Pancreatology xxx (2015) 1–6

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Review article

NEDDylation in liver cancer: The regulation of the RNA binding protein Hu antigen R

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Liver cancer
HuR
NEDDylation
RNA-binding proteins
Post-transcriptional modifications
MLN4924

ABSTRACT

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer death. The current view of cancer progression and malignancy supports the notion that cancer cells must undergo through a post-translational modification (PTM) regulation and a metabolic switch or reprogramming in order to progress in an unfriendly environment. NEDDylation is a post-translational modification of the proteins involved in several processes such as cell growth, viability and development. A ground-breaking knowledge on a new critical aspect of HCC research has been to identify that NEDDylation plays a role in HCC by regulating the liver oncogenic driver Hu antigen R (HuR). HuR is a RNA-binding protein that stabilizes target mRNAs involved in cell dedifferentiation, proliferation, and survival, all well-established hallmarks of cancer. And importantly, HuR levels were found to be highly representative in liver and colon cancer.

These findings open a completely new area of research, exploring the impact that NEDDylation plays in liver diseases and paving the way for novel therapeutical approaches.
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The RNA-binding protein HuR: regulation, functions and implications in liver cancer

The mammalian Hu/elav family of RNA-binding proteins (RBPs) includes the neuronal members HuB, HuC and HuD, and the more ubiquitous member HuR. Whereas the neuronal Hu has been related with neuronal development, neuronal plasticity and memory [1,2], HuR (also known as ELAVL1) was first described to stabilize ARE-containing mRNAs [3]. After this, it has been also shown to modulate the translation, both enhancing and inhibiting it [4,5].

HuR protein contains three RNA recognition motifs (RRMs), in an identical arrangement to the other Hu/elav proteins [6] and a hinge region between RRM2 and RRM3 (Fig. 1). All three RRMs, through which these RBPs bind to the target mRNAs, are conserved among the four Hu family members, indicating to be essentials for the protein function, whereas the hinge region differs [7].

The HuR hinge region has a sequence similar to the nuclear localization signal (NLS), possessing both NLS and nuclear export sequence (NES) activities [8]. This sequence is responsible of HuR shuttling from the nucleus to the cytosol, receiving the name of HuR Nucleocytoplasmic Shuttling (HNS) domain [8]. Although HuR is a predominantly nuclear protein, its function is performed by translocating from the nucleus to the cytosol in response to stimulus, a process in which HNS domain and several transport mechanisms are involved.

Recently, results from high-throughput technology (PAR-CLIP, RIP-chip and whole transcript expression profiling) studying HuR targets, uncovered a role in the nucleus regulating pre-mRNA processing, alternative splicing, the export of mature mRNAs (Fig. 2), and also antagonizing microRNA (miRNA)-mediated repression of miRNAs proximal to HuR binding sites [9,10].

Focusing in the best characterized HuR functions exerted in the cytoplasm, HuR can promote three kinds of effects over the bound mRNAs: mRNA stabilization, mRNA translation upregulation and repression of mRNA translation.

Stabilization of target mRNAs

Some of the HuR-stabilized target mRNAs include p21, c-fos, VEGF, the MAPK phosphatase (MKP)-1, iNOS, granulocyte/macrophage colony-stimulating factor (GMCSF), sirtuin 1 (SIRT1), TNFα,

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http://dx.doi.org/10.1016/j.pan.2015.03.006
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Please cite this article in press as: Fernández-Ramos D, Martínez-Chantar ML, NEDDylation in liver cancer: The regulation of the RNA binding protein Hu antigen R, Pancreatology (2015), http://dx.doi.org/10.1016/j.pan.2015.03.006

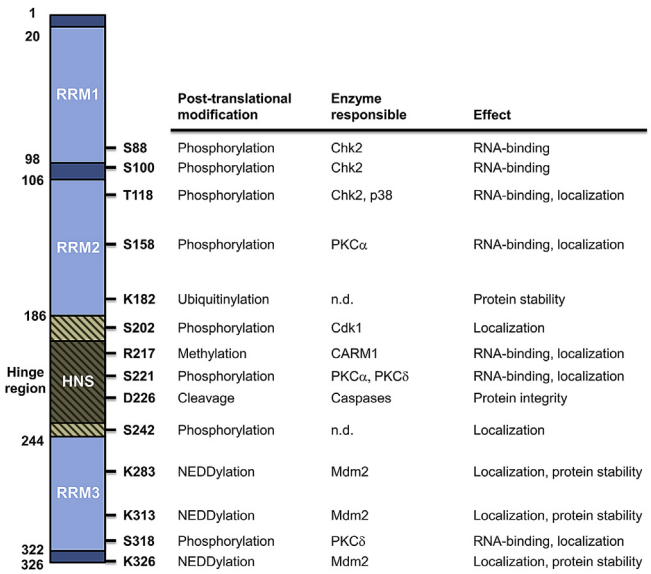

Fig. 1. Schematic representation of HuR protein and its posttranslational modifications by cancer-related enzymes. The HuR RNA recognition motifs and the hinge region containing the HuR nucleocytoplasmic shuttling (HNS) domain are indicated. The posttranslational modifications, enzyme responsible and effects of the modification are listed. n.d., not determined. (Modified from Ref. [12]).

B-cell lymphoma-2 (Bcl2), myeloid cell leukemia-1 (Mcl1), cyclooxygenase-2 (COX-2), γ-glutamylcysteine synthetase heavy subunit (γ-GCSh), urokinase-type plasminogen activator (uPA) and its receptor (uPAR), p53, interleukin (IL)-3, and cyclins A2, B1, E1, and D1 [11,12].

The exact mechanisms by which HuR is able to stabilize mRNAs are not well understood, but is believed that the binding of HuR to the mRNAs blocks the binding of other RBPs or miRNAs that can recruit cellular structures for mRNA degradation (exosome, processing bodies or RISC complex) [13–17].

HuR also promotes the translation of several target mRNAs, such as those that encode the hypoxia-inducible factor (HIF)-1α, p53, prothymosin α (PTMA), MKP-1, cytochrome c, heme oxygenase-1, and cationic amino acid transporter 1 (CAT-1) [11,12].

It is also unclear how HuR is able to promote the translation. In some cases, HuR can interfere with internal ribosome entry sites

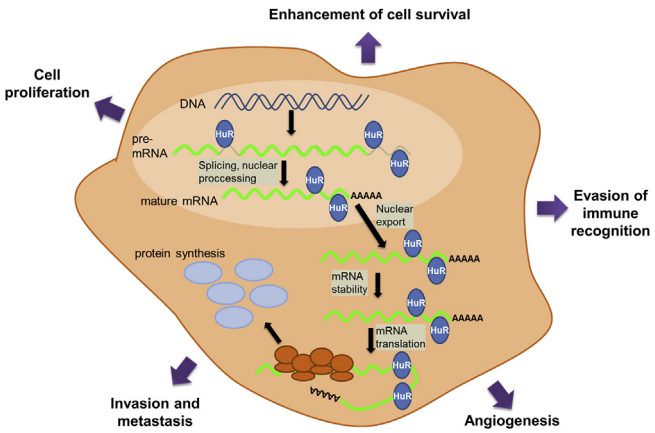

Fig. 2. HuR influence on target gene expression. In the nucleus, HuR binds to the pre-mRNAs participating in their splicing and nuclear processing and collaborates with the mRNA export. In the cytosol HuR enhances mRNA stability and translation in the polysomes. In the case of malignant transformation, the effects over HuR targets enhance cell proliferation, cell survival, evasion of immune recognition, angiogenesis, invasion and metastasis.

(IRESs) in the 5′UTRs of target mRNAs enhancing the translation [18]; in other cases, its effects on translation were due to competition with repressor RBPs or with microRNAs/RISC complex [19–21].

The translation of a small group of mRNAs has also been identified to be repressed by HuR. Between them, p27 and the type I insulin-like growth factor receptor (IGF-IR) are repressed by disrupting the IRESs, and Wnt5a and c-Myc by the recruitment of let-7/RISC [11,12,22–24].

Regulation of HuR function

According with the involvement of HuR in many important biological processes, its function is tightly regulated at many levels: abundance and integrity of the protein, subcellular localization and post-translational modification. The levels of HuR protein are regulated in many ways. Among them, we can find:

Transcriptional regulation

HuR is known to be positively regulated by the transcription factor NFκB. Particularly, in gastric tumors HuR overexpression depends on a mechanism in which PI3K/AKT signaling pathway activation increased p65/RelA binding to a putative NFκB binding site in the HuR promoter, increasing its transcription [25].

HuR auto-regulation

HuR protein is able to bind to a long *HuR* mRNA containing a distal ARE, stabilizing it [26,27]. Moreover, HuR was also found to associate with the 3′UTR of the *HuR* mRNA increasing HuR translation by promoting the nuclear export of *HuR* mRNA [28].

Downregulation of HuR by microRNAs

HuR mRNA is the target for two miRNAs: miR-519 and miR-125a. miR-519 binds to a sequence in the coding region (CR), repressing HuR translation, but not reducing mRNA abundance [29–31]. Similarly, miR-125a associates with the 3′UTR of *HuR* mRNA inhibiting HuR translation [32]. miR-519 miRNA reduces the tumor formation in xenograft models, whereas the miR-125a reduces proliferation and enhances apoptosis in breast cancer cells.

HuR ubiquitination

It was demonstrated that HuR protein is ubiquitinated in K182 after heat shock, which promotes its proteasomal degradation (Fig. 1). This degradation allows the cells to survive to the heat shock stimulus. The phosphorylation of HuR by Chk2 at residues S88, S100 and T118 antagonizes heat shock dependent HuR decay [33].

Caspase-mediated HuR cleavage

After lethal stress, HuR translocates to the cytoplasm and associates with the apoptosome activator pp32/PHAP-I. In the cytoplasm, HuR is caspase-mediated cleaved at aspartate 226 as a regulatory step contributing to an amplified apoptotic response [34].

Regulation of HuR localization

Although HuR is predominantly nuclear, the best characterized HuR functions take place in the cytoplasm. Together with the HuR HNS domain, several transport machinery components are also

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