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Review

# The emerging roles of heterogeneous nuclear ribonucleoprotein C in cancer and other diseases

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**Abstract:** Heterogeneous nuclear ribonucleoprotein C (hnRNPC) is a DNA/RNA-binding protein and regulates a huge range of biological processes and disease pathogeneses. hnRNPC recognizes and binds to specific RNA substrates and DNA motifs and is involved in the transcription, splicing processing and stability of a variety of RNA molecules. Besides, hnRNPC maintains the function of telomere, while the dysregulation of hnRNPC is related to the development of various tumors and virus-related diseases. This paper focuses on the role and mechanism of hnRNPC in RNA metabolism, tumors and virus-related diseases.

**Keywords:** hnRNPC, RNA, cancer

## Introduction

Using immune-purification and two-dimensional gel electrophoresis, the hnRNP complex is found to be composed of at least 20 major heterogeneous nuclear ribonucleoproteins (hnRNPs) and some other minor hnRNPs. Heterogeneous nuclear ribonucleoprotein C (hnRNPC) belongs to the subfamily of ubiquitously expressed hnRNPs, expressed in the nucleus [1,2]. As one of the most abundant pre-mRNA-binding proteins, hnRNPC has a single RNP motif RNA-binding domain by binding the poly (U) motif to a genome-wide effect on poly (A) site [3,4]. hnRNPC is known to stabilize urokinase-type plasminogen activator (uPA) mRNA in the nuclear and cytosolic compartments [5]. Moreover, hnRNPC can interact with both p53 mRNA and protein [6,7]. hnRNPC affects several cellular physiological processes by influencing the expressions of a large number of downstream genes through the metabolic regulation of specific RNA molecules. Meanwhile, hnRNPC combines with functional proteins to activate some signaling pathways and can be phosphorylated to terminate the ability of binding RNA. The abnormal expression of hnRNPC is related to the development of many diseases. This review discusses the changes and mechanisms of hnRNPC in RNA metabolism, tumors, autoimmune diseases and neurodegeneration.

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## 1. Structure and binding motif

The hnRNPC protein undergoes selective splicing in the cell and is eventually translated into two isomeric proteins, hnRNPC 1 and hnRNPC 2, which form a stable tetramer [8]. The hnRNPC contains three main domains: the RNA recognition module (RRM), the nuclear localization signal (NLS) and the acid-rich region [9]. The articles about the structure of hnRNPC reveal that RRM is an RNA docking platform. RRM has a four-stranded antiparallel beta-sheet, two alpha-helices, and relatively unstructured amino-terminal and carboxy-terminal regions, which forms a compact folded structure (beta alpha beta beta alpha beta). The analysis of perturbations of the chemical shifts indicates that the beta sheet and the terminal regions are critical to bind RNA substrates [10]. NLS implies that hnRNPC is specifically retained within the nucleus [8]. The acid-enriched region is associated with protein-protein interactions and can also increase its RNA binding specificity [10].

## 2. The functions of hnRNPC

The unique molecular structure of hnRNPC enables it to recruit into multi-molecular signaling complexes, including a number of kinases and factors involved in the regulation of gene expression, signal transduction and many other cellular processes, including the regulation of transcription, RNA processing and translation (Figure 1).

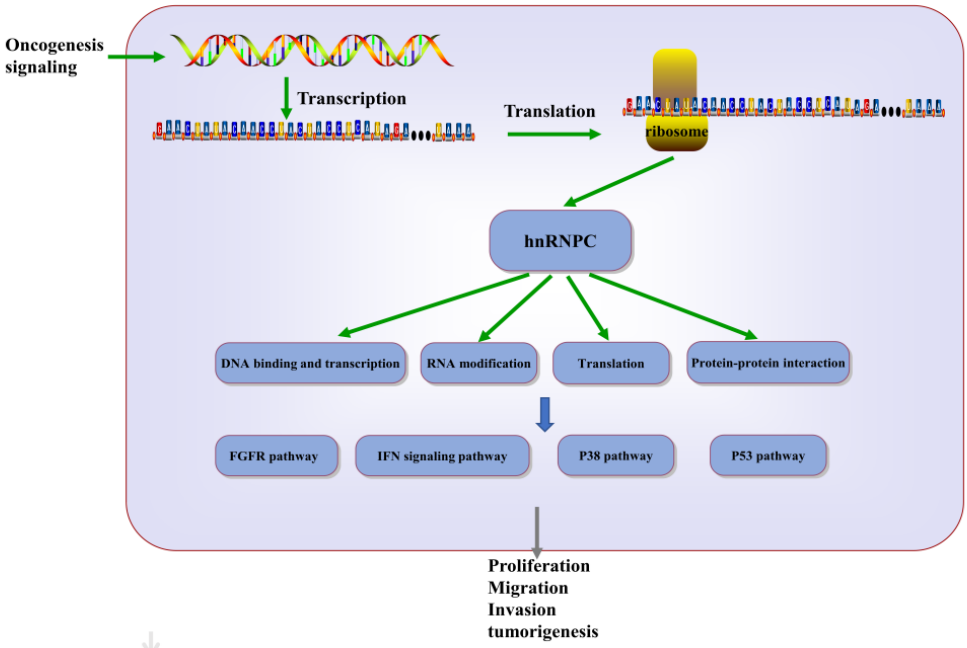


**Figure 1.** TCGA datasets for hnRNPC expression in selected human cancers. (A-P): TCGA expression data for hnRNPC in 16 different tumors. BRCA: breast invasive carcinoma, LUAD: lung adenocarcinoma, LUSC: lung squamous cell carcinoma, LIHC: liver hepatocellular carcinoma, ESCC: esophageal squamous cell carcinoma, PAAD: pancreatic adenocarcinoma, HNSC: head and neck squamous cell carcinoma, STAD: stomach adenocarcinoma, COAD: colon adenocarcinoma, THCA: thyroid carcinoma, CHOL: cholangio carcinoma, BLCA: bladder urothelial carcinoma, UCEC: uterine corpus endometrial carcinoma, GBM: glioblastoma, KIRC: kidney renal clear cell carcinoma, PRAD: prostate adenocarcinoma.

### 2.1 DNA binding and transcription

hnRNPC provides a sequence-specific DNA recognition element for locus control regions (LCR)-associated remodeling complex (LARC) , and the sequence is essential for the enhancement of transcription by hypersensitive 2 (HS2) [11]. Previous studies show that a hnRNPC consists of vitamin D receptor (VDR) transcription complex by interacting with double-stranded DNA cis-elements as a trans-regulatory factor [12-14]. hnRNPC is also reported to regulate the transcription of ELAV-Like Family 2 (CELF2) mRNA [15].

### 2.2 RNA modification

#### 2.2.1 mRNA splicing

Alternative splicing endows the genome of any given organism to expand its protein diversity. It is acknowledged that hnRNPC participates in pre-mRNA splicing [16,17]. RNA-seq also reveals that hnRNPC is significantly involved in alternative splicing (AS) events [18]. However, recent studies have described a different function of hnRNPC in alternative splicing. The knockdown of hnRNPC promotes exon skipping or the use of more internal 3'-splice sites in

some specific cell types, which indicats that hnRNPC acts as a splicing enhancer by enforcing exon inclusion [19]. Some studies describe an opposite role of hnRNPC as a splicing inhibitor [20-23]. For example, hnRNPC interacts with human antigen R (HuR), which promotes the skipping of Fas cell surface death receptor (FAS) gene exon 6 by binding to the exon splicing silencer (ESS) URE6. Due to this event, exon skipping occurs after the inhibition of molecular events [24]. In addition, hnRNPC represses exon 3 inclusion of pro-apoptotic protein, BCL-2-like 11 (BIM) [25], and regulates the splicing of exon 6B of protein SMN6B.

Using individual-nucleotide resolution UV cross-linking and immunoprecipitation (CLIP) and sequencing analysis, Kong et al report that hnRNPC can improve either exon exclusion or inclusion, which relies on the exact binding location of hnRNPC on the primary mRNA. hnRNPC also directly competes with the core splicing factor U2 auxiliary factor 65 (U2AF65) to prevent Alu element ionization [21]. These elements comprise cryptic splice sites, and this makes them dangerous when they are aberrantly incorporated into mature transcripts. The loss of hnRNPC can severely disrupt transcript function by the formation of previously suppressed Alu exons. In addition, Wu et al suggest that hnRNPC promotes the proliferation of breast cancer cells by preventing the export of Alu sequences from the cytosol where they may be partially degraded by the nonsense-mediated decay (NMD) to generate immunostimulatory short Alu-derived dsRNAs [26].

### 2.2.2 Non-coding RNAs (ncRNAs)

hnRNPC participates in ncRNAs-mediated functions, such as microRNA, lncRNA and circRNA. Previous studies show that hnRNPC1 is a possible miRNA transporter in exosomes [27]. In vitro, RNA pulldown reveals that miR-30d binds to hnRNPC1 in exosomes [28]. hnRNPC increases the stability of primary miR-21 (pri-miR-21) and promotes miR-21 expression in glioma cells [29]. CLIP data reveal that hnRNPC can bind to several lncRNA segments [21]. Interestingly, hnRNPC prefers to bind to an N6-Methyladenosine (m6A)-modified hairpin composed of nucleotides 2556-2587 of the lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) [30]. In the G2/M cell cycle phase, MALAT1 transcripts are found to translocate from the nucleus into the cytoplasm by interacting with hnRNPC. hnRNPC can regulate circ RNA biogenesis. In previous studies, three circRNAs are identified to respond to hnRNPC depletion in HeLa cells, including the upregulation of circRARS and circSMARCA5 expressions, as well as the downregulation of circCDYL2 expression. Notably, hnRNPC may regulate the functions of Alu elements, which often act as drivers of RNA circularization [21, 31-34]. In line with this notion, hnRNPC knockdown by siRNA in breast cancer MCF-7 cells is recently reported to promote an increased abundance of double-stranded RNA regions, which are highly enriched in Alu elements [26].

Meanwhile, hnRNPC itself can be regulated by microRNA and lncRNA molecules. hnRNPC is the target of lncRNA, namely ncRNA00201 in systemic sclerosis [35]. In addition, miR-744-5p directly targeting hnRNPC induces cell death in ovarian cancer cells [36]. Lnc SNHG1 binds to hnRNPC and interferes with the interaction of hnRNPC with p53 [7]. However, the specific mechanisms of hnRNPC regulating the transcription, splicing, transportation and degradation of ncRNAs remain unknown and are worth exploring.

### 2.2.3 m6A

m6A modification plays important roles in RNA splicing, nuclear export and decay [30,37]. Recently, hnRNPC is identified as an m6A reader, which recognizes m6A and induces changes in RNA structure [30]. Indeed, an m6A site in the lncRNA MALAT1 is recognized and bound by hnRNPC via structure changing that increases the accessibility of a U5-tract change in RNA structure, termed ‘m6A-switch’, and affects transcriptome-wide mRNA abundance and alternative splicing. Zhou further reveals the specific m6A-induced structural changes in a 32-nucleotide hairpin derived from the m6A-switch in the human lncRNA MALAT1 [38].

### 2.2.4 mRNA stability

mRNA stability is maintained by the internal components in the 3'-UTR region and their specific binding proteins. For example, a class of components known as adenylate- and uridylate-rich elements, which are typically located at the 3'-UTR of mRNA, mediate mRNA degradation.

As an important regulator of pre-mRNA processing, hnRNPC promotes the stabilization of different mRNAs by binding to 3'-UTR. hnRNPC binds to a 110-nt sequence of urokinase-type plasminogen activator receptor (uPAR) mRNA 3'-UTR, thereby preventing its degradation [1,39].

hnRNPC also determines the selection of polyadenylation sites in the pre-mRNA processing of some genes, thereby affecting mRNA half-life. Many studies show that hnRNPC plays a key role in establishing the alternative cleavage and polyadenylation profile of metastatic colon cancer cells [40,41]. Another study reveals that elevated hnRNPC expression promotes cancer proliferation by directly stabilizing miR-21 expression [29].

## 2.3 Translation

The conversion of mRNA to protein can be enhanced or inhibited by specific elements located within the mRNA chain. One of such elements is the internal ribosome entry site (IRES), which collects the ribosome to the mRNA. The effect of hnRNPC on the translation process depends on its incorporated regulatory elements. For example, hnRNPC combines with the IRES in the 5’ UTR region of c-myc to promote the translation of c-myc gene [6,42,43]. In

addition, the overexpression of hnRNPC represses Aurora B binding to eIF4F (an mRNA cap-binding protein and translational initiation factor), and eIF4F must bind to Aurora B mRNA so that the translation occurs [44].

### 2.4 Protein-protein interaction

With regard to RNA binding ability, hnRNPC interacts with many functional proteins. Proteomics analysis reveals that SOX2 has an interaction with hnRNPC [45]. KH-type splicing regulatory protein (KHSRP) can specifically interact with hnRNPC to form a complex to promote the progression of non-small cell lung cancer (NSCLC) [46]. Co-immunoprecipitation (Co-IP) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) identifiy that hnRNPC is a partner of Krüppel-like factor 5 (KLF5) in the promotion of proliferation and/or survival in bladder cancer cells [47]. hnRNPC can be phosphorylated by casein kinase II, DNA-protein kinas and hydrogen peroxide [48-50]. Phosphorylation of hnRNPC promotes the release of the protein from the RNA. Dephosphorylated hnRNPC binds to pre-mRNA [50]. The number and location of phosphorylation present and the kinases involved are not well understood.

## 3. Some important pathways in which hnRNPC is involved

Given the broad spectrum of gene expression in which hnRNPC is involved, it is not surprising that some signaling pathways are upregulated or downregulated by hnRNPC. GSEA analysis shows that the expression of hnRNPC is significantly related to phospholipase C-mediated cascade, type II diabetes mellitus, signaling by fibroblast growth factor receptor (FGFR), downstream signaling of activated FGER, calcium signaling pathway, signaling by FGFR in disease, adipocytokine signaling pathway and vascular smooth muscle contraction and metastasis in pancreatic cancer [51]. RNA-seq of hnRNPC knockdown cells reveals a massive upregulation of IFN-stimulated genes indicative of IFN signaling in breast cancer [26]. Furthermore, hnRNPC dissociates with HuR by the activation of the p38 pathway kinase MK2, resulting in the translocation of HuR to cytoplasm and the stabilization of TNF-α and IFN-γ transcripts in T cells [52]. hnRNPC, reportedly, enhances p53 translation, and polo-like kinase 1 (Plk1) inhibitor may increase the expression of hnRNPC to activate the p53 pathway, thus causing the apoptosis of melanoma cells [6]. In a model of Japanese encephalitis virus, the ablation of hnRNPC leads to the downregulation of cleaved caspase 3 [53].

## 4. The functions of hnRNPC in diseases

hnRNPC can regulate a wide range of target genes by its binding sequences. The complexity of regulation and the diversity of target molecules allow hnRNPC to assume different physiological functions in various tissues and cells, which endows hnRNPC with many identities in various pathophysiological processes, including cancers, neurodegenerative diseases and autoimmune diseases.

### 4.1 Cancer

As shown in Figure 2, hnRNPC is overexpressed in various tumor types. However, the prediction of survival outcome by the expression of hnRNPC is different in different cancers (Figure 3).

#### 4.1.1 Lung cancer

Several studies show that hnRNPC can be used as a potential biomarker for the early detection and prognosis of lung cancer. hnRNPC mRNA and protein expressions are elevated in lung adenocarcinoma (LUAD) [54]. Higher hnRNPC expression is related to higher pathological stages and M stages, and poor survival outcomes [55,56]. hnRNPC knockdown significantly inhibits the proliferation, migration and invasion of LUAD cells *in vitro* and *vivo* [46]. hnRNPC also significantly increases in lung squamous cell carcinoma (LUSC) compared to control tissues from The Cancer Genome Atlas (TCGA) database [57]. Quantitative real-time polymerase chain reaction (qRT-PCR) analysis also confirms that the mRNA expression of hnRNPC is elevated in human LUAD cells (A549) and LUSC cells (H520) compared to the control HBE cells [57]. The high expression of hnRNPC is closely associated with the malignancy and prognosis of LUSC [58,59]. A computational motif-based analysis platform identifies hnRNPC as a potential modulator of the drug resistance of recurrent NSCLC after cisplatin treatment [60]. In this case, hnRNPC may be a therapeutic target for lung cancer.

#### 4.1.2 Breast cancer

hnRNPC is identified as an aberrant splicing factor through RNA-seq data from 105 breast patients [61]. Wu et al point out that even a partial repression of hnRNPC expression can result in the arrestment of cell proliferation and tumorigenesis of the breast cancer cell lines MCF7 and T47D, which suggests an indispensable role of hnRNPC in these cells [26]. These data suggest the potential usefulness of hnRNPC as a prognostic and therapeutic marker of breast cancer.

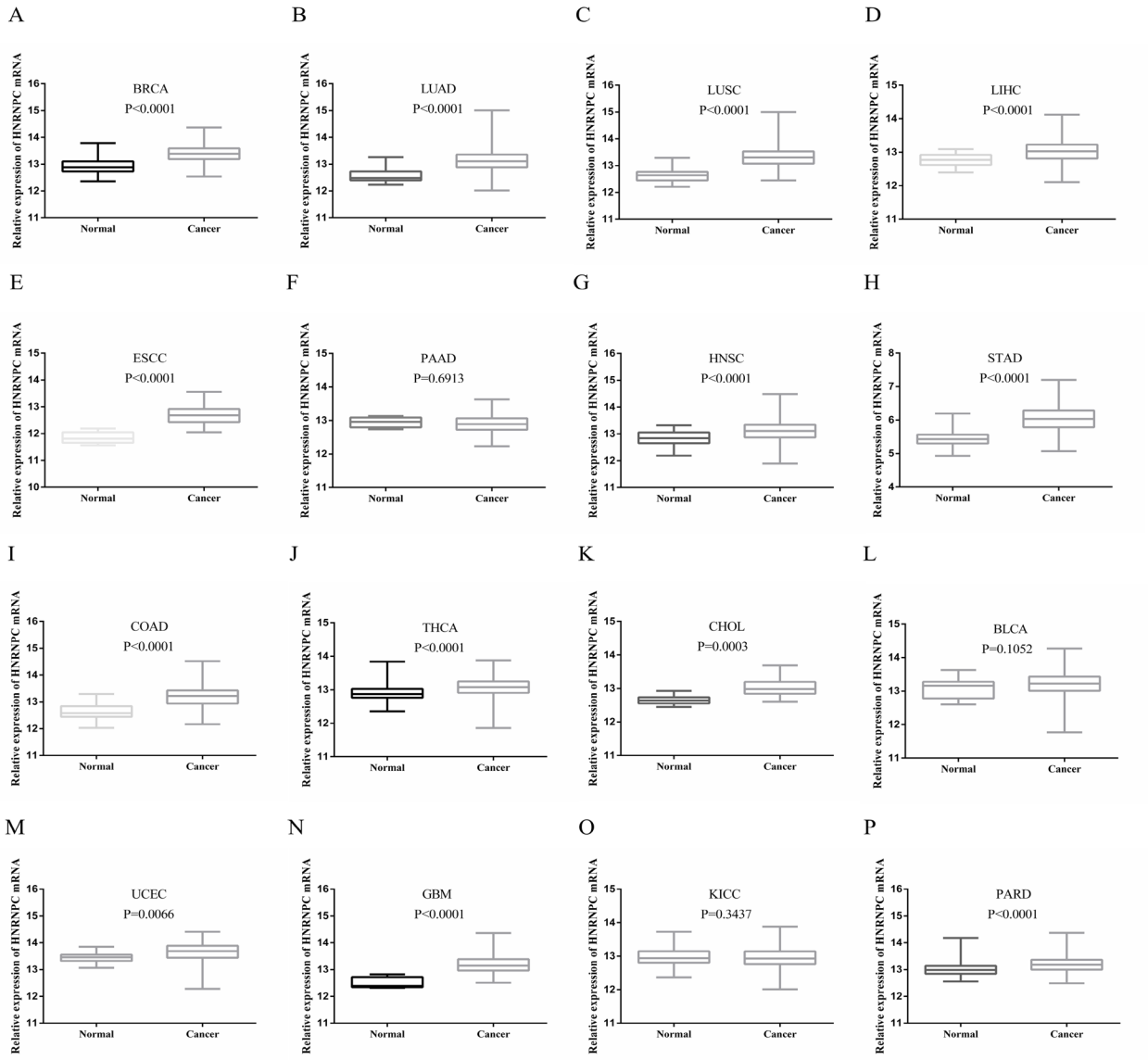


**Figure 2.** TCGA datasets for the overall survival of selected human cancers based on the expression of hnRNPC. (A-P): Overall survival of 16 different tumors based on the expression of hnRNPC. BRCA: breast invasive carcinoma, LUAD: lung adenocarcinoma, LUSC: lung squamous cell carcinoma, LIHC: liver hepatocellular carcinoma, ESCC: esophageal squamous cell carcinoma, PAAD: pancreatic adenocarcinoma, HNSC: head and neck squamous cell carcinoma, STAD: stomach adenocarcinoma, COAD: colon adenocarcinoma, THCA: thyroid carcinoma, CHOL: cholangio carcinoma, BLCA: bladder urothelial carcinoma, UCEC: uterine corpus endometrial carcinoma, GBM: glioblastoma, KIRC: kidney renal clear cell carcinoma, PRAD: prostate adenocarcinoma.

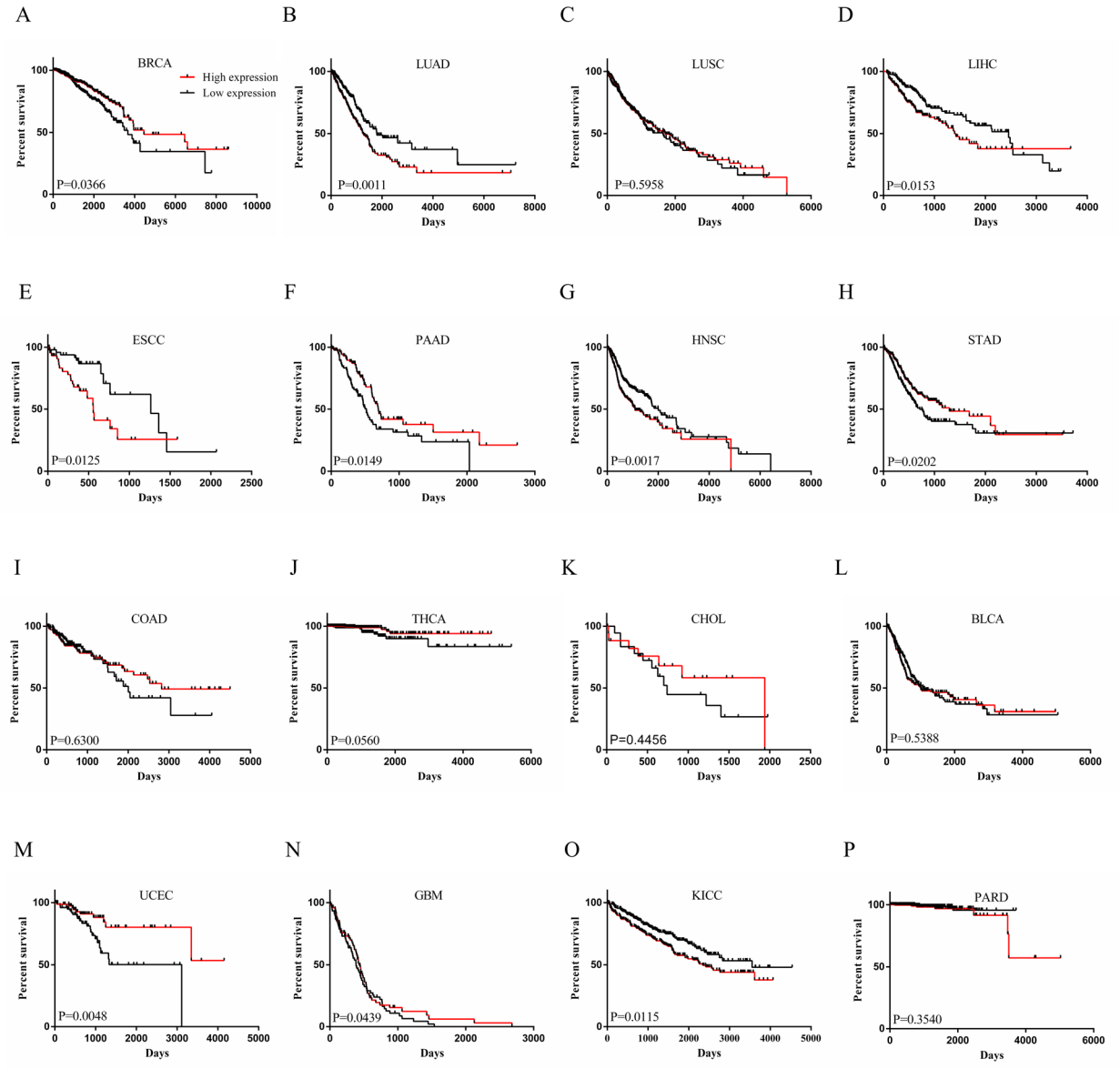


**Figure 3**. TCGA datasets for the overall survival of selected human cancers based on the expression of hnRNPC. (A-P): Overall survival of 16 different tumors based on the expression of hnRNPC. BRCA: breast invasive carcinoma, LUAD: lung adenocarcinoma, LUSC: lung squamous cell carcinoma, LIHC: liver hepatocellular carcinoma, ESCC: esophageal squamous cell carcinoma, PAAD: pancreatic adenocarcinoma, HNSC: head and neck squamous cell carcinoma, STAD: stomach adenocarcinoma, COAD: colon adenocarcinoma, THCA: thyroid carcinoma, CHOL: cholangio carcinoma, BLCA: bladder urothelial carcinoma, UCEC: uterine corpus endometrial carcinoma, GBM: glioblastoma, KIRC: kidney renal clear cell carcinoma, PRAD: prostate adenocarcinoma.

### 4.1.3 Esophageal cancer

The mRNA expression level of hnRNPC is significantly increased in esophageal cancer (ESCA) compared with normal tissues. The high expression level of hnRNPC is associated with advanced TNM stage and poor survival [62]. Functionally, hnRNPC knockdown efficiently suppresses cell migration and reverses epithelial-mesenchymal transition (EMT) progress through promoting the decay of ZEB1 and ZEB2 mRNAs [63].

### 4.1.4 Hepatocellular carcinoma

According to TCGA, hnRNPC expression shows a significant upregulation in tumors compared with that in the adjacent normal tissues in hepatocellular carcinoma (HCC). It is found that patients with high expression of hnRNPC have a significantly worse survival [64]. A large-scale screen from 377 liver tissue samples using high-throughput RNA sequencing data reveals that hnRNPC in HCC tissues significantly correlates with patient survival [65]. In addition, the increased expression of hnRNPC in HCC stem-like cells is observed, and hnRNPC accelerates HCC cell proliferation through inducing multinucleation by the repression of Aurora B expression [44,66]. These results highlight the oncogenic role of hnRNPC in HCC.

### 4.1.5 Oral squamous cell carcinoma

Studies show that the expression of hnRNPC increases in oral squamous cell carcinoma (OSCC) cells [67-69]. By using univariate and multivariate cox regression analysis, among 13 m6A-related genes, hnRNPC is found to be the only one independent biomarker and mean unfavorable overall survival in OSCC [67,68]. Functional studies reveal that the overexpression of hnRNPC promotes the development of OSCC via EMT process [67]. hnRNPC binds to adenylate kinase 4 (AK4) mRNA to stabilize AK4 mRNA which enhances cell radio-resistance by promoting cell viability and proliferation, inhibiting cell cycle arrest and apoptosis and facilitating migration and invasion. LncRNA LINC00662 also interacts with hnRNPC protein to promote AK4 mRNA stability [69].

### 4.1.6 Pancreatic carcinoma

Gene Expression Omnibus (GEO) and TCGA data confirm that the expression of hnRNPC is elevated in pancreatic carcinoma (PC) [51]. The high expression of hnRNPC predicts poor survival outcomes in PC [51,70]. qRT-PCR analysis also finds that the mRNA expression of hnRNPC is changed in human PC cells (Mia-PaCa-2 and BXPC-3) compared to the control HDE-CT cells [51]. The GSEA results show that the expression of hnRNPC is significantly related to oncogenic pathways, such as signaling by FGFR, the downstream signaling of activated FGER and signaling by FGFR in disease and metastasis [51]. The inhibition of hnRNPC expression significantly suppresses the proliferative ability of PC cells [51].

### 4.1.7 Other cancers

hnRNPC is also overexpressed in a variety of other tumors. For example, hnRNPC is significantly overexpressed in papillary thyroid carcinoma, testicular germ cell tumor, head and neck squamous cell carcinoma and gastric cancer [71-74]. Bioinformatic analysis reveals that hnRNPC may be a key gene associated with the progression of osteosarcoma [75]. hnRNPC is identified as a factor involved in the overall survival of patients with diffuse large B cell lymphoma, gastric cancer and colon cancer [18,74,76]. GEO dataset analysis reveals that hnRNPC can be an independent prognostic factor of overall survival in neuroblastoma [77]. The silencing of hnRNPC reduces cell proliferative, migratory and invasive activities, and enhances etoposide-induced apoptosis [29].

Overexpressing hnRNPC in gastric cancer cells promotes the chemoresistance, and the knockdown of hnRNPC reverses the chemoresistance [74]. Moreover, a couple of novel oncogenic reciprocal fusion genes involving hnRNPC gene and the retinoic acid receptor gamma (RARG) gene are found in acute promyelocytic-like leukemia (APLL) [78]. Considering its dysregulated expression and oncogenic effects in a variety of tumors, hnRNPC has the potential to become a new tumor marker, gene therapeutic target and prognostic predictor.

## 4.2 Virus-related diseases

A recent study indicates that hnRNPC is involved in the regulation of innate immune system, especially for the replication of viruses. Hepatitis B virus (HBV) benefits from the ability of trans-active response DNA binding protein (TARDBP) to assemble hnRNPC that supports the viral life cycle in hepatocytes [79]. Moreover, hnRNPC binds to the 3' UTR region of hepatitis C virus (HCV) RNA enriched in pyridine, thus initiating and/or regulating HCV replication [80]. It seems credible that similar to other hepatitis viruses, hnRNPC may also be involved in hepatitis D virus (HDV) replication [81]. hnRNPC has been shown to interact with the 5' and 3' ends of poliovirus negative-strand RNA intermediates and with poliovirus protein precursors, which promotes the viral RNA synthesis of poliovirus and viral replication complex assembly [82]. The reduced hnRNPC expression decreases the percentage of dengue virus (DENV) antigen-positive cells as well as the number of dengue virus RNAs [83]. hnRNPC binds specifically to three functionally important UUUUU-motifs in the 3' UTR sequence of human papillomavirus-1(HPV-1) [84]. hnRNPC has also been shown to interact with Japanese encephalitis viral RNA in neural stem cells to hasten death [53]. However, more evidence is needed to reveal the roles of hnRNPC protein in the development of immune diseases and the specific mechanisms.

### 4.3 Other diseases

The abnormal expression of hnRNPC is related to adenomyosis, vitamin D-resistant rachitic bone disease, folate deficiency-induced neural crest cell dysfunction, early and post-implantation and schizophrenia [8,85-88].

## 5. Conclusion

In summary, hnRNPC protein is highly conserved in many species, which indicates that the protein plays a central role in the signal network. In view of the close relationship between hnRNPC and ncRNAs, studying the functions of hnRNPC can help us better understand the ncRNAs-protein network. The hnRNPC protein is also involved in cancer biology and virus-related diseases, and the exact mechanisms have not been determined. The future research on hnRNPC and cancer should focus on establishing hnRNPC as a target for treatment or diagnosis. The involvement of hnRNPC in virus-related diseases is emerging but has not yet been determined. Future work can focus on the interactive proteins of hnRNPC, and further mechanism studies will be able to provide a better understanding of the pathogeneses of the diseases associated with the abnormal expression of hnRNPC.

## Abbreviations:

hnRNPC heterogeneous nuclear ribonucleoprotein C
RRM RNA recognition module
NLS nuclear localization signal
LCR locus control region
HS2 hypersensitive 2
AS alternative splicing
HuR human antigen R
FAS Fas cell surface death receptor
ESS exon splicing silencer
BIM BCL-2-like 11
U2AF65 U2 auxiliary factor 65
NMD nonsense-mediated decay
ncRNAs non-coding RNAs
CLIP cross-linking and immunoprecipitation
M6A N6-methyladenosine
MALAT1 metastasis associated lung adenocarcinoma transcript 1
IRES internal ribosome entry site
Co-IP co-immunoprecipitation
LC-MS/MS liquid chromatography-tandem mass spectrometry
Plk1 polo-like kinase 1
LUAD lung adenocarcinoma
LUSC lung squamous cell carcinoma
ESCA esophageal cancer
HCC hepatocellular carcinoma
OSCC oral squamous cell carcinoma
PC pancreatic carcinoma
RARG retinoic acid receptor gamma
APLL acute promyelocytic-like leukemia
TARDBP trans-active response DNA binding protein
HPV-1 human papillomavirus-1
DENV dengue virus
HDV hepatitis D virus
HCV hepatitis C virus
HBV hepatitis B virus
GEO Gene Expression Omnibus
TCGA The Cancer Genome Atlas
NSCLC non-small cell lung cancer
AK4 adenylate kinase 4
FGFR fibroblast growth factor receptor

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## Author contributions

H.L. and J.L. conducted the literature screening and wrote the manuscript. K.H. initiated the study and edited the manuscript.

## Disclosure

The authors declare no conflict of interests.

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