein production. While some of these influences may be direct (HuR and microRNAs compete for the very same mRNA site), it is likely that both cooperation and competition occur even when HuR and microRNA-RISC interact with distant sites on the shared target mRNA. According to a widespread view, binding of HuR can trigger a conformational change in the local RNA that hides or reveals sites for binding the microRNA-RISC (Fig. 1). Conversely, binding of the microRNA-RISC can cover or uncover a site of HuR interaction on the mRNA. We anticipate that detailed RNA conformation analyses will provide experimental backing to this model in the near future.

MicroRNAs were also found to influence HuR production, while HuR affected the levels of certain microRNAs. In this regard, it was intriguing to find that HuR bound miR-16 and yet it *reduced* miR-16 abundance. It will be interesting to elucidate the mechanisms behind this loss of a target microRNA. In addition, the fact that HuR binds to multiple microRNAs suggests that it might function as a 'sponge' (a 'sequestering' factor) of microRNAs to make them unavailable for binding to Ago/RISC. Perhaps HuR may also or alternatively preserve a pool of microRNAs in 'storage' or simply protect it from decay. These are interesting possibilities that warrant future study.

Finally, although HuR is one of the best-known proteins that affect target mRNA stability and translation, it is easy to envision how the function of other TTR-RBPs may be regulated by similar interplays with microRNAs [75]. It is increasingly apparent that the coordinated actions of TTR-RBPs and microRNAs add a dynamic layer of complexity to gene regulatory mechanisms that ensure proper development, differentiation and adaptive responses to stimuli.

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Fig. 1. Schematic of competitive and cooperative interactions of HuR and microRNAs on shared target mRNAs

Top, under the 'competition' model, binding of miRNA-RISC may trigger a conformational change that hides the site of HuR binding to the mRNA, in turn lowering expression of the mRNA (*left*); conversely, HuR binding may trigger changes in RNA structure that conceal the site of interaction with miRNA-RISC, causing increased expression of the mRNA (*right*). *Bottom*, in the 'cooperation' model, binding of HuR may trigger conformational changes that allow binding of miRNA-RISC or vice versa, resulting in repression of the mRNA.

Table 1
Coordinant influence of microRNAs and HuR on shared target mRNAs

The table lists the reported examples of microRNAs (column 1) that interact with HuR target mRNAs (column 2) and either compete (top set) or cooperate (bottom set) with HuR in controlling expression (stability and/or translation) of the shared target mRNA.

MicroRNA	Target shared with HuR	Effect of miRNA	Effect of HuR	Type of Interaction	References
miR-122	<i>CAT1</i> mRNA	Repression	Induction	Competitive	[25]
miR-548c	<i>TOP2A</i> mRNA	Repression	Induction	Competitive	[52]
miR-494	<i>NCL</i> mRNA	Repression	Induction	Competitive	[53]
miR-16	<i>COX2</i> mRNA	Repression	Induction	Competitive	[55]
miR-331	<i>ERBB2</i> mRNA	Repression	Induction	Competitive	[56]
let-7	<i>MYC</i> mRNA	Repression	Repression	Cooperative	[26]
miR-19	<i>RhoB</i> mRNA	Repression	Repression	Cooperative	[58]
(RISC)	<i>p16</i> mRNA	Repression	Repression	Cooperative	[59]

Table 2
Influence of microRNAs on HuR expression and vice versa

The table lists the microRNAs that associate with the *HuR* mRNA (at the CR or 3'UTR) and repress HuR production (top set), and the association of HuR with some mature or primary microRNAs reported to lower their expression levels (bottom set).

Regulator	Target	Effect of Regulator	References
miR-519	<i>HuR</i> mRNA (CR)	Repression	[61]
miR-125a	<i>HuR</i> mRNA (3'UTR)	Repression	[64]
miR-16	<i>HuR</i> mRNA (3'UTR)	Repression	[65]
miR-34a	<i>HuR</i> mRNA (3'UTR)	Repression	[74]
HuR	pri-miR-7	Repression	[16]
HuR	miR-16 (?)	Repression	[65]