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Post-transcriptional regulation of cancer traits by HuR

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Abstract

Cancer-related gene expression programs are strongly influenced by post-transcriptional mechanisms. The RNA-binding protein HuR is highly abundant in many cancers. Numerous HuR-regulated mRNAs encode proteins implicated in carcinogenesis. Here, we review the collections of HuR target mRNAs that encode proteins responsible for implementing five major cancer traits. By interacting with specific mRNA subsets, HuR enhances the levels of proteins that 1) promote cell proliferation, 2) increase cell survival, 3) elevate local angiogenesis, 4) help the cancer cell evade immune recognition, and 5) facilitate cancer cell invasion and metastasis. We propose that HuR exerts a tumorigenic function by enabling these cancer phenotypes. We discuss evidence that links HuR to several specific cancers and suggests its potential usefulness in cancer diagnosis, prognosis, and therapy.

INTRODUCTION

The expression of distinct collections of proteins allows cancer cells to develop, survive, proliferate, and colonize other tissues (1). Although some changes in the expression of cancer-related proteins arise through gene mutation, most cancer-specific protein expression patterns involve genes that are not mutated, but are expressed aberrantly (2). Besides modified transcription, protein production can change through altered post-transcriptional mechanisms such as mRNA splicing, transport, storage, translation, and degradation (3–5). These processes are governed by two types of RNA-binding factors, RNA-binding proteins (RBPs) and noncoding RNAs, particularly microRNAs (6, 7).

The impact of RBPs on the expression of cancer-associated genes is well recognized. Many oncoproteins, tumor suppressor proteins, and other cancer-related proteins are encoded by mRNAs whose half-lives and/or translation are tightly regulated. The sequences that confer differential turnover or translation typically reside in the 5′- and 3′-untranslated regions (UTRs) of the mRNA. Accordingly, several RBPs that associate with these regions and modulate mRNA turnover and translation (e.g., tristetraprolin, AUF1, and Sam68) have been found to influence cancer-associated protein expression (3, 4, 8, 9). Among the earliest RBPs that were identified as being associated with tumorigenesis (10) are the members of the Hu/elav (embryonic lethal abnormal vision) protein family, which comprises three primarily neuronal proteins (HuB, HuC, and HuD), and one ubiquitous protein, HuR [ELAVL1, also known as HuA (11, 12)].

HuR FUNCTION

HuR has three RNA recognition motifs (RRMs) through which it interacts with target mRNAs, preferentially those bearing U- or AU-rich sequences in their 5′-UTRs and 3′-UTRs (11, 13). The association of HuR and target transcripts is modulated following

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phosphorylation by protein kinase C (PKC), the mitogen-activated protein kinase (MAPK) p38, and the checkpoint kinase Chk2, which also modulates HuR levels by influencing its ubiquitination (14–18). HuR is primarily nuclear and has been implicated in mRNA splicing (19), but its nuclear functions remain obscure. By contrast, HuR's ability to stabilize and/or modulate the translation of many of its target mRNAs is closely linked to its translocation to the cytoplasm (11). The transport of HuR across the nuclear envelope involves a specific HuR domain (the HuR nucleocytoplasmic shuttling sequence or HNS) and several transport machinery components, including CRM1, transportins 1 and 2, and importin-1 (20–23). HuR nucleocytoplasmic transport is also influenced by kinases [cyclin-dependent kinase (Cdk)1, AMP-activated protein kinase (AMPK), PKC, and p38] that phosphorylate HuR and HuR transport components (15, 16, 24–27). These and other post-translational modifications (28, 29) of HuR that affect HuR abundance, subcellular localization, and mRNA binding are summarized in Fig. 1.

HuR-stabilized target mRNAs include those that encode p21, c-fos, vascular endothelial growth factor (VEGF), the MAPK phosphatase (MKP)-1, inducible nitric oxide synthase (iNOS), granulocyte/macrophage-colony-stimulating factor (GM-CSF), sirtuin 1, tumor necrosis factor (TNF)- , Bcl-2, Mcl-1, COX-2, glutamylcysteine synthetase heavy subunit (GCSh), urokinase-type plasminogen activator (uPA) and its receptor (uPAR), p53, interleukin (IL)-3, and cyclins A2, B1, E, and D1 (14, 30–41). The exact mechanisms by which HuR stabilizes these mRNAs are not fully understood, but HuR likely competes with other RBPs whose interaction with the same labile mRNAs might lead to their recruitment to cellular structures for mRNA degradation, such as the exosome and processing (P) bodies (42–49).

HuR can repress the translation of many target mRNAs, like those encoding p27, the type-I insulin-like growth factor receptor (IGF-IR), Wnt5a, and c-Myc (41, 50–53). Additionally, HuR can promote the translation of many other target transcripts, such as those that encode the hypoxia-inducible factor (HIF)-1 , p53, prothymosin (ProT), MKP-1, cytochrome *c*, heme oxygenase-1, and CAT-1 (54–59). The molecular mechanisms whereby HuR modulates translation are also poorly characterized. In some cases, HuR was proposed to interfere with internal ribosome entry sites (IRESs) in the 5 UTRs of target mRNAs (50, 52); in other cases, its effects on translation were due to competition or cooperation with microRNAs (53, 56).

Through its influence on collections of expressed proteins, HuR has been implicated in many cellular processes, including differentiation, the cellular response to damaging stimuli, and the immune and inflammatory responses (reviewed in 11, 41). In addition, HuR is increasingly recognized as a pivotal factor in cancer-related gene expression. This function is based on HuR's ability to promote the expression of proteins that enhance proliferation, inhibit apoptosis, increase angiogenesis, reduce immune recognition, and facilitate invasion and metastasis (Table 1). Accordingly, a direct role for HuR in tumorigenesis is beginning to emerge (11, 60, 61). In this review, we will first describe the subsets of HuR target transcripts that promote each of these traits of cancer cells. We will then describe the evidence linking HuR to specific malignancies and its growing recognition as a diagnostic, prognostic, and therapeutic target in human cancer.

HuR-REGULATED mRNAs ENCODING PROTEINS IMPLICATED IN CANCER TRAITS

As proposed by Hanahan and Weinberg, normal cells evolve into cancer cells through the acquisition of specific phenotypes, including enhanced abilities to proliferate, survive apoptotic stimuli, develop local angiogenesis, and colonize other tissues (1). Over the past

decade, numerous HuR-regulated mRNAs have been identified that contribute directly to the acquisition of each of these cancer traits (11, 61, 62). In this section, we will review these hallmark features of cancer cells and identify the HuR target mRNAs through which HuR can elicit cancer-related phenotypes (Fig. 2).

Promotion of cell proliferation

Cancer cells must divide actively in order for the tumor mass to grow. This trait is usually accompanied by altered abundance of cell cycle regulators, leading to shortened cell division times and to expansion of the tumor population. By associating with the mRNAs that encode them, HuR increases the levels of many cell cycle regulators, particularly cyclins, which activate cdks during different cell cycle phases; cyclins and cdks have been directly implicated in cancer progression (63). Additionally, the process of cellular senescence, widely considered to be a tumor suppressive mechanism linked to the cessation of cell division (64, 65), is suppressed by HuR overexpression (66). HuR inhibits cellular replicative senescence at least in part by enhancing the expression of several cyclins (66).

Cyclin D1—This cyclin is an essential activator of Cdk4 and Cdk6, which participate in the progression through the G1 phase of the cell division cycle. Elevated Cyclin D1 expression has been reported in tumor cells, associated with a shortened G1 phase (67, 68). HuR associates with the 3 UTR of *Cyclin D1* mRNA and stabilizes it, at least partly by competing with decay-promoting RBPs, as observed in human cervical carcinoma cells (37).

Cyclin E—An activator of Cdk2, Cyclin E is critical for progression through the G1/S transition. Cyclin E is highly expressed in several malignancies, including gastric, ovarian, breast and colorectal cancers, and plays an important role in oncogenic transformation (70–73). HuR was recently found to bind to the *Cyclin E* 3 UTR and promoted Cyclin E expression in the breast cancer cells (74, 75). Downregulation of HuR significantly lowered *Cyclin E* mRNA stability and protein levels, while HuR overexpression elevated Cyclin E1 production, in turn accelerating cell proliferation (74, 75).

Cyclin A2—Also a Cdk2 cofactor, Cyclin A2 promotes progression through the S phase. Cyclin A2 levels increase in tumors, associated with elevated proliferation (76, 77). HuR was shown to interact with the *Cyclin A2* 3 UTR and stabilized the *Cyclin A2* mRNA in a cell cycle-dependent manner in colon cancer cells (31). In cervical carcinoma cells, HuR phosphorylation at serine 202 (S202) by the G2 kinase Cdk1 caused the nuclear retention of HuR, leading to marked reductions in both *Cyclin A2* mRNA stability and Cyclin A2 translation (25). Conversely, the nonphosphorylatable mutants HuR(S202A) and HuR(S242A) accumulated in the cytoplasm, enhancing Cyclin A2 expression and increasing cell proliferation (25–27).

Cyclin B1—A major activator of Cdk1 and hence a key factor for progression through the G2 phase, cyclin B1 abundance is elevated in tumors (78, 79). HuR associated with the 3 UTR of the *cyclin B1* mRNA and stabilized it during the S and G2 phases in colon cancer cells (31, 66). As described for *Cyclin A2* mRNA, the cytoplasmic accumulation of the nonphosphorylatable mutant HuR(S242A) also led to the stabilization of *Cyclin B1* mRNA (26).

p27—By inhibiting Cdk2, p27 prevents cell proliferation (80). Reductions in p27 levels are associated with cancer, both because low p27 levels enhance cell division and because p27 is strongly pro-apoptotic (81). HuR interacts with the 5 UTR of *p27* mRNA and represses p27 translation (50); the precise mechanisms of repression is unclear, but HuR may disrupt the activity of an IRES in the *p27* 5 UTR (50).

Epidermal growth factor (EGF)—Besides acting on cell cycle regulatory factors, HuR can promote the expression of factors that promote proliferation. EGF is a key signaling molecule that stimulates cell growth and proliferation. It functions by interacting with the EGF receptor (EGFR), which triggers proliferative signaling pathways and promotes tumorigenesis (82). HuR associates with the *EGF* 3′UTR, although its exact influence upon EGF expression awaits further study (83).

Eukaryotic translation initiation factor (eIF4E)—Eukaryotic mRNAs possess a 7-methyl-guanosine (m7G) *cap* structure at their 5′-end. The protein eIF4E binds the m7G cap and brings mRNAs to the ribosome for translation (84). eIF4E is found elevated in human cancers, is considered to be oncogenic, since its overexpression leads to transformation and enhances tumorigenesis, and is a therapeutic target (85). HuR was recently found to interact with the 3′UTR of the *eIF4E* mRNA, stabilizing the *eIF4E* mRNA and increasing eIF4E expression (86). As postulated by Topisirovic and co-workers, eIF4E and HuR could jointly upregulate the expression of proliferative proteins encoded by shared target mRNAs (86).

Enhancement of cell survival

Tumor cells develop under stress conditions, including reduced access to nutrients and growth factors and increased exposure to oxidative damage. In order to thrive, they must overcome death-causing signals, particularly those leading to apoptosis (programmed cell death). Apoptosis resistance is engendered by the expression of specific anti-apoptotic genes. As discussed below and elsewhere (39, 55, 87), HuR stabilizes and modulates the translation of numerous mRNAs and thereby promotes the expression of anti-apoptotic proteins and represses the expression of pro-apoptotic proteins. In addition, HuR was recently reported to regulate the splicing of the apoptosis-promoting receptor Fas; the resulting exclusion of an exon rendered a soluble Fas isoform that prevented cell death (19). It is important to note that under conditions of prolonged or severe stress, HuR can exert a pro-apoptotic influence instead (reviewed in 87).

Prothymosin α (ProTα)—ProTα protects against apoptosis by inhibiting the formation of the apoptosome, a cytosolic macromolecular complex that assembles in cells committed to apoptotic death. The apoptosome activates caspase-9, which in turn activates effector caspases culminating in apoptotic cell death (88). In this capacity, ProTα plays a key role in cell survival and is highly expressed in several cancers (88, 89). HuR was shown to promote ProTα expression by interacting with the 3′UTR of *ProTα* mRNA and enhancing its translation (55). In turn, the HuR-mediated increase in ProTα expression protected cervical carcinoma cells against irradiation with short-wavelength ultraviolet light (UVC) (55).

B-cell lymphoma 2 (Bcl-2)—The proto-oncogene Bcl-2 is expressed in many cancers and is a major anti-apoptotic protein, inhibiting the release of cytochrome *c* from the mitochondria (90). In leukemia and carcinoma lines, HuR was shown to bind the *Bcl-2* mRNA, stabilized it, and promoted Bcl-2 translation, leading to a significant increase in Bcl-2 abundance (39, 91).

Myeloid cell leukemia-1 (Mcl-1)—Mcl-1 is highly similar to Bcl-2, both structurally and functionally, and is also highly expressed in several cancer cells (92). Although molecular details of the influence of HuR on Mcl-1 expression are unknown, in cervical carcinoma cells HuR interacts with the *Mcl-1* mRNA and HuR downregulation lowers *Mcl-1* mRNA and protein abundance (39).

Sirtuin 1 (SIRT1)—SIRT1 promotes cell survival by deacetylating and thereby suppressing the activities of pro-apoptotic proteins such as p53, Foxo-3a and Ku70

(reviewed in 93). SIRT1 is highly expressed in different cancers including colon, prostate, and cervical cancers and has been ascribed a number of pro-tumor functions (94). HuR was found to interact with the *SIRT1* 3 UTR, enhanced *SIRT1* mRNA stability, and thereby increased SIRT1 levels (14). In turn, cells expressing high SIRT1 showed heightened resistance to apoptosis triggered by various damaging agents (14, 95).

p21^{WAF1}—A universal inhibitor of cdks, p21 reduces cell cycle progression and proliferation (96). p21 has been proposed to be pro-oncogenic by its ability to inhibit apoptosis in response to stress signals, through both p53-dependent and p53-independent mechanisms (97, 98). Accordingly, decreased p21 expression following preoperative chemoradiotherapy for rectal cancer was associated with improved disease-free survival (99). HuR interacts with the 3 UTR of the *p21* mRNA (32); after exposure to UVC or ionizing irradiation, HuR increased the stability of *p21* mRNA and elevated p21 expression (17, 32). These findings suggest that HuR could enhance p21 expression during the course of radiotherapy, conferring increased resistance to the cancer cell.

Mdm2—The Mdm2 p53-binding protein promotes cell survival. It inactivates p53 function by binding to its transactivation domain and targeting it for proteasome-mediated proteolysis. Recently, HuR was reported to interact with the *Mdm-2* mRNA, although the specific region of binding was not determined (100). In inducible HuR-null mice, *Mdm-2* mRNA stability was markedly reduced, leading to the reduced expression of Mdm-2, which the authors linked to widespread apoptosis in the intestinal epithelium, loss of intestinal villi, and lethality by 10 days after induction of the HuR-null phenotype (100).

c-Myc—Among many complex cellular functions, the c-Myc transcription factor is potently pro-apoptotic (101, 102). Aknown HuR target (103), the *c-Myc* mRNA was recently shown to be subject to translational repression by HuR; this process required the recruitment of the microRNA let-7 to a site adjacent to the HuR-binding region on the *c-Myc* 3 UTR (53). Together with the enhanced expression of the anti-apoptotic proteins listed above, the repression of the pro-apoptotic c-Myc solidifies a role of HuR as a strong anti-apoptotic factor.

Elevation of local angiogenesis

In order to expand, tumor cells need to develop local vasculature. This process, termed angiogenesis, permits the delivery of nutrients and oxygen and allows tumors to thrive (104). Numerous signals can promote or inhibit angiogenesis. Below we include examples of HuR promoting the expression of pro-angiogenic factors and halting the production of anti-angiogenic factors.

Hypoxia-inducible factor alpha (HIF-1α)—The transcription factor HIF-1 is robustly expressed in cells growing in the presence of low oxygen concentrations (hypoxia). Under these conditions, HIF-1 plays a key role in the transcriptional activation of several genes that are essential for the cell's adaptation to hypoxia (105, 106). Several studies have reported increased HIF-1 abundance in tumors, a correlation between HIF-1 levels and aggressive cancer phenotypes, and a role for HIF-1 as a potential target for cancer therapy (107, 108). Among the many factors that associate with *HIF-1* mRNA and modulate its expression, HuR interacts with the *HIF-1* 5 UTR and promotes HIF-1 translation, and with the *HIF-1* 3 UTR and stabilizes it (83,109–111). Among other cancer-related functions, HIF-1 is potently cytoprotective (112).

Vascular endothelial growth factor (VEGF)—VEGF enhances cancer development by promoting cell growth, angiogenesis, proliferation, and migration (113–116). VEGF is

highly expressed in tumor cells growing in hypoxic conditions. The *VEGF* mRNA was one of the first HuR targets identified (30); binding of HuR to the *VEGF* 3′UTR increased *VEGF* mRNA stability and VEGF production in cultured cells and in tumors (30, 117). As the *VEGF* gene is also a transcriptional target of HIF-1, increases in HuR both enhance the transcription of *VEGF* mRNA (via the heightened abundance of HIF-1) and stabilize the *VEGF* mRNA, potently elevating VEGF production.

Cyclooxygenase-2 (COX-2)—COX-2 is highly expressed in many cancers, associated with increased VEGF levels and angiogenesis (118, 119). Although COX-2 plays a major role in mediating inflammation, its inhibitors are also effective anticancer drugs which function by blocking angiogenesis and tumor proliferation (119, 120). HuR binds to an AU-rich sequence in the *COX-2* 3′UTR, stabilizes the *COX-2* mRNA, and increases COX-2 biosynthesis (121). Colon, ovarian, and prostate cancer cells with elevated cytoplasmic HuR levels also expressed higher levels of COX-2 and in one recent report, HuR was shown to regulate COX-2 levels during colon carcinogenesis (122–125). The same correlation between HuR and COX-2 levels was seen in human mesothelioma, where it was further established that overall survival was strongly influenced by the subcellular localization of HuR (126).

Thrombospondin—Expression of the oncogene and inhibitor of angiogenesis thrombospondin (TSP1) is often lost in tumors (127, 128). HuR associates with the *TSP1* 3′UTR and enhances its translation (62). Interestingly, in a model of breast cancer progression, the association of HuR with *TSP1* mRNA was progressively reduced as the cells displayed increasingly tumorigenic phenotypes. In highly malignant cells, this reduced interaction resulted in the diminished expression of TSP1; in turn, reduced TSP1 levels enhanced the pro-angiogenic phenotype of the cancer cells (62). Considering that HuR increases pro-angiogenic factors (VEGF, HIF-1, and COX-2), the inhibition of TSP1 synthesis by HuR's dissociation from *TSP1* mRNA underscores HuR's efficient coordination of an angiogenic program in cancer cells.

Reduced immune recognition

Surveillance by the immune system leads to the elimination of tumor cells. Therefore, cancer cells have adopted mechanisms to avoid recognition by immune cells. Despite the scarcity of examples to-date of HuR regulating proteins to escape immune surveillance, it is worth mentioning that HuR-mediated increase in MKP-1 levels in immune cells could help to accomplish the same phenotype, as MKP-1 potently suppresses immune function (129, 130). As reported in cervical carcinoma cells, HuR was interacted with the *MKP-1* mRNA, stabilized it, and enhanced its translation following exposure to oxidative stress (58).

Transforming growth factor β (TGF-β)—The cytokine TGF-is involved in cell proliferation, differentiation, and apoptosis (131). Although TGF-can suppress the development of early-stage tumors, it promotes late-stage tumor growth by stimulating proliferation, invasiveness, and metastasis (132, 133). Some studies have linked the tumorigenic influence of TGF-to the fact that it enables tumor cells to escape immune recognition (134, 135). HuR binds with high affinity the 3′UTR of *TGF-*mRNA and was shown to regulate its expression post-transcriptionally in malignant brain tumors (136); this function could be important to evade immune recognition and allow cancer development.

Invasion and metastasis

Eventually, tumor cells will invade adjacent tissues and colonize distant tissues. These complex processes implicate changes in the interaction of the cancer cell with its local environment and the increased function of extracellular proteases.

Snail—Overexpression of the transcription factor *snail* is responsible for the induction of the epithelial-to-mesenchymal transition (EMT), through the repression of epithelial factors such as E-cadherin and cytokeratins, and the induction of mesenchymal proteins like fibronectin and metalloproteases (137). HuR was found to interact with the 3 UTR of *snail* mRNA and stabilized it following oxidative stress (138).

Matrix metalloproteinase 9 (MMP-9)—MMPs are metallopeptidases capable of cleaving most extracellular matrix (ECM) substrates, including collagens, laminin, fibronectin, vitronectin and proteoglycans in both physiological and pathological conditions (139, 140). MMP-9 is highly expressed in different cancers and is normally associated with high levels of invasion and/or metastasis of cervical, colorectal, gastric, pancreatic, breast, and oral cancers, as well as in glioma and skin tumors (141–144). In MMP-9-null mice, tumors that mimic human recurrent primary tumors did not grow; likewise, inhibition of MMP-9 limited or inhibited local tumor invasion and metastasis (144, 145). HuR was reported to bind to the 3 UTR of *MMP-9* mRNA and stabilized it, an effect that was enhanced by extracellular ATP and was suppressed by nitric oxide-triggered reduction in HuR levels (146, 147).

Urokinase A (uPA) and uPA-receptor (uPAR)—The urokinase-type plasminogen activator (uPA) and uPA receptor (uPAR) are members of a serine proteinase system that participates in ECM degradation, thereby affecting cell adhesion, invasion, and metastasis (148). uPA and uPAR are overexpressed in several malignant tumors, associated with poor disease outcome (148, 149). In an interesting example of coordinate regulation of functionally related proteins, HuR interacted with the 3 UTRs of both *uPA* and *uPAR* mRNAs, increased their stabilities, and enhanced expression of the encoded proteins (36). In this manner, HuR stimulates the uPA/uPAR signaling pathway leading to ECM degradation and facilitating tumor invasion and metastasis (150).

HuR EXPRESSION IN CANCER

The discovery that HuR was broadly elevated in cancer tissues compared with the corresponding non-cancer tissues (60) has been complemented by the analysis of HuR levels in specific cancers. To-date, the bulk of the studies on HuR in cancer have examined correlations between HuR abundance in cancer tissues and the stage and grade of the cancer. Recent studies have begun to assess the possible diagnostic, prognostic, and therapeutic value of HuR in cancer.

Breast cancer

Increased cytoplasmic HuR levels were found to be associated with high-grade, invasive ductal breast carcinoma, as well as with poor outcome, large tumor size, and poor survival rates (151). In breast cancer cells, HuR increased expression of Cyclin E1, IL-8, estrogen receptor, TSP1, and c-fms (62, 74, 152–154). HuR was found to be more abundant in the cytoplasm after treatment with tamoxifen, suggesting that HuR could modulate the sensitivity to tamoxifen (155). Interestingly, in human breast epithelial cells, HuR was found to interact with the *Wnt5a* 3 UTR and repressed the translation of *Wnt5a*, a protein that inhibits tumor growth (52). HuR also associated with the *BRCA1* 3 UTR and reduced BRCA1 expression, although the molecular details of this influence were not studied (156). HuR was identified as an important prognostic factor in a subset of breast cancers, where it constituted an independent marker of reduced patient survival (157).

Colon cancer

Increased expression of HuR in colon cancer tissues promoted the expression of COX-2 and VEGF (121, 123), while the cytoplasmic abundance of HuR was associated with COX-2 expression levels and with high tumor stage (158). Importantly, overexpression of HuR increased the growth of colon cancer cells in a nude mouse xenograft model (60).

Ovarian cancer

HuR was found in the cytoplasm of ~50% of serous-type ovarian carcinoma, associated with elevated COX-2 expression, high grade, and poor patient prognosis (125). HuR was also found to interact with the 3 UTR of the *ARHI/DRAS3* mRNA, which encodes a tumor suppressor protein, and likely increases ARHI expression (159). However, in ovarian cancer cells, HuR showed diminished interaction with *ARHI* mRNA, associated with the reduced expression of AHRI (159). One study examining the distribution of HuR in ~100 ovarian carcinomas revealed that HuR was primarily nuclear, but was found in the cytoplasm of 45% of ovarian carcinomas; this localization was associated with increased COX-2 expression, tumor grade, and mitotic activity, and with reduced overall patient survival (160). On the other hand, a large screen of ovarian carcinomas revealed an association between *nuclear* HuR and invasive cancer, high tumor grade, and decreased disease-free survival, indicating that nuclear HuR may also play a key role in ovarian tumorigenesis (161).

Prostate cancer

The analysis of HuR in over 100 primary prostate carcinoma samples revealed that HuR was predominantly nuclear in normal prostate glands but showed an elevated cytoplasmic presence in prostate carcinoma; the shift in localization that was linked to the levels of prostate-specific antigen (PSA) (162). Patients whose tumors showed elevated cytoplasmic HuR expressed higher COX-2, had shorter disease-free survival times, and had adverse prognosis, supporting the view that cytoplasmic HuR promotes prostate tumor development and relapse (124, 162).

Pancreatic cancer

In a recent study, elevated abundance of cytoplasmic HuR in pancreatic ductal adenocarcinoma (PDA) was associated with a 7-fold *lower* risk of patient mortality (163). The authors linked the cytoplasmic levels of HuR with binding of HuR to the *deoxycytidine kinase* (*dCK*) mRNA leading to its stabilization and the enhanced expression of dCK. This observation was significant because dCK metabolizes, and thereby activates, gemcitabine, a major component of a common chemotherapeutic regimen for PDA. Accordingly, Costantino and colleagues proposed that the presence of elevated HuR enhances the efficacy of gemcitabine in PDA and improves patient outcome (163).

Oral cancer

HuR expression levels were determined in salivary pleomorphic adenoma and salivary mucoepidermoid carcinoma. One third of pleomorphic adenomas and most mucoepidermoid carcinomas exhibited high cytoplasmic HuR levels; in the latter group, COX-2 expression was also elevated. This study suggests that in salivary carcinoma, cytoplasmic HuR levels correlate with COX-2 expression and that COX-2 and cytoplasmic HuR immunoreactivity could be used to evaluate malignancy in the salivary glands (164). A comparison between oral cancer and normal cells in culture revealed that HuR was nuclear in normal cells, but it was abundantly cytoplasmic in the oral cancer lines (165). Moreover, while inhibition of CRM1 reportedly blocked HuR export to the cytoplasm, in oral cancer cells HuR was readily exported to the cytoplasm despite CRM1 inhibition. These findings suggest that the

cytoplasmic export of HuR is different in oral carcinoma cells compared with normal cells (165). Whether HuR nuclear export is also aberrant in other tumor types awaits further study.

Other cancers

In gastric cancer, HuR concentration also correlated with COX-2 expression and with poor survival rates, suggesting that HuR may also enhance gastric carcinogenesis (166, 167). Similarly, a comparison of primary Merkel cell carcinoma (MCC) and non-neoplastic skin showed that cytoplasmic HuR was higher in a subset of MMC tumors than in non-neoplastic skin, supporting a role for HuR in MMC carcinogenesis (168). In tumors of the central nervous system (CNS), HuR overexpression was linked to the enhanced expression of COX-2, VEGF, TGF- and other factors involved in CNS tumor proliferation and angiogenesis (136).

CONCLUDING REMARKS

HuR interacts with and regulates many mRNAs encoding cancer-related proteins (11, 12, 41, 60). By modulating their expression in a coordinated manner, HuR can have a profound impact on multiple phenotypic traits central to tumorigenesis. The heightened expression of HuR, particularly cytoplasmic HuR, in virtually all cancers examined suggests that HuR could be a useful diagnostic marker. However, it is important to measure HuR protein levels instead of *HuR* mRNA levels, as the latter do not change markedly between normal and cancer tissues (9, 169). Why HuR protein levels change with cancer without changes in *HuR* mRNA levels is not fully understood, but may be linked to the stability of the protein itself (18) or to the translational repression of HuR by microRNAs such as miR-519 and miR-125a, which inhibit HuR translation without affecting *HuR* mRNA levels (169, 170). Similarly, the subcellular localization of HuR and its ability to bind mRNAs strongly influences the expression of target mRNAs. These facets of HuR are modulated by several post-translational modifications and transport machineries; virtually all of the HuR-modifying enzymes (Chk2, PKC, CARM1, Cdk1, p38, caspases) have been implicated in cancer-related processes (Fig. 1). Further studies to understand the complex mechanisms that regulate HuR abundance, localization, and binding to target transcripts in cancer cells are warranted.

Given the extensive catalog of genes that HuR controls, and HuR's positive influence on angiogenesis, proliferation, survival, invasion, etc, strategies to reduce HuR expression or inhibit its function could be successful in reducing tumor progression. Silencing approaches using small interfering (si)iRNA or microRNAs appear to be effective in cultured cells and might be attempted in tumors. In addition, small chemical inhibitors of HuR have been reported, but their usefulness in organisms also remain untested (171). However, it is important to note that most studies on HuR and cancer have not examined how HuR might affect anti-cancer therapy. In the Costantino report mentioned above, the elevated presence of cytoplasmic HuR in pancreatic cancer cells paradoxically correlated with better prognosis in patients treated with the standard drug of choice, gemcitabine; that HuR increased the expression of deoxycytidine kinase, which metabolizes and thus activates gemcitabine, helped to explain why elevated HuR was associated with positive response to therapy. Similarly, low HuR levels were associated with high risk of breast cancer recurrence, although the specific mediators of this effect were not identified (172). Therefore, interventions to reduce HuR function should be devised carefully. In some cases, the elevated presence of HuR may be advantageous for therapy and could be exploited to that end.

While the use of cultured cells has advanced greatly our understanding of HuR function and influence on cancer-associated proteins, major efforts must now focus on mammalian models of carcinogenesis (173). Mouse HuR-null thymocytes showed aberrant cell division cycle, activation, selection, and survival (174). A role for HuR in the establishment of a physiologic thymocyte pool was confirmed in another mouse model with inducible global HuR-null phenotype, which showed widespread death of progenitor cells in hematopoietic organs and in the intestinal epithelium (100). While the mouse phenotypes agree with HuR's roles in proliferation and survival, more studies are needed to elucidate if an HuR-null status affects tumorigenesis. Transgenic mice overexpressing HuR will also be highly informative in providing insight into the role of HuR in cancer. With the knowledge gained thus far of HuR-regulated gene expression programs, the stage is ready for direct assessment of HuR's diagnostic, prognostic, and therapeutic potential in human cancer.

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Abbreviations

AMPK	AMP-activated protein kinase
Bcl-2	B-cell lymphoma 2
Cdk1	cyclin-dependent kinase 1
Chk2	checkpoint kinase 2
CNS	central nervous system
COX-2	cyclooxygenase-2
CR	coding region
dCK	deoxycytidine kinase
eIF4E	eukaryotic translation initiation factor 4E
Elav	embryonic lethal abnormal vision
GM-CSF	granulocyte/macrophage-colony-stimulating factor
HIF	hypoxia-inducible factor
HNS	HuR nucleocytoplasmic shuttling sequence
IGF-IR	type-I insulin-like growth factor receptor
IL	interleukin
iNOS	inducible nitric oxide synthase
IRES	internal ribosome entry site
MAPK	mitogen-activated protein kinase
Mcl-1	myeloid cell leukemia-1
MKP-1	MAPK phosphatase-1
MMP-9	matrix metalloproteinase 9
PKC	protein kinase C
PSA	prostate-specific antigen

RBP	RNA-binding protein
RRM	RNA recognition motif
SIRT1	sirtuin 1
TGF-	transforming growth factor
TNF	tumor necrosis factor
TSP1	thrombospondin
uPA	urokinase-type plasminogen activator
uPAR	uPA receptor
UTR	untranslated region
VEGF	vascular endothelial growth factor

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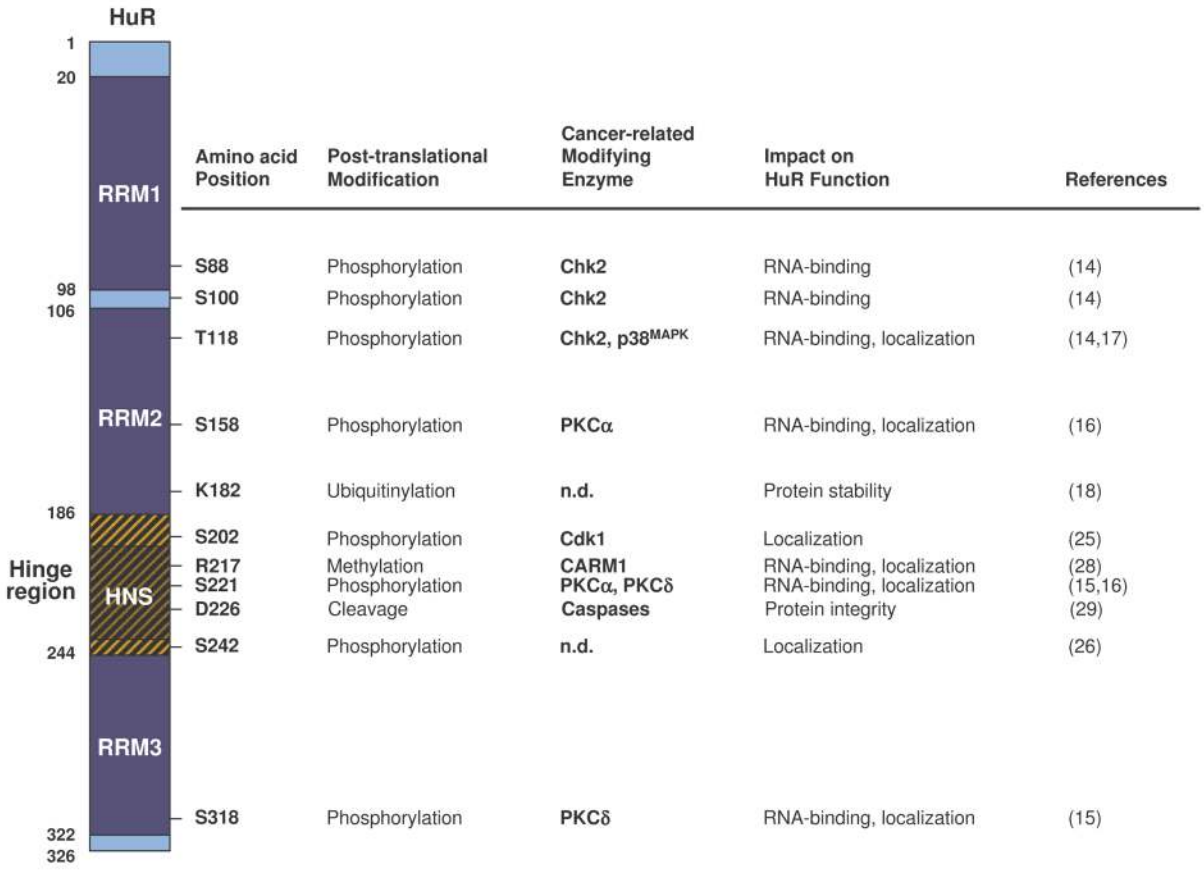

Amino acid Position	Post-translational Modification	Cancer-related Modifying Enzyme	Impact on HuR Function	References
S88	Phosphorylation	Chk2	RNA-binding	(14)
S100	Phosphorylation	Chk2	RNA-binding	(14)
T118	Phosphorylation	Chk2, p38^{MAPK}	RNA-binding, localization	(14,17)
S158	Phosphorylation	PKCα	RNA-binding, localization	(16)
K182	Ubiquitinylation	n.d.	Protein stability	(18)
S202	Phosphorylation	Cdk1	Localization	(25)
R217	Methylation	CARM1	RNA-binding, localization	(28)
S221	Phosphorylation	PKCα, PKCδ	RNA-binding, localization	(15,16)
D226	Cleavage	Caspases	Protein integrity	(29)
S242	Phosphorylation	n.d.	Localization	(26)
S318	Phosphorylation	PKCδ	RNA-binding, localization	(15)

Figure 1. HuR protein and post-translational modification by cancer-related enzymes

The HuR three RNA recognition motifs (*RRMs*) and hinge region (amino acids 186-244), containing the HuR nucleocytoplasmic shuttling (*HNS*) domain, are indicated. The specific residues (*Amino Acid Positions*, first column) implicated in different post-translational modifications (second column) and the cancer-related enzymes that carry out the modifications (third column) are listed. The consequences of modification at each residue are listed under 'Impact on HuR Function'. n.d., not determined.

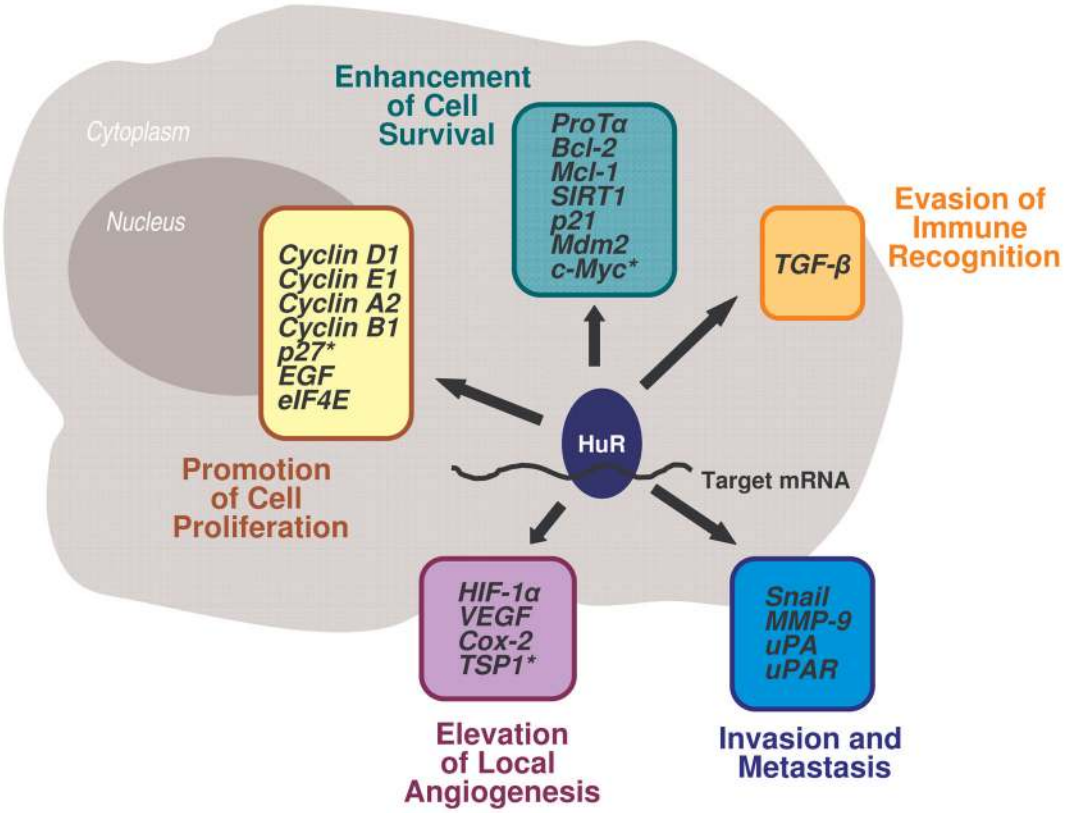

Figure 2. HuR-target mRNAs implicated in establishing cancer traits

The subsets of HuR target mRNAs involved in five major cancer-acquired phenotypes are listed. * denotes transcripts whose expression decreases in the presence of HuR, either because HuR represses their translation (c-Myc, p27) or because its association with HuR is reduced in cancer (TSP1).

Table 1

Specific regulation of HuR-target mRNAs encoding cancer proteins

Listed are HuR target transcripts, the regions (3 UTR, 5 UTR) where the binding sites are located, and HuR's influence on the stability or translation of each mRNA. The main cancer traits influenced by the encoded proteins are indicated under 'Main Cancer Traits'.

Target mRNA	Binding Site	Influence on mRNA	Main Cancer Traits	Reference
Cyclin D1	3 UTR	Stability	Proliferation	(37)
Cyclin E1	3 UTR	Stability	Proliferation	(74,75)
Cyclin A2	3 UTR	Stability Translation	Proliferation	(25,26,31)
Cyclin B1	3 UTR	Stability	Proliferation	(26,31,66)
p27	5 UTR	Translation	Proliferation, Survival	(50)
EGF	3 UTR	(n.d.)	Proliferation, Survival	(83)
eIF4E	3 UTR	Stability	Proliferation, Survival	(86)
ProT	3 UTR	Translation	Proliferation, Survival	(55)
Bcl-2	3 UTR	Stability Translation	Survival	(39,91)
Mcl-1	n.d.	Stability	Survival	(39)
SIRT1	3 UTR	Stability	Survival	(14)
p21	3 UTR	Stability	Proliferation, Survival	(17,32)
Mdm-2	n.d.	Stability	Survival	(100)
c-Myc	3 UTR	Translation	Proliferation, Survival	(53,103)
HIF-1	5 UTR, 3 UTR	Stability	Angiogenesis, Survival	(83,111)
VEGF	3 UTR	Stability Translation	Angiogenesis, Proliferation	(30,117)
COX-2	3 UTR	Stability	Angiogenesis	(120,121)
TSP1 *	3 UTR	Translation	Angiogenesis	(62)
TGF-	3 UTR	(n.d.)	Immunity/inflammation	(136)
Snail	3 UTR	Stability	Invasion	(138)
MMP-9	3 UTR	Stability	Invasion	(146, 147)
uPA	3 UTR	Stability	Invasion	(36)
uPAR	3 UTR	Stability	Invasion	(36)
BRCA1	3 UTR	(n.d.)	Tumor suppression	(156)
Wnt5a	3 UTR	Translation	Oncogenesis	(52)
c-fms	3 UTR	Stability	Oncogenesis	(154)

Target mRNA	Binding Site	Influence on mRNA	Main Cancer Traits	Reference
ARHI	3 UTR	Stability	Tumor suppression	(159)

Bottom, HuR target mRNAs encoding proteins with broad cancer-related functions. HuR stabilizes or increases translation; HuR represses translation; * the interaction of HuR with *TSP1* mRNA declines in cancer. n.d., molecular mechanisms not determined.