Investigational New Drugs (2019) 37:1107–1116
https://doi.org/10.1007/s10637-018-00723-x

REVIEW

# Human antigen R and drug resistance in tumors

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Received: 30 September 2018 / Accepted: 27 December 2018 / Published online: 5 January 2019


**Summary**
The human embryonic lethal abnormal visual protein, HuR, belongs to the Hu family of RNA-binding proteins. Over the past two decades, HuR has been extensively associated with multiple biological characteristics of tumors, including tumor development and progression, angiogenesis, invasion, migration and prognosis, since this protein regulates the stability of cancer-associated target mRNAs due to its posttranscriptional regulatory mechanisms. A recent investigation of the multiple functions of HuR has provided emerging evidence of its role in drug resistance in various tumors. Herein, we demonstrate the roles of HuR proteins in the development of drug resistance, examine their involvement in various mechanisms, including apoptosis, the ABC transporter family, the cell cycle and the DNA damage response, and provide insight into ongoing studies for developing therapeutic strategies aimed at targeting this molecule in tumor cells.

**Keywords** HuR · Drug therapy · Neoplasms · RNA-binding proteins · Multidrug-resistant

## Introduction

Tumors are diseases that pose a serious threat to human health. Drug therapy still plays an irreplaceable role in the treatment of tumors, especially in patients with advanced stage diseases or those who cannot undergo surgery. However, the emergence of drug resistance has become an important obstacle affecting therapeutic effects. Even the development of multidrug resistance (MDR) greatly limits the efficacy of agents. Studies have been devoted to finding a safer and more effective therapeutic scheme for tumors. For example, immunotherapy and gene-targeted therapy have become research hotspots in recent years. However, there is still no safe and effective treatment option. In recent years, studies have found that posttranscriptional regulatory mechanisms play key regulatory roles in a variety of tumor biological properties (including drug resistance). Among the most important molecules are human antigen R and miRNAs. Tumor-targeted treatment strategies for related molecules are expected to be a secure and efficient treatment.

Human embryonic lethal abnormal visual-like protein, HuR, is a member of the Hu family of RNA-binding proteins. This molecule, first described in tumors nearly two decades ago, has received much attention in tumor-related research in recent years because it regulates the expression of various tumor-associated molecules through posttranscriptional regulation, which conversely affects the biological characteristics of tumors. In recent years, studies have demonstrated that HuR is associated with tumor drug resistance, suggesting that HuR may be a novel target for tumor therapy and a marker for therapeutic response and prognosis assessment. Emerging evidence has demonstrated that HuR is associated with drug resistance in multiple tumors, including pancreatic cancer, colorectal cancer, prostate cancer, lung cancer, breast cancer, bladder cancer, glioma, oral cancer and ovarian cancer. Thus, therapeutic strategies targeting this small molecule may set a new chapter in the treatment of cancers. This review will discuss the various mechanisms of the role of HuR in drug resistance and explore the application prospects of targeted therapeutic strategies.

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## Expression of HuR in tumors

Human antigen R (HuR) is a member of the ELAV family of RNA-binding proteins. HuR is extensively expressed in the cytoplasm of multiple tumors compared with other ELAV family members (HuB, HuC, and HuD), which are exclusively expressed in neuronal tissues [1]. In the resting state, HuR is predominantly located in the nucleus. Under various stimulating factors, HuR can recognize and bind to tumor-associated mRNAs that are enriched with adenine/uridine (AU) or uridine (U) elements through three typical RNA recognition motifs (RRMs), and the HuR-mRNA complex is then transferred to the cytoplasm to exert its function of stabilizing the target mRNA and regulating translation (Fig. 1) [2]. The cellular and subcellular localization of HuR may be the basis for regulating the biological properties of tumors. Scholars have confirmed that the mRNA stabilizing function of HuR is essential for cancer development, although the mechanisms by which HuR mediates cancer progression have not been fully elucidated.

Although HuR plays a crucial role in the posttranscriptional regulation of many transcripts, the regulation of its own function and expression remains obscure. For example, HuR has been shown to be stabilized by NEDDylation mediated by the murine double minute 2 (Mdm2) protein [3]. Sousa et al. [4] found that treatment of ovarian cancer cells with the NEDDylation inhibitor MLN4924 can inhibit the NEDDylation process of HuR and overcome the drug resistance of ovarian cancer cells to carboplatin. In addition, HuR mRNA can be regulated by Smad, TTP, RNPC1, Mdm2, pp32 and Hsf1 [5–8]. Interestingly, studies have consistently shown that HuR plays a significant role in stabilizing target mRNA. However, Winkler et al. [9] found that HuR can bind to the caspase-2-5′ untranslated region (UTR) and negatively regulate mRNA and inhibit the protein level of caspase-2, leading us to consider another class of molecules that bind to the 5′ untranslated region (UTR) or 3'UTR of target mRNA, namely, miRNAs, which inhibit the degradation or translation of target mRNAs and thus negatively regulate the expression of cancer-related molecules [10]. Whether the stability of mRNA is increased or decreased may depend on the binding strength of HuR and miRNA to the target mRNA [11–13]. In addition, miRNAs can also interact with specific sites in the 3'UTR and 5'UTR of HuR mRNA. Notably, HuR regulates the expression of many molecules through different posttranscriptional mechanisms, including mRNA trafficking, mRNA decay and protein translation.

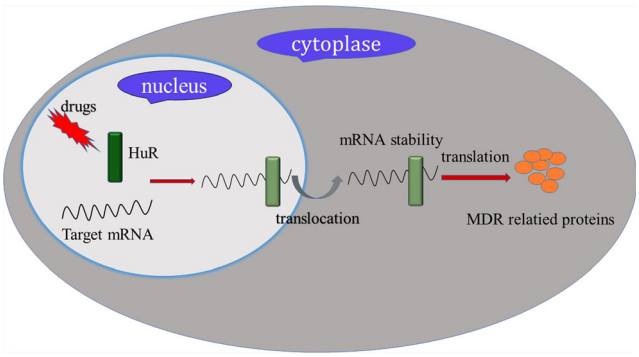


**Fig. 1** HuR is localized in the nucleus of resting cells. Under chemotherapy drug stimulation, HuR binds to mRNAs and is then transported to the cytoplasm. Once HuR is localized in the cytoplasm, it stabilizes the mRNA message and promotes the expression of MDR-related proteins

## HuR and tumor drug resistance

Drug therapy plays an irreplaceable role in the treatment of cancers. However, the emergence of drug resistance is the most relevant obstacle in treatment efficacy. Accumulating studies have explored specific mechanisms to overcome this phenomenon. In recent years, HuR has been widely studied in terms of drug resistance. In pancreatic cancer, Aldona Jakstaite et al. [14] found that HuR silencing can promote the sensitivity of pancreatic cancer cells to gemcitabine (GEM). Similarly, Blanco et al. [15] found that the inhibition of HuR homodimerization and its cytoplasmic translocation by the HuR inhibitor MS-444 can significantly enhance the sensitivity of PDA cells to oxaliplatin and 5-fluorouracil under physiological hypoxic conditions. Romeo et al. [16] also showed that the treatment of PDA cells with the HuR inhibitor (MS-444) enhanced TRAIL sensitivity. However, Costantino et al. [17] found that HuR enhances the sensitivity of tumor cells to gemcitabine by stabilizing the mRNA of deoxycytidine kinase, a key metabolic enzyme involved in gemcitabine activity. We speculate that the function of HuR may be attributed to the regulation of different types of cancer-related proteins. In addition, in numerous tumors, such as prostate cancer, breast cancer, lung cancer, colorectal cancer, oral cancer, bladder cancer and glioma, recent studies have shown that the differential expression of HuR was associated with chemoresistance in tumors (Table 1). In conclusion, overexpression of HuR mediates the development of multidrug resistance in tumors, and HuR is expected to be a target for drug therapy and reverse multidrug resistance.

## HuR-mediated pathways in drug resistance

### Regulation of the ABC transporter family

The ATP-binding cassette transporter superfamily belongs to a family of transporter genes that utilize ATP hydrolysis for energy, and approximately 48 ABC transporters have been associated with drug resistance [18], the most important of which include P-glycoprotein (P-gp) (encoded by ABCB1),

**Table 1** HuR and drug resistance in tumors

| Cancer | Cell lines | Drugs | Targets | Regults | First author, year and refs |
|---|---|---|---|---|---|
| Colorectal cancer | S1 and its resistant subline S1 M1 80 | 5-fluorouracil (5-FU)、irinotecan | ABCG2 | The effect of concomitant HuR and ABCG2 overexpression may be a more general phenomenon that mediates resistance to common ABCG2 substrate anticancer drugs in CRC. | Kenneth K.W., [22] |
| Pancreatic ductal adenocarcinoma | MiaPaCa2, CaPan1, Panc-1, Su.86.86, Hs766T, BxPC3 | TRAIL | DR4 | HuR contributes to TRAIL resistance by Restricting Death Receptor 4 expression in pancreatic cancer cells | Carmella Romeo, [16] |
| Pancreatic ductal adenocarcinoma | MiaPaca2,Su.86.86, Capan-1, and Capan-2 | gemcitabine | COX-2,HO-1 | HuR silencing significantly increased the effectiveness of GEM treatment in vitro | Aldona Jakstaite, [14] |
| Pancreatic Cancer | MiaPaCa2,PL5,Panc1 | DNA-damaging anticancer agents (mitomycin C, oxaliplatin, cisplatin, carboplatin, and a PARP inhibitor) | WEE1 | Silencing HuR in PDA cells sensitized the cells to these agents, whereas overexpressing HuR caused resistance | Shruti Lal, [63] |
| Pancreatic ductal adenocarcinoma | Patient samples | gemcitabine | COX-2,VEGF | Cytoplasmic HuR Expression is a Positive Predictive Marker in the Context of GEM Treatment | Nathan G. Richards, [70] |
| Colon cancer | SW620,HCT116 | epirubicin | galectin-3, β-catenin, cyclin D1, Bcl-2, P-gp, MRP1, MRP2 | HuR silencing intensified the cytotoxic effect of Epi on colon cancer cells | Guan-Liang Lin, [40] |
| pancreatic ductal adenocarcinomas | MIA PaCa-2, PANC-1, Capan-1, Hs 766 T, PL11 | PARP inhibitors | PARG | Genetic deletion of HuR enhances PARPi sensitivity | Saswati N. Chand, [67] |
| Pancreatic adenocarcinoma | MiaPaCa2,PL5 | gemcitabine | dCK, VEGF | siRNA knockdown of endogenous pp32 expression sensitizes cells to gemcitabine and pp32 overexpression reduce the association of HuR with the mRNA | Timothy K. Williams, [74] |
| Pancreatic ductal adenocarcinoma | MiaPaCa2 | oxaliplatin, 5-fluorouracil | PIM1 | The mRNA-binding protein HuR promotes hypoxia-induced chemoresistance through posttranscriptional regulation of the proto-oncogene PIM1 in pancreatic cancer cells | FF Blanco, [15] |
| Pancreatic ductal adenocarcinoma | MiaPaca2, PL-5, Hs766T | gemcitabine, Ara-C | dCK | HuR overexpression preferentially sensitized pancreatic cancer cell lines to the nucleoside analogues gemcitabine and Ara-C | Christina L. Costantino, [17] |
| Pancreatic ductal adenocarcinoma | MiaPaCa2, panc-1, BxPC3, Hs776 T | gemcitabine, oxaliplatin | IDH1 | Silencing HuR combined with nutrient withdrawal inhibits tumor growth in vivo | Mahsa Zarei, [73] |
| Breast cancer | MCF-7 | doxorubicin | MYC, SOCS3, FOS | HuR downregulation mediates doxorubicin drug resistance | Elisa Latorre, [75] |
| Prostate Cancer | DU145,PC-3 | docetaxel | ABCG2 | Posttranscriptional regulation of HuR by miR-133b enhances DTX cytotoxicity through inhibition of ABCG2 | Hui Liu, [23] |
| Glioblastoma | U251 | docetaxel | Bcl-2 | Inducible overexpression of HuR enhances Bcl-2 expression and chemoresistance | Natalia Filippova, [46] |
| Lung cancer | | NA | Bcl-2,p27 | | Ranganayaki Muralidharan, [49] |

**Table 1** (continued)

| Cancer | Cell lines | Drugs | Targets | Regults | First author, year and refs |
|---|---|---|---|---|---|
| | H1299, A549, HCC827, H1975 | | | CMLD-2,a small-molecule inhibitor,activates caspases and induces apoptotic cell death | |
| Bladder cancer | 5637,T24 | cisplatin, doxorubicin, vincristine, oxaliplatin | DNA ligase IV, BRCA2 | Inhibiting cytoplasmic accumulation of HuR synergizes genotoxic agents in bladder cancer | Jiawei Guo, [68] |
| Lung cancer | A549, CRL-1848, CRL-5803, HTB-177 | cisplatin | Snail | Loss of Scribble Promotes Snail Translation through Translocation of HuR and Enhances Cancer Drug Resistance | Yi Zhou, [76] |
| Colon carcinoma | DLD-1,HCT-15 | doxorubicin, paclitaxel | caspase-2 | Knockdown of HuR significantly increased the sensitivity of colon cancer cells to drug-induced apoptosis | Amel Badawi, [50] |
| Prostate Cancer | PC3 | paclitaxel | SIRT1,Bcl2 | miR-34a not only directly but also indirectly via regulating HuR expression acts on the 3'-UTR of SIRT1 and Bcl2 mRNAs, thereby attenuating paclitaxel-Resistance | Keitaro Kojima, [51] |
| Oral squamous cell carcinoma | UMSCC | paclitaxel | COX-2 | Silencing of HuR by shRNA reduced the rate of cell death in 74B cells, indicating that HuR partly facilitated apoptosis in paclitaxel treated cells | Harinarayanan Janakiraman, [71] |
| Ovarian tumour | ES-2 | carboplatin | SLC25A44, RAB5B, AQP3,KLF5 | Inhibition of the NEDDylation process overcomes cellular resistance mediated by HuR and cullin proteins | Graziele Fonseca de Sousa, [4] |

breast cancer resistant protein (BCRP) (encoded by ABCG 2) and multidrug resistance protein (MRP) (encoded by ABCC family) [19, 20]. The expression level of ABC transporters is generally higher in drug-resistant cells, and these proteins exert protective and excretory functions by expelling drugs from cells [21]. Therefore, it is easy to understand that the overexpression of ABC transporters plays a significant role in the development of MDR. A recent study showed that HuR regulates the expression of ABC transporters in tumors, which may provide new clues for HuR in regulating the mechanisms of MDR (Fig. 2).

For instance, Kenneth et al. [22] showed that compared with adjacent normal tissues, the tumor tissues from colorectal cancer patients who did not respond to 5-FU-based chemotherapy had a higher level of ABCG2. The high expression of ABCG2 in tumors is associated with the overexpression of HuR and low expression of miR-519c because miR-519c targets both ABCG2 and HuR. Furthermore, the overexpression of ABCG2 was caused by the interaction of miR-519c, HuR and the 3′ untranslated region (UTR) of ABCG2. Thus, miR-519c and HuR may also be potential drug targets that modulate ABCG2 against resistance in CRC chemotherapy (Fig. 3). Liu et al. [23] found that in prostate cancer, there is a downregulation of miR-133b and an upregulation of HuR. miR-133b can target and inhibit the expression of HuR. The ectopic expression of miR-133b and knockdown of HuR can inhibit cell viability and promote DTX-induced apoptosis in DTX-treated prostate cancer cells, whereas the overexpression of HuR reverses this effect. In addition, both miR-133b and HuR can target the ATP binding cassette (ABC) subfamily G member 2 (ABCG2), and the overexpression of HuR partially eliminates the inhibitory effect of miR-133b on ABCG2 expression. In conclusion, the posttranscriptional regulation of HuR by miR-133b enhances DTX cytotoxicity by inhibiting ABCG2, revealing a novel miR-133b / HuR / ABCG2 regulatory pathway to reverse chemotherapy resistance in prostate cancer. In addition, we found that multiple miRNAs are associated with chemoresistance in prostate cancer, including

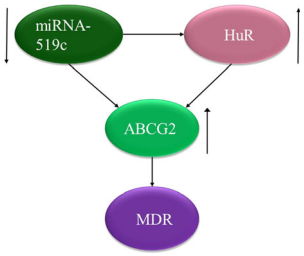


**Fig. 3** In colorectal cancer cells, the expression of miR-519c is decreased and the expression of HuR is increased. Both molecules promote the expression of ABCG2, thus regulating drug resistance in colorectal cancer

miR-205 [24, 25], miR-31, miR-212 [26], miR-200c [27], miR-21 [28], miR-34a [29, 30], miR-181a [31], miR-195 [32], miR-130a [33], miR-143 [34], miR-148a [35], miR-199 [36], miR-375 [37], miR-155 [38], miR-133b, and miR-204 [39]. The relationship between the above miRNAs and HuR has not been fully elucidated. We speculate that the miRNA/HuR/target gene regulatory axis plays an important role in tumor chemoresistance. Furthermore, Lin et al. [40] found that in colorectal cancer, HuR knockdown enhanced Epi-induced apoptosis by decreasing the cellular mRNA levels of MDR1, MRP1 and MRP2. We can conclude that HuR-mediated posttranscriptional regulation and its own regulatory mechanisms play a crucial role in tumor resistance associated with the ABC transporter family.

## Regulation of cell apoptosis

Apoptosis is one of the most important mechanisms by which multicellular organisms respond to environmental changes and maintain tissue homeostasis [41, 42]. Therefore, any disturbances in apoptotic mechanisms will have serious consequences. The inactivation or deficiency of apoptotic ability is a key factor in the development of cancer. Apoptosis is controlled by two closely related signaling pathways: the intrinsic pathway, which responds to DNA damage in cells, and the extrinsic pathway, whose extracellular signal is mainly

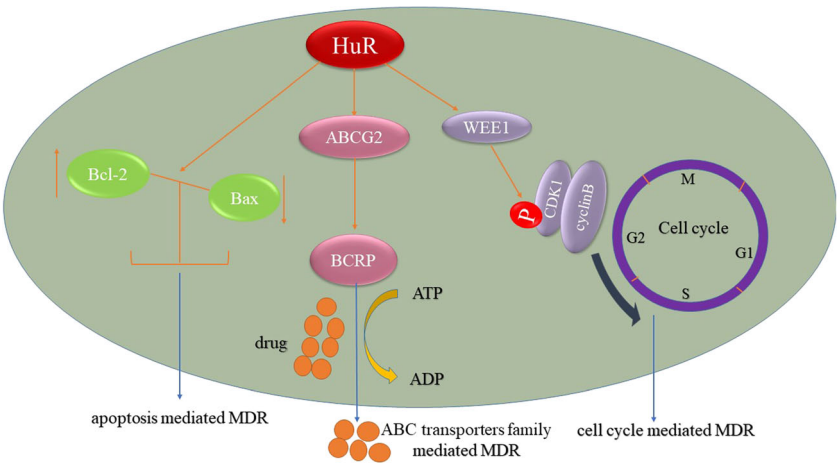


**Fig. 2** HuR regulates drug resistance in tumor cells through various cellular processes. The upregulation of HuR regulates multiple target mRNAs and proteins in MDR-related pathways

derived from toxic cells of the immune system [43]. These two approaches have considerable cross-talk and can be performed simultaneously. Members of the Bcl-2 family are activated in the intrinsic pathway to play a central role in response to DNA damage and p53 activity. There are three different Bcl-2 subfamilies [44, 45],, including anti-apoptotic proteins (Bcl-2, Bcl-XL, Mcl-1, Bcl-w), pro-apoptotic proteins (Bax, Bak, Bok) and regulatory proteins (BH3-only protein). The first two groups of proteins with multiple Bcl-2 homology domains (BH) have antagonistic effects on the regulation of apoptosis. Regulatory proteins, including Puma, Noxa, Bid, Bad, Bim and Bmf, comprising only a single Bcl-2 homology 3 domain (BH3-only protein), promote apoptosis by modulating the interaction of the other two groups. Recent studies have shown that HuR plays a crucial role in regulating apoptosis and its relationship with chemoresistance in tumors.

For instance, Lin et al. showed that the knockout of HuR increases Bax mRNA levels but decreases Bcl-2 mRNA levels. The combination of siHuR and Epi further amplifies the mRNA level of Bax and gently reduces Bcl-2 expression in the colorectal cancer cell line HCT116. These results explain that HuR knockdown enhanced Epi-induced apoptosis, but HuR overexpression did not rescue cells from Epi-induced apoptosis. In addition, Filippova et al. [46] found that HuR was required for anchorage-independent growth, survival and chemoresistance (etoposide, cisplatin, and topotecan) in gliomas; the mechanisms were partially attributed to the fact that HuR can bind to the 3'UTR of Bcl-2 family proteins and regulate their expression. Gliomas are characterized by the significant overexpression of the anti-apoptotic Bcl-2 family, which is associated with poor prognosis and therapeutic resistance [47, 48]. Muralidharan et al. [49] found that treatment of non-small cell lung cancer cells with CMLD-2 produced dose-dependent cytotoxicity, causing cell cycle arrest in the G1 phase and apoptosis. As a HuR small molecule inhibitor, CMLD-2 can decrease the mRNA of HuR and HuR-regulated proteins (Bcl-2 and p27) in tumor cells. In addition, in CMLD-2-treated NSCLC cells, the expression of HuR, Bcl-2, cyclin E and Bcl-XL decreased, accompanied by the increased expression of Bax and p27. Recently, Badawi et al. [50] found that the knockdown of HuR significantly increased the sensitivity of colon cancer cells to drugs (doxorubicin and paclitaxel). Functionally, doxorubicin and paclitaxel increased the interaction of cytoplasmic HuR with the 5′untranslated region (5′UTR) of caspase-2, suggesting the activation of a new HuR-mediated survival mechanism. Similarly, in prostate cancer, MiR-34a, HuR and its downstream targets SIRT1 and Bcl-2 play important roles in the development of paclitaxel resistance, all molecules can be useful biomarkers and promising therapeutic targets for chemoresistance in hormone-refractory prostate cancer [51].

## Cell cycle and DNA damage response

With advancements in our understanding of the basic mechanisms of tumor-related research, cell cycle physiology, and apoptotic mechanisms, it is becoming increasingly apparent that the cell cycle plays a key role in chemosensitivity, especially combined chemotherapy. The cell cycle is a mechanism of cell division, which is driven by the CDK protein family [52]. These kinases are positively regulated by cyclins (A, B, D, and E) and negatively regulated by CDKIs [53]. For instance, Cdk6 and Cdk4, as key regulators of Rb, interact with cyclin D isoforms and drive the progression of a cell through G1 [54, 55]. CDK inhibitors serve as important checkpoints at various stages of the cell cycle [56–58]. An important function of these checkpoints is to prevent damaged DNA from replicating in future daughter cells. These checkpoints act as fail-safe mechanisms to repair damaged DNA and, if not repaired, initiate cell death. The most important checkpoints include p21, p27, and p57. p27 is a G1 checkpoint CDK inhibitor, and the increased function of p27 regulates drug resistance by enhancing apoptosis [59]. Recent studies have shown that HuR participates in the process of cell cycle-related chemotherapy resistance in tumors.

Cell cycle checkpoints enable cells to repair DNA in response to DNA damage, and defects in the DNA damage response (DDR) can lead to tumor development [60]. The DDR network contains several signaling pathways that eventually recruit a range of proteins to the DNA damage site. In normal cells, damaged DNA is usually repaired during the G1/S checkpoint [61]. However, most cancer cells, including PDA cells, are defective in the G1/S checkpoint. Therefore, many cancer cells rely on the G2/M checkpoint to repair damaged DNA. The G2/M checkpoint is predominantly determined by the posttranslational modification of cyclin-dependent kinase-1 (CDK1) by the tyrosine kinase WEE1 [62]. WEE1 and Myt1 phosphorylate CDK1 at tyrosine-15 (Y15) and threonine-14 (T14), causing G2/M arrest during DNA replication. Lal et al. [63] showed that silencing HuR sensitized PDA cells to DNA-damaging anticancer agents (mitomycin C, oxaliplatin, cisplatin, carboplatin, and a PARP inhibitor). The positive regulation of WEE1 by HuR increases γH2AX levels, induces Cdk1 phosphorylation and promotes cell cycle arrest at the G2/M transition, thereby promoting tumor growth. In addition, PARP-1 senses and initiates DNA damage repair (DDR) through self-modification by covalently adding poly(ADP-ribose) (PAR) to itself and transforming other receptor proteins [64]. PARP inhibitors are a promising treatment, but most responsive tumors develop drug resistance [65, 66]. Recently, Chand et al. [67] found that PARPi monotherapy combined with targeted silencing of HuR significantly reduced tumor growth compared with PARPi therapy alone. Therefore, the strategy of inhibiting HuR directly promotes the accumulation of DNA damage.

In addition, in bladder cancer, Guo et al. [68] showed that pyrvinium pamoate, a HuR small molecule inhibitor, dramatically downregulated several key DNA repair genes by inhibiting HuR in genotoxically stressed cells, including DNA ligase IV and BRCA2, leading to genomic instability and cell death. The combination of this inhibitor with chemotherapeutic drugs (such as cisplatin, doxorubicin, vincristine and oxaliplatin) not only enhances the cytotoxicity of bladder cancer cells but also synergistically inhibits the growth of bladder tumor xenografts derived from mouse patients. In general, HuR mediates tumor progression and chemoresistance by targeting multiple DNA damage repair genes, and the strategy of inhibiting HuR directly promotes DNA damage accumulation.

### Other regulatory signaling pathways

Drug resistance mechanisms in tumors are complex and diverse. In addition to the regulatory mechanisms mentioned above, HuR can also modulate drug resistance through other novel signaling pathways.

Jakstaite et al. [14] found that in pancreatic cancer, silencing of HuR significantly enhanced the therapeutic effect of gemcitabine by inhibiting the expression of cyclooxygenase-2 (COX-2) and heme oxygenase-1 (HO-1). COX-2 induces cancer development and progression by producing 15(R)-15-methyl prostaglandin E2 (mPGE2), which inhibits apoptosis, promotes cell proliferation, stimulates angiogenesis, and reduces the immune response [69]. In addition, Richards et al. [70] also found that HuR mediates gemcitabine resistance by targeting cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF) in pancreatic cancer. Janakiraman et al. [71] found that overexpression of COX-2 inhibits the cleavage of caspase-3 and HuR to promote paclitaxel resistance and tumor growth in oral cancer. Therefore, the HuR/COX-2 regulatory pathway plays a crucial role in drug resistance.

HuR and pancreatic cancer chemoresistance have been extensively studied. Pancreatic ductal adenocarcinoma (PDA) exhibits a high level of hypoxia and is characterized by low oxygen pressure (pO2) and reduced O2 intracellular perfusion. Chronic hypoxia is strongly associated with chemoresistance, and this phenomenon is known as hypoxia-induced chemoresistance. Hypoxia-inducible preoncogenic serine-threonine kinase PIM1 (proviral integration site of Moloney murine leukemia virus 1) is a key regulator of hypoxia-induced chemoresistance in PDA and other cancers [72]. PIM1 drives chemoresistance by phosphorylating and inactivating key apoptosis and tumor suppressor proteins. The molecular mechanism of PIM1 overexpression in PDA is closely related to HuR. HuR is mainly expressed in the nucleus of PDA cells. Under hypoxic stress, HuR translocates to the cytoplasm and binds to ARE-rich elements (AREs) in the 38 base pair region of the 3′-untranslated region of PIM1 mRNA, resulting in the overexpression of PIM1. The HuR inhibitor MS-444 eliminates hypoxia-induced PIM1 overexpression by inhibiting HuR homodimerization and cytoplasmic translocation and enhances the sensitivity of PDA cells to oxaliplatin and 5-fluorouracil under physiological hypoxia. HuR protects PDACs from hypoxia and nutrient-related stress. Since nutrient deprivation and chemotherapy induce a surge in reactive oxygen species (ROS), the adaptive mechanisms required for PDACs to maintain oxidative stress in the microenvironment may also contribute to chemoresistance. HuR can mediate pancreatic cancer chemotherapy resistance by regulating the expression of isocitrate dehydrogenase 1 (IDH1) under low nutrient conditions [73]. In addition, in pancreatic cancer cells, HuR stabilizes dCK mRNA and promotes the expression of deoxycytidine kinase. Deoxycytidine kinase (dCK) is a key metabolic enzyme that activates GEM by phosphorylation and produces the active metabolites gemcitabine diphosphate and triphosphate, thus inhibiting DNA chain elongation and causing cell death [74]. Additionally, HuR-mediated drug resistance mechanisms may also be associated with autophagy [75] and EMT processes [76].

## HuR may be a new tumor biomarker

The cytoplasmic HuR status of tumors has been shown to be associated with poor prognostic value in many tumor types, including pancreatic cancer, colorectal cancer, lung cancer, gastric cancer, breast cancer and ovarian cancer [77–81]. In most of the published retrospective studies, immunohistochemistry was used to evaluate the intracellular expression pattern of HuR in human malignancies. HuR cytoplasmic expression was associated with poor patient survival, disease-free survival, metastasis-free survival or overall survival. In about a previous study on the relationship between HuR and urinary tumors, we revealed that HuR may be a significant urological tumor biomarker. Furthermore, in colorectal cancer, Kenneth et al. found that most CRC samples from nonresponsive patients to 5-FU-based chemotherapy expressed higher ABCG2 and HuR but lower miR-519c. Therefore, miR-519c, HuR and ABCG2 may be useful biomarkers for predicting the patient response to adjuvant chemotherapy. In pancreatic cancer, Richards et al. showed that cytoplasmic HuR expression is a positive predictor of GEM treatment. Costantino et al. also showed that HuR levels in PDA regulate the therapeutic efficacy of gemcitabine, serving as a marker of the clinical utility of this conventional chemotherapeutic drug and a potential target for pancreatic cancer intervention. Studies in multiple tumors have shown that HuR may be a biomarker of potential value for diagnosis and prognosis. However, previous reviews were insufficiently based on retrospective studies.

Therefore, the validation of HuR as a predictor marker should be performed in a prospective manner with studies focusing on clinical trials with advanced or metastatic patients.

## Potential role of HuR as a drug treatment target

The multidrug resistance mechanisms of tumors are complex and diverse. The exploration of drug resistance mechanisms has never stopped. In recent years, post-transcriptional regulatory mechanisms have played a key role in drug resistance. HuR, which was first described in tumors nearly two decades ago, has received much attention in tumor-related research, and its mediated post-transcriptional regulation mechanism is closely related to tumor drug resistance. We hypothesized that the therapeutic effect of targeting HuR is stronger than targeting a single drug-resistant protein since HuR can target various drug resistance-related proteins. Currently, there are two strategies to target HuR, including transfection(siRNA) and inhibition(small molecules). Knockdown of HuR through siRNA transfecting inhibits tumors cell migration, invasion, proliferation, apoptosis and epithelial–mesenchymal transition process. In bladder cancer, pyrvinium pamoate, as a novel HuR inhibitor that dose-dependently inhibits cytoplasmic accumulation of HuR. Combining pyrvinium pamoate with chemotherapeutic agents not only led to enhanced cytotoxicity but also synergistically suppressed the growth of patient-derived bladder tumor xenografts in mouse. Interestingly, mice bearing primary bladder cancer xenografts did not lose weight or suffer other significant side effects at tested dosages, which demonstrating the safety of HuR**.** In addition, other HuR inhibitors include MS-444, CMLD-2, DHTS. However, the concept of targeted therapy still needs further exploration. For example, How effective and safe is the targeting of HuR? how long HuR can promote survival effects? We believe that targeted therapy strategies for HuR will open a new era in drug treatment.

## Conclusion

HuR mediates tumor chemotherapeutic resistance by regulating the stability of a variety of cancer-associated target mRNAs and the translation of proteins via post-transcriptional regulatory mechanisms. Recent genetic studies have shown that HuR silencing can promote the sensitivity of tumors to chemotherapeutic drugs. The function of HuR is also regulated by other molecules. For example, miRNA can bind to the 3′-UTR of HuR mRNA and regulate the expression of this molecule, which can cause the chemotherapy resistance of tumors. Therefore, understanding the role of HuR in tumor sensitivity to chemotherapeutic drugs may provide insight to guide ongoing research of tumor-targeted drugs. However, large-scale animal model experiments and clinical trials are needed. In addition to HuR, the embryonic lethal abnormal vision (ELAV) family proteins found in mammalian cells include HuB, HuC, and HuD. The characteristics and roles of several other ELAV proteins have not been fully elucidated. The research on HuR also provides direction for the study of other ELAV family proteins.

**Availability of data and materials** Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

**Funding** The Talent Innovation and Enterprise Program of Lanzhou (grant no. 2015-RC-16).

## Compliance with ethical standards

**Ethics approval and consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Competing interests** The authors declare that they have no competing interests.

**Conflict of interest** None.

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