Heterogeneous nuclear ribonucleoprotein K in cancer biology and its therapeutic applications (Review)

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Abstract. Heterogeneous nuclear ribonucleoprotein K (hnRNPK) is a multifunctional protein belonging to the heterogeneous nuclear ribonucleoprotein family. The K-homology domain is the most evolutionarily conserved feature of hnRNPK and is responsible for RNA-binding. hnRNPK interacts with both chromatin and RNA in numerous species. Initially characterized as an RNA-binding protein, hnRNPK functions as a structural protein, integrating a number of signaling pathways and participating in gene expression regulation, RNA processing, cell cycle control and apoptosis. hnRNPK exhibits aberrant expression in numerous tumors, functioning paradoxically as either an oncogene or tumor suppressor depending on cellular context, expression levels and post-translational modifications. Recent advancements have outlined the involvement of hnRNPK in tumor cell migration, angiogenesis and chemoresistance through interactions with long non-coding RNAs and the regulation of key signaling pathways. The present review summarizes current knowledge regarding the structure, function and clinical importance of the hnRNPK in cancer, highlighting its potential as both a biomarker and therapeutic target.

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1. Introduction

Cancer remains one of the leading causes of mortality worldwide and involves the dysregulation of molecular pathways that control fundamental cellular processes, including proliferation, apoptosis, migration and invasion. The regulation of gene expression serves a key role in maintaining cellular homeostasis and preventing malignant transformation. Accumulating evidence has highlighted the key role that RNA-binding proteins (RBPs) serve in orchestrating these regulatory networks, particularly in cancer development and progression (1). Among RBPs, heterogeneous nuclear ribonucleoproteins (hnRNPs) represent a particularly important subfamily that governs RNA metabolism, including transcription, splicing, stability and translation. The hnRNP family comprises >20 members, each with distinct structural domains and functional capabilities. These proteins exhibit notable versatility in shuttling between the nuclear and cytoplasmic compartments and participating in diverse cellular processes, ranging from chromatin remodeling to signal transduction. Evidence suggests that the dysregulation of hnRNP proteins markedly contributes to oncogenesis and tumor progression in a number of cancer types (2). hnRNPK has emerged as a promising member of this family owing to its multifaceted roles and aberrant expression patterns in numerous malignancies, including gastric cancer, colorectal cancer, hepatocellular carcinoma, lung cancer, acute myeloid leukemia and bladder cancer (3). Characterized by its signature K-homology (KH) domains, hnRNPK functions as a multifunctional regulator that interfaces with DNA, RNA and protein components. The ability of hnRNPK to modulate gene expression at multiple levels serves as a key hub in the molecular networks governing cell fate decisions. With this, the dynamic subcellular localization of hnRNPK underscores its potential as a therapeutic target and biomarker. Despite increasing awareness of the importance of hnRNPK, key questions remain regarding its dual nature as both an oncogene and a tumor suppressor in different contexts. The present comprehensive review summarizes the current knowledge on the structure, function and clinical importance of hnRNPK in cancer, while identifying key areas for future investigation of novel therapeutic strategies.

2. hnRNP family

Precursor mRNA processing requires the participation of numerous proteins. At different stages of mRNA processing,

these proteins may form RNP complexes with RNA. Based on the type of bound RNA, RNP complexes can be classified into three types, hnRNPs, small nuclear RNP complexes and messenger RNP complexes (2). RBPs are the primary components involved in the formation of these complexes, sharing similar structural features and subcellular distribution patterns, but differing from other nuclear protein complexes.

The RNP-conserved sequence RNA-binding domain (RNP-CS-RBD) and KH domain are the two most frequently occurring RNA-binding domains in hnRNPs. The three-dimensional crystal structures of these two domains differ notably, suggesting that the RNA-binding sequences recognized are distinct (4). A stretch of ~80 amino acids, known as the RNP-CS-RBD or RNA-recognition motif (RRM), contains two highly conserved sequences, the RNP1 octamer and the RNP2 hexamer, which are positioned adjacently and directly interact with RNA. Proteins that bind to RNA typically contain 1-4 RRM. The KH domain, first identified in hnRNPK, is primarily responsible for recognizing RNA and single-stranded DNA (5). KH domains are classified into two subtypes, KH1 and KH2, based on their extended regions at the N and C termini. RBPs may contain ≤15 KH domains.

hnRNP complexes comprise ≥20 hnRNPs, with molecular weights ranging from 32-120 kDa. Members of the hnRNP family, A-U, are named according to their molecular weights. The hnRNP family is widely distributed and found in plants, yeast and various vertebrate tissues and organs. Additionally, the expression levels vary across tissues and organs, with relatively high expression in metabolically active tissues, such as the brain and lungs. Expression patterns also vary across developmental stages, even within the same tissue type (3). hnRNPs can be divided into two groups based on their physiological functions, namely those confined to the nucleus, such as hnRNPB and hnRNPC and those capable of shuttling between the nucleus and cytoplasm, including hnRNPA, D, E, I and K (5). The survival and growth of multicellular organisms depend heavily on the presence of hnRNPs. These proteins interact with chromatin and kinases involved in transcription, splicing and translation and serve key roles in chromatin remodeling and gene expression regulation. Tumorigenesis is associated with alterations in hnRNP activity due to various factors, including environmental and genetic influences (6). Distinct hnRNPs have unique functions within the same tumor type. The primary mechanism by which hnRNPs contribute to cancer is the regulation of tumor-related gene expression. Table I (7-25) provides a comprehensive overview of the differential expression patterns of numerous hnRNP family members in different tumor types. For example, hnRNPA1 is upregulated in liver and colorectal cancer, whereas hnRNPA2/B1 shows decreased expression in breast cancer but increased expression in pancreatic cancer, demonstrating context-dependent roles.

3. hnRNPK structure

Through alternative cleavage, hnRNPK can freely move between the cytoplasm and nucleus to create five distinct cleaved entities, hnRNPK A-E. The majority of the hnRNPK protein comprises two bidirectional nuclear localization signals (NLS), three functional regions (KH domains) and one K protein interaction (KI) region (26). The KH region, a tertiary structure composed of three helices and three folds (βααββα), is involved in the binding of DNA or RNA, splicing of mRNA and control of transcription. The proline-rich KI region primarily serves as a binding site for sarcoma (Src) kinase family proteins. The mRNA export process is highly selective. The nucleus has a bilayer membrane structure and the only channel present is the nuclear pore complex (NPC). The export of mRNA molecules through the NPC requires energy and the formation of an mRNA-protein complex (23). After forming this complex with the precursor mRNA, hnRNPK transports it into the cytoplasm through the NPC. Together with additional proteins, such as RNA polymerase II, it undergoes splicing and modification before dissociating from the complex and returning to the nucleus to participate in the subsequent round of transport (27). The molecular structure of hnRNPK is illustrated in Fig. 1.

4. hnRNPK function

Functional domains and molecular interactions. With the presence of the KH, NLS and KI domains, hnRNPK can bind to DNA, RNA and proteins with specificity. This allows it to participate in numerous biological processes, including the regulation of gene transcription, alternative mRNA splicing, mRNA polyadenylation, mRNA stability, mRNA translation and cell signal transduction.

Regulation of gene transcription. hnRNPK attaches to specific DNA locations on genes and participates in the regulation of gene transcription by interacting with DNA proteins. hnRNPKs serve roles in both transcriptional activation and inhibition. hnRNPK can bind to the promoters of numerous genes, including those of the simian vacuolating virus 40, neuronal nicotinic acetylcholine receptor, BRCA1, cellular Src (c-Src), cellular Myc (c-Myc) and eukaryotic translation initiation factor 4E, to increase transcription of the corresponding genes (28). hnRNPK can also bind to the human thymidine kinase gene promoter to inhibit transcription.

Regulation of mRNA variable splicing. Gene expression is regulated by alternative splicing of mRNA. Gene function can be enhanced by altering the splicing of the same DNA segment to produce mRNA, which can subsequently be translated into proteins that exhibit specific biological effects. The most notable cell splicing regulators are hnRNPs, which are found in precursor mRNA and contain splicing enhancement and inhibition elements that selectively bind to cytokines, to open and close splicing sites (22). hnRNPK serves a key role in regulating the variable splicing of Runt-related transcription factor 1 and synaptosome-associated protein 25 kDa mRNA during neuronal differentiation. hnRNPK binds to the enhancer of chicken P-tropomyosin precursor mRNA and promotes exon splicing, specifically when hnRNPK is combined with a splicing inhibitor to suppress the synthesis of the apoptosis-promoting gene Bcl-x short-isoform. Subsequently, ~50% of alternative splicing events in apoptotic genes are affected (29).

Regulation of mRNA stability. Cells tightly regulate mRNA stability through RNA-binding proteins and controlled

Table I. Expression of hnRNPs in different tumors.

First author, year	hnRNP type	Tumor	Expression	Methods	Mechanism	(Refs.)
Zhou, 2013	hnRNPA1	Liver cancer	Increased	RT-qPCR and IHC	Regulates the level of CD44v6	(7)
Huang, 2024	hnRNPA1	Colorectal cancers	Increased	Two-dimensional electrophoresis and image analysis	Promotes tumor metastasis	(8)
Liu, 2020	hnRNPA2/B1	Breast cancer	Decreased	Tissue chips, mouse models and publicly available data	Inhibits STAT3 and Wnt/TCF4 signaling pathways	(9)
Gu, 2013	hnRNPA2/B1	Pancreatic cancer	Increased	RT-qPCR	Regulates the levels of E-cadherin and MMP-2	(10)
Huang, 2017	hnRNPA2/B1	Gastric cancer	Increased	Proteomics technique, western blotting, laser confocal microscope and RT-qPCR	Interacts with oncogenes and tumor-suppressor genes	(11)
Bidot, 2001	hnRNPA2/B1	Thyroid carcinoma	Decreased	IHC	Loss of hnRNPA2/B1 expression appears to be a characteristic feature of thyroid malignant lesions	(12)
Matsuyama, 2000	hnRNPB1	Esophageal cancer	Increased	IHC	Acts as a unique diagnostic marker with regard to association between expression level and histopathological grading	(13)
Sueoka, 2005	hnRNPB1	Lung cancer	Increased	RT-qPCR	Plasma hnRNPB1 mRNA is a useful non-invasive marker for detection of lung cancer	(14)
Tani, 2003	hnRNPB1	Lymphoma/ leukemia	Increased	IHC	Process of hnRNPB1 expression in ATLL differs from those in other lymphoid neoplasms and carcinoma	(15)
Dos Santos, 2022	hnRNPC	Thyroid carcinoma	Increased	RT-qPCR	Directly affects the expression of miR-17-92 miRNAs	(16)
Wu, 2018	hnRNPC	Breast cancer	Increased	RT-qPCR	Controls the endogenous dsRNA and the down-stream interferon response	(17)
Howley, 2022	hnRNPE1	Breast cancer	Increased	RT-qPCR	Interacts with ARIH1	(18)
Roychoudhury, 2007	hnRNPE2	Oral cancer	Decreased	RT-qPCR	Enhances the resistance of cancer cells to apoptosis	(19)
Li, 2019	hnRNPF	Bladder cancer	Increased	Proteomic methods and RNA immunoprecipitation	Mediates the stabilization of Snail1 mRNA by binding to its 3'UTR	(20)
Xu, 2018	hnRNPF	Gastric cancer	Decreased	RT-qPCR	ECD prevents E3 ligase ZFP91-mediated hnRNPF ubiquitination and degradation	(21)
Peng, 2019	hnRNPK	Pancreatic cancer	Increased	RT-qPCR	SGLT2 activates the Hippo signaling pathway through the hnRNPK-YAP1 axis	(22)
Peng, 2021	hnRNPK	Colorectal cancer	Increased	RNA pulldown, RNA sequencing and RT-qPCR	Circ-GALNT16 could enhance the formation of the hnRNPK-p53 complex	(23)
Zhang, 2024	hnRNPM	Breast cancer	Increased	RT-qPCR	Promotes breast cancer metastasis by activating the switch of alternative splicing	(24)

Table I. Continued.

First author, year	hnRNP type	Tumor	Expression	Methods	Mechanism	(Refs.)
Chen, 2019	hnRNPM	Colon cancer	Increased	Proteomic and bioinformatic analyses	hnRNPM-IRES-mediated translation in transforming hypoxia-induced proteome toward malignancy	(25)

hnRNP, heterogeneous nuclear ribonucleoproteins; RT-qPCR, reverse transcription quantitative PCR; IHC, immunohistochemistry; IRES, internal ribosome entry site; IRF-3, interferon regulatory factor 3; CD44v6, CD44 variant alternative exon 6; miRNA, microRNA; dsRNA, double stranded RNA; TCF4, transcription factor 4; ATLL, adult T-cell leukemia-lymphoma; ARIH1, ariadne RBR E3 ubiquitin protein ligase 1; ZFP91, zinc finger protein 91 homolog; SGLT2, sodium-glucose cotransporter-2; YAP1, yes1 associated transcriptional regulator; GALNT16, polypeptide N-acetylgalactosaminyltransferase 16; ECD, ecdysoneless; E3, enzyme 3.

degradation pathways. The biological functions of expressed proteins and the half-life of mRNA are closely related. mRNA stabilization can be achieved through controlled degradation (30). Currently, four mechanisms of mRNA decay have been recognized (31), including the deadenylation-dependent process, endogenous ribozyme-mediated system, nonsense-mediated pathway and non-stop degradation pathway. Numerous cis-regions in the mRNA sequence can be detected and bound by hnRNPs, which affect mRNA stability primarily through the deadenylation-dependent and nonsense-mediated decay pathways. Proreninogen mRNA is stabilized and renin production is aided by the interaction of hnRNPK with the 3'-untranslated region (UTR) of proreninogen mRNA. To improve viral mRNA stability, the KH domain of hnRNPK interacts with poliovirus RNA-splicing regulatory components (32). Collagen I and III are expressed more efficiently when hnRNPK interacts with the 3'-UTRs of their mRNAs.

Regulation of mRNA translation. hnRNPK is key for controlling cytoplasmic mRNA translation. The final step in the transition from reticulocytes to mature erythrocytes is mediated by reticulocyte 15-lipoxygenase (r15-LOX). Gradual translation of r15-LOX mRNA occurs during cell development. The 3'-UTR of LOX mRNA contains a differentiation control element (DICE), which serves a role in regulating this translation (33). The interaction between hnRNPK and DICE halts translation and hinders the assembly of complete 80S ribosomes. hnRNPK functions as a substrate for c-Src during erythrocyte maturation. To enable the translation of LOX mRNA, active c-Src phosphorylates hnRNPK and disrupts its binding to DICE. hnRNPK can bind to the 5'-UTR of the proto-oncogene Myc *in vivo* and *in vitro*, promoting ribosome entry and enhancing c-Myc translation. In addition to the DNA or RNA binding involved in signal transduction, hnRNPK influences the transcription and translation of signaling pathways by interacting with key signaling proteins, such as Vav and c-Src (34). The proto-oncogene Vav is a key regulator of the B cell receptor (BCR) signaling pathway. According to previous studies (2,6), hnRNPK binds to the SH3 domain of the Vav protein and promotes cell transformation through the BCR pathway. c-Src regulates the MAPK/ERK, integrin/focal adhesion kinase and STAT signaling pathways, amongst others, serving a role in biological processes such as cell division and apoptosis (35). Upon hnRNPK binding to the SRC homology 3 domain of c-Src, c-Src is activated, thereby controlling downstream signaling molecules.

Regulation of chromatin remodeling. Chromatin remodeling factors regulate chromatin structure by altering the position and configuration of nucleosomes during DNA replication and transcription. These changes affect the binding of transcription-related proteins to DNA, thereby controlling gene transcription (36). hnRNPK can directly interact with DNA methyltransferase, EED (a core component of polycomb repressive complex 2) and nuclear scaffold attachment factor B to regulate chromatin remodeling, which, in turn, affects gene expression. The structural framework that remains in the eukaryotic nucleus after removal of the nuclear membrane, soluble proteins and chromatin is

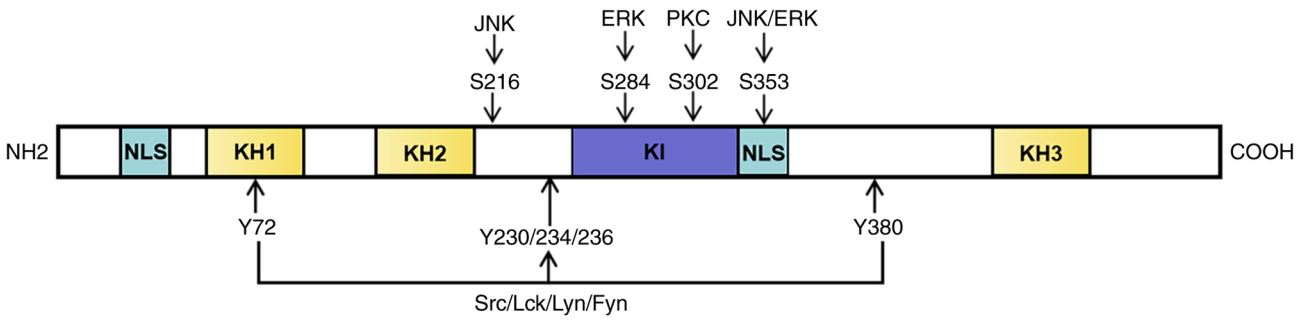

Figure 1. Molecular structure of heterogeneous nuclear ribonucleoprotein K. NLS, nuclear-localization signals; KH, functional regions; KI, protein interaction region; Src, serine family protein kinases; Lck, tyrosine kinase like protein kinase; Lyn, non-receptor tyrosine kinase; Fyn, proto-oncogene tyrosine protein kinase; PKC, phospholipid inositol signal pathway. NH_2, amine group; COOH, carboxyl group.

known as the nuclear matrix (37). Nuclear matrix proteins constitute the majority of these structures, while DNA, RNA and lipids make up the remainder. The nuclear matrix is important for chromatin remodeling, DNA replication, gene transcription and post-transcriptional regulation. Nuclear matrix proteins, including hnRNPK, are key in maintaining the grid-like structure of the nuclear matrix (38). Changes in the internal structure of the nuclear matrix can affect various biological processes, including chromatin remodeling and gene transcription.

Interaction between hnRNPK and non-coding RNAs (ncRNAs). hnRNPK exhibits the ability to interact with numerous ncRNAs and participate in the regulation of various cellular pathways. Long ncRNAs (lncRNAs), small nucleolar RNAs and cyclic RNAs are the three primary categories of ncRNAs (39). lncRNAs, which are >200 nucleotides in length, are key for the biological functions of various types of cancer, including colorectal, hepatocellular, breast and bladder cancer, serving an important role in disease etiology and acting as primary regulators of hnRNPK. Table II illustrates how hnRNPK interacts with cellular processes and contributes to the regulation of protein-coding gene networks. These interactions include: i) lncRNA-hnRNPK interactions, such as lncRNA-p21, Tcl1 upstream neuron-associated lncRNA, lncRNA essential for naïve ESC self-renewal 1, promoter-associated noncoding RNA of ETS1, Ewing sarcoma-associated transcript 1, cancer susceptibility candidate 11, MYC-inducible lncRNA 2 and lncRNA91H, which regulate gene transcription; ii) the regulation of mRNA stability and translation by lncRNA-hnRNPK interactions, including c-Myc-upregulated lncRNA, translation regulatory lncRNA and linc0046660; iii) the promotion of lncRNA nuclear localization, as observed with short interspersed nuclear element-derived nuclear RNA localization; iv) the regulation of genes involved in X-inactive specific transcript activity through lncRNA-hnRNPK interactions; and v) hnRNPK-mediated alternative splicing of lncRNAs such as nuclear paraspeckle assembly transcript 1 (40). Table II (26,27,41-53) summarizes the specific mechanisms underlying these interactions and highlights the diverse roles of hnRNPK in the regulatory networks of protein-coding genes. Notable examples include MYU stabilizing CDK6 expression in the cytoplasm, CTHCC activating YAP1 transcription in the nucleus and CASC11 promoting the Wnt/β-catenin pathway.

5. Biological function of hnRNPK in tumors

Overview of the roles of hnRNPK in cancer. hnRNPK controls the expression of numerous oncogenes and tumor suppressor genes in malignancies, as well as the proliferation, apoptosis, migration and invasion of tumor cells. Fig. 2 presents a comprehensive overview of the hnRNPK functional network in malignant tumors, illustrating its multifaceted roles in cancer biology through a number of molecular mechanisms and signaling pathways.

hnRNPK and tumor cell proliferation. In certain malignancies, hnRNPK has been implicated in the regulation of tumor growth. A previous study suggested that hnRNPK controls the p53/p21/cyclin-D1 axis to suppress tumor cell proliferation, colony formation and tumor progression in gastric cancer cells (11). An association has also been observed between hnRNPK expression and poor prognosis in patients with bladder cancer (54). The primary mechanism of this involves the regulation of cyclin-D1, a key cell cycle protein, by hnRNPK to promote the proliferation and survival of bladder cancer cells. The human telomerase reverse transcriptase and c-Myc genes, which are involved in tumor cell proliferation, are also closely associated with hnRNPK (55).

hnRNPK and tumor apoptosis. One of the key hallmarks of cancer is its ability to evade apoptosis. hnRNPK regulates tumor apoptosis through a number of pathways. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a novel and efficient therapeutic agent that targets tumor cell death (56). The NF-κB pathway, which is implicated in apoptosis, is activated by phosphatidylinositol signaling and can induce apoptosis in non-small-cell carcinomas. Additional research has revealed that TRAIL treatment of H1299 cells promotes hnRNPK accumulation and induced apoptosis. However, ERK1/2 inhibitors and ERK phosphorylation receptor mutations were shown to reduce TRAIL-induced cytoplasmic accumulation of hnRNPK and act as anti-apoptotic agents (57).

hnRNP, DNA repair and tumor formation. If cellular DNA is not repaired promptly after exposure to ionizing radiation, chemotherapeutic agents or other external stimuli, it can lead

Table II. Mechanism of interaction between a number of lncRNAs and hnRNPK.

First author, year	lncRNA type	hnRNPK location	Function	Mechanism	(Refs.)
Kawasaki, 2016	MYU	Cytoplasm	Promotes cell proliferation	Stabilizes CDK6 expression	(41)
Xu, 2019	treRNA	Cytoplasm	Promotes cell proliferation	Inhibits epithelial cadherin	(26)
Xia, 2022	CTHCC	Nucleus	Promotes cell proliferation and invasion	Activates YAP1 transcription	(42)
Huarte, 2010	LincRNA-p21	Nucleus	Promotes cell proliferation and inhibits p53 mediated apoptosis	Transcriptional regulation	(43)
Lin, 2014	TUNA	Nucleus	Promotes stem cell differentiation	Activates multiple signal paths	(44)
Li, 2018	pancEts-1	Nucleus	Promotes cell proliferation and invasion	Activates β Annexin	(45)
Xi, 2024	ELF3-AS1	Nucleus	Promotes cell proliferation and invasion	Regulates the downstream target gene, C-C motif chemokine 20	(46)
Wang, 2022	CRLM	Nucleus	Promotes metastasis and regulating gene expression	Associated with the chromatin regions of genes involved in cell adhesion and DNA damage	(47)
Lee, 2021	LINC00263	Nucleus	Promotes cell proliferation and invasion	Acts as a miR-147a decoy and thus upregulating CAPN2	(27)
Ji, 2020	LINC01413	Nucleus	Facilitates cell proliferation, migration, invasion and EMT	LINC01413 as a positive regulator through the LINC01413/hnRNP-K/ TAZ1/YAP1/ZEB1 axis	(48)
Zhang, 2016	CASC11	Nucleus	Promotes cell proliferation and invasion	Activates the Wnt/ β Annexin pathway	(49)
Gu, 2019	LBCS	Nucleus	Activates androgen receptor signaling	LBCS interacted directly with hnRNPK to suppress and rogen receptor translation	(50)
Gu, 2019	lncRNA-LBCS	Nucleus	Inhibits tumor drug resistance	Inhibits SOX2 transcription	(50)
Pintacuda, 2017	Xist	Nucleus	Interacts with X chromosome	Modifies chromosome	(51)
Gao, 2018	lncRNA 91H	Exosomes	Promotes tumor occurrence and metastasis	Regulates the expression of HnRNPK	(52)
Peng, 2020	FAM84B-4	Nucleus	Promotes tumorigenesis	Lnc-FAM84B-4 regulates MAPK pathway by restraining DUSP1 expression	(53)

lnc, long non-coding; DUSP1, dual specificity protein phosphatase 1; SOX2, SRY-box transcription factor 2; LINC01413, long intergenic non-protein coding RNA 1413; YAP1, Yes-1 associated transcriptional regulator; ZEB1, zinc finger E-box binding homeobox 1; CAPN2, calpain 2; miR-147a, microRNA 147a; EMT, epithelial-mesenchymal transition; Xist, X inactive specific transcript; CASC11, cancer susceptibility 11; CRLM, colorectal liver metastasis ELF3-AS1, ELF3 antisense RNA 1; CDK6, cyclin dependent kinase 6; treRNA, translation regulatory long non-coding RNA; TUNA, Tcl1 upstream neuron-associated.

to chromosomal remodeling, gene loss and genome instability, thereby promoting cancer development (47). Aberrant hnRNPK expression in tumor cells has been shown to impair DNA repair capacity. When the expression of hnRNPK was downregulated in irradiated bronchial epithelial cells, DNA strand repair was notably impeded. Proteomics analysis has shown that hnRNPK binds to chromatin in response to DNA damage in HeLa cells (58).

hnRNPK and tumor angiogenesis. Tumor metastasis occurs through direct extension, hematogenous and lymphatic spread and implantation of tumor cells. The early diffusion stage involves the adhesion plaque complex precursor, in which hnRNPK is expressed. Disruption of hnRNPK synthesis increases tumor cell metastasis, indicating that hnRNPK serves a rate-limiting role in tumor growth (59). The relationship between hnRNPK and metastasis has been established in

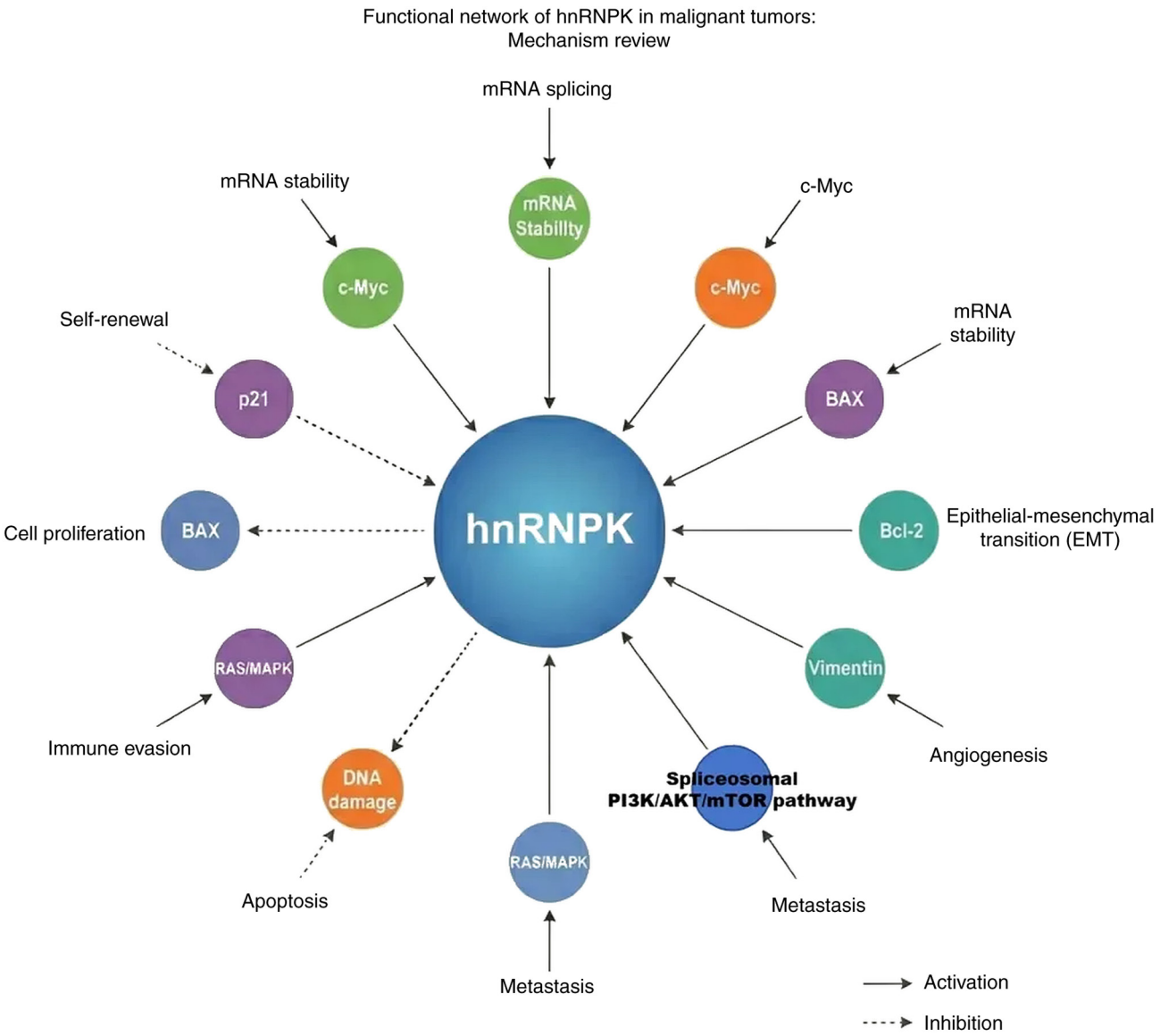

Figure 2. Functional network of hnRNPK in malignant tumors. hnRNPK, heterogeneous nuclear ribonucleoprotein K; c-Myc, cellular Myc.

colon, prostate and gallbladder cancer types. Notably, tumor size typically does not exceed 2-3 mm without blood supply and the angiogenic agents that facilitate this include vascular endothelial growth factor (VEGF) and fibroblast growth factor. Therefore, hnRNP proteins have been shown to regulate angiogenic factors and under hypoxic conditions, hnRNPL preferentially binds to the 3'-UTR of VEGF mRNA (60). Inhibition of hnRNPK expression suppresses glioma growth and invasion, suggesting that hnRNPK promotes tumor angiogenesis and facilitates malignant progression.

hnRNPK and tumor cell migration and invasion. hnRNPK is further associated with tumor metastasis. Through the Ras-Raf-MAPK pathway, hnRNPK promotes the expression of metastasis-related genes, such as MMP3 and MMP10, prostaglandin G/H synthase 2 and thymosin. Ras and cholecystokinin expression further promotes tumor spread. DAB2-interacting protein stimulates hnRNPK nuclear accumulation, enhances MMP2 transcription and drives colorectal cancer invasion and metastasis through the MAPK/ERK pathway (61). hnRNPK also promotes tumor spread in nasopharyngeal cancer by upregulating MMP12 expression. Strozynski *et al* (62) found that hnRNPK was markedly expressed in irradiated cells using two-dimensional electrophoresis and mass spectrometry.

Targeted inhibition of hnRNPK expression can reduce the metastatic potential of head and neck squamous cell carcinoma cells. In small-cell renal carcinoma, cytoplasmic aggregation of hnRNPK promotes tumor cell invasion into surrounding tissues. hnRNPK deletion results in transcriptional inactivation of p53 target genes and defective cell cycle arrest. DNA damage-induced hnRNPK undergoes small ubiquitin-related modifier (SUMO)-ylation, which regulates p53 transcriptional activation (63). Additionally, methylation of arginine residues at positions 296 and 299 inhibits the phosphorylation of serine at position 302 by the pro-apoptotic protein kinase C, thereby reducing apoptosis induced by DNA damage. This suggests that hnRNPK serves a key role in anti-apoptotic mechanisms in tumor cells. Chen *et al* (25) demonstrated that hnRNPK exhibits anti-apoptotic activity by regulating downstream genes. Specifically, hnRNPK binds to the promoter

Table III. Context-dependent dual roles of hnRNPK in cancer.

First author, year	Cancer type	K function	Expression level	Key mechanisms	Regulatory factors	Clinical outcome	(Refs.)
Huang, 2017	Gastric cancer	Tumor suppressor	Low	p53/p21/CCND1 pathway activation	p53 interaction	Poor prognosis with low expression	(11)
Zhang, 2016	Acute myeloid leukemia	Tumor suppressor	Low/ haploinsufficient	Cell cycle regulation	SUMO modifications	Increased susceptibility in knockout mice	(68)
Wu, 2020	Colorectal cancer	Oncogene	High	MAPK/ERK activation and MMP2 upregulation	DAB2IP interaction	Poor prognosis with high expression	(61)
Li, 2020	Nasopharyngeal cancer	Oncogene	High	MMP12 upregulation	Post-translational modifications	Associated with metastasis	(6)
Li, 2019	Lung cancer	Oncogene	High	Cytoplasmic accumulation	Subcellular localization shift	Associated with invasion	(55)
Xu, 2019	Bladder cancer	Oncogene	High	CCND1 regulation and ERCC4 modulation	Nuclear localization	Poor prognosis	(26)
Meng, 2021	Hepatocellular carcinoma	Oncogene	High	c-Myc activation through IRES	HBV interaction	Associated with HBV+ tumors	(33)

hnRNPK, heterogeneous nuclear ribonucleoprotein K; CCND1, cyclin D1; ERCC4, excision repair cross-complementation group 4; c-Myc, cellular Myc; IRES, internal ribosome entry site; HBV, hepatitis B virus; DAB2IP, disabled homolog 2-interacting protein; SUMO, small ubiquitin-related modifier.

of anti-apoptotic FLICE inhibitory protein and activates its expression. The lncRNA CASC11 interacts with hnRNPK to activate the WNT/β-catenin pathway, ultimately contributing to colorectal cancer development (43).

hnRNPK and drug resistance of tumor cells. hnRNPK has been shown to be associated with drug resistance in tumor cells. After radiotherapy, hnRNPK increased in a dose-dependent manner and accumulated in the cytoplasm of melanoma cells with neuroblastoma RAS viral oncogene homolog mutations, causing the cells to become radiotherapy-tolerant (64). Mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors can downregulate hnRNPK expression, which, when combined with radiation, markedly increases apoptosis and promotes radiosensitivity (65). Targeted inhibition of hnRNPK expression was found to be consistent with the pro-apoptotic effects of MEK inhibitors. A similar conclusion was reached in colorectal cancer (CRC) cells. Kirsten rat sarcoma virus-mutant CRC cells exhibited rapid upregulation of hnRNPK following radiation therapy, which increased their tolerance to irradiation. MEK inhibitor therapy downregulates hnRNPK, improving sensitivity to radiation (66). hnRNPK is highly expressed in resistant cell lines and the bone marrow of patients with drug-resistant acute myeloid leukemia (AML). Drug-resistant cells lose their tolerance to doxorubicin through targeted suppression of hnRNPK expression. In addition, hnRNPK may contribute to doxorubicin resistance by regulating autophagy.

hnRNPK may serve as a prognostic and chemosensitivity marker in nasopharyngeal carcinoma, as it regulates thymidine phosphorylase expression. Cells with high thymidine phosphorylase levels are sensitive to doxifloruridine treatment (67). Interferon-stimulated gene 15 (ISG15) regulates hnRNPK expression in lung cancer cells. ISG15 downregulation induces cell cycle arrest, allowing extended repair of cisplatin-damaged DNA, stabilization of p53 and increased hnRNPK expression. This process can enhance cisplatin resistance. In lung adenocarcinoma cells, hnRNPK blocks the phosphorylation of glycogen synthase kinase-3 at Ser9 to stabilize cellular FLICE inhibitory protein and increase TRAIL resistance. Zhang *et al* found that hnRNPK increases AML resistance to adriamycin through modulation. These findings suggest that hnRNPK regulates tumor cell sensitivity to chemotherapy and may serve as a marker for chemosensitivity (68).

Tumor therapy targeting hnRNPK. In Traditional Chinese Medicine, certain therapeutic compounds can target hnRNPK to exert antitumor effects. Further research using bioinformatics and biochemical methods revealed that the ethanol extract of Indian ginseng serves a role in inhibiting tumor metastasis and angiogenesis by downregulating metastasis-related proteins, including hnRNPK, VEGF and MMPs (69). The ethanol extract of Indian ginseng selectively inhibits tumor cell activity and suppresses metastasis, invasion and angiogenesis. Gambogic acid in *Garcinia nujiangensis* extract can lower hnRNPK levels by promoting the ubiquitin-proteasome-dependent degradation of hnRNPK, leading to cell cycle arrest and antitumor effects. The protein hnRNPK, associated with human telomerase reverse transcriptase, is a potential biomarker for liver cancer prognosis and may also serve as a therapeutic target for liver cancer (70). The primary antigen target is located at the N-terminus of hnRNPK and contains a glutamic acid-rich domain. Therefore, hnRNPK may be used as a biomarker for the detection of hepatocellular carcinoma associated with hepatitis B virus (HBV). hnRNPK is a biomarker of chemoresistance in gastric cancer (GC). Additionally, upregulation of hnRNPB1 has been identified as a useful biomarker for the early diagnosis of lung cancer and human squamous cell carcinomas. While these preclinical findings are promising, it is important to note that hnRNPK-targeted therapeutic development remains in early stages. Unlike established targets such as HER2 or EGFR, to the best of our knowledge, no hnRNPK-specific inhibitors have yet entered clinical trials. The primary challenge lies in the multifunctional nature and context-dependent role of the protein, which complicates the development of selective therapeutic strategies. Current research focuses primarily on understanding the mechanistic roles of hnRNPK across different cancer types to identify optimal intervention points.

6. Expression and prognostic value of hnRNPK in malignant tumors

Although hnRNPK contributes markedly to the occurrence and progression of specific cancer types, it still remains unclear as to whether it functions as an oncogene or a tumor suppressor gene. The ability of hnRNPK to regulate both carcinogenesis and tumor-inhibitory pathways has been demonstrated in numerous studies (49,71). Cell proliferation and apoptosis inhibition have been linked to the upregulation and downregulation of hnRNPK. Clinical reports present varying perspectives. hnRNPK functions as an oncogene in gastric, colorectal, nasopharyngeal, prostate, melanoma and oral squamous cell carcinoma (OSCC). Upregulation of this gene was found to be positively associated with tumor progression and a poor prognosis. Conversely, hnRNPK has been shown to act as a tumor suppressor gene in acute myeloid leukemia (72). Mice with haploinsufficient hnRNPK expression are more susceptible to lymphoma and acute myeloid leukemia. Therefore, hnRNPK cannot be categorized solely as an oncogene or tumor suppressor gene based on these cytological and clinical findings. The paradoxical dual nature of hnRNPK appears to be determined by several key factors: i) Cellular context and tissue type, where gastric epithelial cells show tumor-suppressive responses while mesenchymal-derived cancers exhibit oncogenic effects; ii) subcellular localization, with nuclear hnRNPK often being protective while cytoplasmic accumulation promotes malignancy; iii) expression levels, where both upregulation and haploinsufficiency can promote tumorigenesis through different mechanisms; iv) post-translational modifications including phosphorylation, SUMOylation and methylation that modulate the protein interactions and functions of hnRNPK; and v) interaction partners, particularly p53 status, which fundamentally alter the role of hnRNPK in cell fate decisions. Table III summarizes these context-dependent factors including cancer type, hnRNPK function (oncogene vs. tumor suppressor), expression levels, key regulatory mechanisms and clinical outcomes (6,11,26,33,55,61,68).

Chronic myeloid leukemia (CML). CML, specifically the late acute phase, has a poor prognosis. With this, research

into hnRNPK and its family members during the acute phase of CML is relatively common. Other chromosomal and molecular abnormalities are also present in patients with CML, in addition to the aberrant BCR/ABL fusion gene (73). Together with other defective genes, the BCR/ABL gene can influence transcription, protein function and mRNA translation, and improperly abnormally activate downstream signaling pathways, thereby contributing to disease progression. The ability of hnRNPK, hnRNPE1 and hnRNPE2 to limit the proliferation of BCR/ABL-positive cells is inhibited by the upregulation of CML-blast crisis expression (74). The leukemogenic activity of BCR/ABL, which can increase c-Myc gene expression, enhance CML cell proliferation, block apoptosis and potentially promote rapid transformation, relies heavily on hnRNPK-mediated regulation of mRNA translation. The homologous region of the hnRNPK is the structural motif shared by hnRNPK and hnRNPE1/E2. The structural basis of the hnRNPK-mRNA interaction is described as follows. MAPK/ERK1/2 can enhance hnRNPK transcription and mRNA stability in bone marrow cells and lymphocytes expressing the BCR/ABL fusion gene through a BCR/ABL-dependent mechanism (75). Leukemia can be induced by hnRNPK, which inhibits cytokine-dependent colony formation in BCR/ABL-positive cells. hnRNPK binds to MYC mRNA through the internal ribosome entry site (IRES) and upregulates MYC expression at both the transcriptional and translational levels, ultimately promoting cell proliferation and inhibiting apoptosis in hepatocellular carcinoma cells. These effects may be linked to the dysregulation of the oncogene, MYC (76). To identify hnRNPK expression at the protein and transcriptional levels in the bone marrow cells of patients with CML in the chronic and acute phases, Zhu *et al* (77) used western blotting and reverse transcription-quantitative PCR techniques, finding that hnRNPK expression varied before and after the acute phase of CML, indicating that mRNA translation regulation may underlie changes in hnRNPK protein levels.

Lung cancer. Although hnRNPK expression was not observed during the aberrant proliferation of healthy alveolar and bronchiolar epithelial cells, it was slightly upregulated in cells with bronchial epithelial dysplasia (78). The localization of hnRNPK was also shown to gradually shift from the nucleus to the cytoplasm in the study by Huang *et al* (79) on lung cancer cell lines, suggesting that this shift is associated with the biological state of tumor cells. According to Li *et al* (55), hnRNPK was expressed in both the cytoplasm and nucleus of lung cancer tissues and control lung tissues. These findings suggest that the hnRNPK positivity rate in lung cancer tissues is higher than that in non-cancerous lung tissues. A total of three histological subtypes of lung cancer stained positive for hnRNPK and the positivity rates for small cell and non-small cell lung cancers did not differ significantly. Although hnRNPK was notably expressed in lung cancer tissues, there was no clear association between hnRNPK expression and the tissue type. In addition, this study found that invasive and metastatic lung cancer tissues showed notable levels of hnRNPK expression, which may indicate a connection between hnRNPK and tumor aggressiveness. However, the precise role of hnRNPK in lung cancer initiation, progression and metastasis remains elusive.

GC. In accordance with findings by Huang *et al* (8), hnRNPK is a useful prognostic marker in patients with GC. Han *et al* (80) discovered that hnRNPK is a GC-related antigen, with tissue microarray analysis revealing that hnRNPK expression was elevated in GC tissue. Patients with high hnRNPK expression exhibited a poor prognosis, suggesting that hnRNPK may be associated with GC occurrence, progression and prognosis. Poor prognosis in GC is linked to low hnRNPK transcription levels, particularly in patients with early-stage disease without metastasis. Through the p53/p21/cyclin D1 pathway, hnRNPK upregulation decreases tumor cell proliferation and colony formation *in vitro* and tumor growth *in vivo* (81). hnRNPK interacts with tumor-associated genes, including p53 and p21. High hnRNPK expression has been observed in GC tissue. Infection with the L-form of *Helicobacter pylori* may promote the expression of hnRNPK. The expression of hnRNPK and *Helicobacter pylori* L-form infection may work together to increase the risk of GC. The degree of differentiation, lymphatic metastasis and clinical stage of GC are associated with hnRNPK expression (82). Research has demonstrated that hnRNPK is primarily expressed in the nucleus of human GC SGC-7901 cells, with a minor quantity expressed in the cytoplasm of *in vitro* cultured gastric mucosal cell lines and GC SGC-7901 cells (53). The expression of hnRNPK was found to be higher in human GC SGC-7901 cells than in gastric mucosal gastric epithelial-1 cells, both in the cytoplasm and nucleus. hnRNPK was also marginally expressed in the nucleus of gastric mucosal GES-1 cells, but not in the cytoplasm of these cells. Knockdown of hnRNPK reduced the proliferation, migration and invasion of human GC SGC-7901 cells. The cytoplasmic localization and elevated expression of hnRNPK in SGC-7901/DDP cells indicated that hnRNPK was associated with drug resistance in human GC SGC-7901 cells.

Liver cancer. To demonstrate that hnRNPK is primarily expressed in the nucleus, Meng *et al* (33) examined hnRNPK expression in hepatocellular carcinoma and adjacent tissues. Findings revealed that hnRNPK protein expression was higher in 70% of hepatocellular carcinoma tissues than in the corresponding adjacent tissues (83), suggesting that it promotes liver cancer cell development. By separating the cytoplasm and nucleus of hepatoma cells at various densities, changes were observed in hnRNPK expression during cell proliferation. These findings indicate that hnRNPK expression in the nucleus increases with higher cell density, suggesting that elevated nuclear hnRNPK expression may promote cell proliferation (84). In addition, while only 50% of HBV-negative liver cancer tissues showed higher hnRNPK expression than their adjacent tissues, 80% of HBV-positive liver cancer tissues did, indicating an association between hnRNPK expression and HBV infection. Further research is needed to determine whether hnRNPK has a synergistic effect with HBV in promoting liver cancer development and whether HBV upregulates hnRNPK expression in liver cancer tissues. Harris *et al* (85) demonstrated that hnRNPK can interact with the 3'-UTR of the hepatitis C virus and participate in viral replication. The IRES, located at the 3' end, is a key regulatory element in viral gene translation. IRES and hnRNPK work together to notably enhance the mRNA translation efficiency,

thereby increasing viral expression and replication, thus accelerating disease progression.

OSCC. With regard to OSCC, researchers used isotope-labeled relative and absolute quantitative techniques combined with liquid chromatography-mass spectrometry and found that hnRNPK protein expression increased with higher tumor-lymph node-metastasis tumor staging levels and was associated with poor prognoses. Therefore, hnRNPK has the potential to be a useful marker for the early detection and prognostic monitoring of OSCC (86). N6-methyladenosine (m6A) levels in OSCC tissues were notably higher than those in adjacent non-tumor tissues and eight m6A-modified genes, including hnRNPC, exhibited differential expression patterns. HnRNPC alone may serve as a standalone biomarker and therapeutic target in OSCC. Compared with healthy oral mucosal tissues, OSCC tissues exhibit markedly elevated levels of hnRNPL, which is primarily concentrated in discrete nuclear regions, forming a punctate structure (87). The expression of hnRNPL was higher in mesenchymal tissues than in epithelial tissues. A novel target of hnRNPL, Ser/Arg-rich splicing factor 3, may be regulated by hnRNPL at both the transcriptional and post-transcriptional alternative splicing levels.

Tumors of the urinary system. In accordance with results from a study by Mukhopadhyay *et al* (88), while the androgen receptor (AR) can control the production of androgen-responsive genes and the proliferation of prostate cancer cells, hnRNPK can reduce AR expression by inhibiting the translation of AR mRNA. Analysis of hnRNPK expression in 188 patients with bladder cancer (89) revealed that bladder cancer tissues had markedly higher levels of hnRNPK expression and that hnRNPK expression levels were associated with prognosis. Additionally, research has demonstrated that hnRNPK inhibits tumor growth *in vivo* by enhancing proliferation, inhibiting apoptosis and contributing to treatment resistance in bladder cancer cells (90). This mechanism involves hnRNPK-mediated transcriptional regulation of cyclin D1, excision repair cross-complementing group four, amongst other components that influence bladder cancer activity.

After examining modifications in hnRNPK protein functionality in patients with advanced prostate cancer, researchers have found that reducing cholesterol levels inhibited the release of hnRNPK protein and hnRNPK-containing exosomes from prostate cancer cells (91). Prostate cancer cells release exosomes to facilitate the spread of the disease to other organs. hnRNPK helps regulate the quantity of exosomes produced by prostate cancer cells, thereby preventing the spread of malignancy to other parts of the body (92). Exosomes act as regulators prior to metastasis, conditioning the microenvironment of distant tissues to facilitate tumor cell colonization. According to Iwabuchi *et al* (93), decreasing cellular cholesterol levels may prevent hnRNPK from exiting tumor cells and transmitting oncogenic signals.

Current status of clinical translation. Despite extensive mechanistic studies, the clinical translation of hnRNPK research faces several limitations. The majority of current evidence derives from retrospective analyses of tumor samples and correlative studies. For instance, while multiple studies have demonstrated associations between hnRNPK expression and prognosis across numerous cancer types (30,35), these findings have not yet been incorporated into clinical practice guidelines. The lack of standardized detection methods and validated cut-off values for hnRNPK expression limits its immediate clinical utility. Furthermore, the dual nature of hnRNPK as both oncogene and tumor suppressor in different contexts presents unique challenges for therapeutic targeting, requiring more sophisticated patient stratification processes than currently available.

7. Conclusion

There is an association between hnRNPK and the initiation and progression of numerous cancer types. Identifying tumor markers is one of the primary strategies used to address key challenges in modern cancer research and hnRNPA2/B1 has been utilized as a marker for the early detection of lung cancer. Current findings suggest that hnRNPK holds promise as a molecular biomarker for related malignancies. Although research in this area is still in its early stages, several notable issues remain. Studies specifically focusing on hnRNPK are still limited. To establish the groundwork for future screening of human tumor molecular markers applicable to early clinical diagnosis, treatment, prognosis evaluation and disease monitoring, it is important to further elucidate the specific mechanisms by which members of the hnRNP family, including hnRNPK, contribute to the genesis, development and metastasis of tumors.

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Availability of data and materials

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Authors' contributions

YZ and YQ wrote the manuscript. YQ performed the literature search and revised the manuscript. YZ generated the figures. YQ. Both authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Holmgaard AB, Askou AL, Jensen EG, Alsing S, Bak RO, Mikkelsen JG and Corydon TJ: Targeted knockout of the Vegfa gene in the retina by subretinal injection of RNP complexes containing Cas9 protein and modified sgRNAs. Mol Ther 29: 191-207, 2021.
2. Chaudhury A, Chander P and Howe PH: Heterogeneous nuclear ribonucleoproteins (hnRNPs) in cellular processes: Focus on hnRNP E1's multifunctional regulatory roles. RNA 16: 1449-1462, 2010.
3. Wang Z, Qiu H, He J, Liu L, Xue W, Fox A, Tickner J and Xu J: The emerging roles of hnRNPK. J Cell Physiol 235: 1995-2008, 2020.
4. Zhao E, Li J, Xie Y, Jin W, Zhang Z, Chen J, Zeng L, Yin G, Qian J, Wu H, *et al*: Cloning and identification of a novel human RNPC3 gene that encodes a protein with two RRM domains and is expressed in the cell nucleus. Biochem Genet 41: 315-323, 2003.
5. Moujalled D, Grubman A, Acevedo K, Yang S, Ke YD, Moujalled DM, Duncan C, Caragounis A, Perera ND, Turner BJ, *et al*: TDP-43 mutations causing amyotrophic lateral sclerosis are associated with altered expression of RNA-binding protein hnRNP K and affect the Nrf2 antioxidant pathway. Hum Mol Genet 26: 1732-1746, 2017.
6. Li H, Liu J, Shen S, Dai D, Cheng S, Dong X, Sun L and Guo X: Pan-cancer analysis of alternative splicing regulator heterogeneous nuclear ribonucleoproteins (hnRNPs) family and their prognostic potential. J Cell Mol Med 24: 11111-11119, 2020.
7. Zhou ZJ, Dai Z, Zhou SL, Fu XT, Zhao YM, Shi YH, Zhou J and Fan J: Overexpression of HnRNP A1 promotes tumor invasion through regulating CD44v6 and indicates poor prognosis for hepatocellular carcinoma. Int J Cancer 132: 1080-1089, 2013.
8. Huang Y, Liu Y, Pu M, Zhang Y, Cao Q, Li S, Wei Y and Hou L: SOX2 interacts with hnRNPK to modulate alternative splicing in mouse embryonic stem cells. Cell Biosci 14: 102, 2024.
9. Liu Y, Li H, Liu F, Gao LB, Han R, Chen C, Ding X, Li S, Lu K, Yang L, *et al*: Heterogeneous nuclear ribonucleoprotein A2/B1 is a negative regulator of human breast cancer metastasis by maintaining the balance of multiple genes and pathways. EBioMedicine 51: 102583, 2020.
10. Gu WJ and Liu HL: Induction of pancreatic cancer cell apoptosis, invasion, migration, and enhancement of chemotherapy sensitivity of gemcitabine, 5-FU, and oxaliplatin by hnRNP A2/B1 siRNA. Anticancer Drugs 24: 566-576, 2013.
11. Huang H, Han Y, Yang X, Li M, Zhu R, Hu J, Zhang X, Wei R, Li K and Gao R: HNRNPK inhibits gastric cancer cell proliferation through p53/p21/CCND1 pathway. Oncotarget 8: 103364-103374, 2017.
12. Bidot P, Morgan M, Zhukov T, Tannenbaum M and Tockman MS: Loss of heterogeneous ribonucleoprotein A(2)/B(1) expression in thyroid neoplasms. Endocr Pract 7: 157-161, 2001.
13. Matsuyama S, Goto Y, Sueoka N, Ohkura Y, Tanaka Y, Nakachi K and Sueoka E: Heterogeneous nuclear ribonucleoprotein B1 expressed in esophageal squamous cell carcinomas as a new biomarker for diagnosis. Jpn J Cancer Res 91: 658-663, 2000.
14. Sueoka E, Sueoka N, Iwanaga K, Sato A, Suga K, Hayashi S, Nagasawa K and Nakachi K: Detection of plasma hnRNP B1 mRNA, a new cancer biomarker, in lung cancer patients by quantitative real-time polymerase chain reaction. Lung Cancer 48: 77-83, 2005.
15. Tani H, Ohshima K, Haraoka S, Hamasaki M, Kamma H, Ikeda S and Kikuchi M: Reduced expression of heterogeneous nuclear ribonucleoprotein B1 in adult T-cell lymphoma/leukemia. Int J Oncol 22: 529-534, 2003.
16. Dos Santos MGP, Gatti da Silva GH, Nagasse HY, Fuziwara CS, Kimura ET and Coltri PP: hnRNP A1 and hnRNP C associate with miR-17 and miR-18 in thyroid cancer cells. FEBS Open Bio 12: 1253-1264, 2022.
17. Wu Y, Zhao W, Liu Y, Tan X, Li X, Zou Q, Xiao Z, Xu H, Wang Y and Yang X: Function of HNRNPC in breast cancer cells by controlling the dsRNA-induced interferon response. EMBO J 37: e99017, 2018.
18. Howley BV, Mohanty B, Dalton A, Grelet S, Karam J, Dincman T and Howe PH: The ubiquitin E3 ligase ARIH1 regulates hnRNP E1 protein stability, EMT and breast cancer progression. Oncogene 41: 1679-1690, 2022.
19. Roychoudhury P, Paul RR, Chowdhury R and Chaudhuri K: HnRNP E2 is downregulated in human oral cancer cells and the overexpression of hnRNP E2 induces apoptosis. Mol Carcinog 46: 198-207, 2007.
20. Li F, Zhao H, Su M, Xie W, Fang Y, Du Y, Yu Z, Hou L and Tan W: HnRNP-F regulates EMT in bladder cancer by mediating the stabilization of Snail1 mRNA by binding to its 3' UTR. EBioMedicine 45: 208-219, 2019.
21. Xu SH, Zhu S, Wang Y, Huang JZ, Chen M, Wu QX, He YT, Chen D and Yan GR: ECD promotes gastric cancer metastasis by blocking E3 ligase ZFP91-mediated hnRNP F ubiquitination and degradation. Cell Death Dis 9: 479, 2018.
22. Peng WZ, Liu JX, Li CF, Ma R and Jie JZ: hnRNPK promotes gastric tumorigenesis through regulating CD44E alternative splicing. Cancer Cell Int 19: 335, 2019.
23. Peng C, Tan Y, Yang P, Jin K, Zhang C, Peng W, Wang L, Zhou J, Chen R, Wang T, *et al*: Circ-GALNT16 restrains colorectal cancer progression by enhancing the SUMOylation of hnRNPK. J Exp Clin Cancer Res 40: 272, 2021.
24. Zhang S, Zhang B, Liao Z, Chen Y, Guo W, Wu J, Liu H, Weng R, Su D, Chen G, *et al*: Hnrnpk protects against osteoarthritis through targeting WWC1 mRNA and inhibiting Hippo signaling pathway. Mol Ther 32: 1461-1478, 2024.
25. Chen TM, Lai MC, Li YH, Chan YL, Wu CH, Wang YM, Chien CW, Huang SY, Sun HS and Tsai SJ: hnRNPM induces translation switch under hypoxia to promote colon cancer development. EBioMedicine 41: 299-309, 2019.
26. Xu Y, Wu W, Han Q, Wang Y, Li C, Zhang P and Xu H: New insights into the interplay between non-coding RNAs and RNA-binding protein HnRNPK in regulating cellular functions. Cells 8: 62, 2019.
27. Lee WJ, Shin CH, Ji H, Jeong SD, Park MS, Won HH, Pandey PR, Tsitsipatis D, Gorospe M and Kim HH: hnRNPK-regulated LINC00263 promotes malignant phenotypes through miR-147a/CAPN2. Cell Death Dis 12: 290, 2021.
28. Choufani S, McNiven V, Cytrynbaum C, Jangjoo M, Adam MP, Bjornsson HT, Harris J, Dyment DA, Graham GE, Nezarati MM, *et al*: An HNRNPK-specific DNA methylation signature makes sense of missense variants and expands the phenotypic spectrum of Au-Kline syndrome. Am J Hum Genet 109: 1867-1884, 2022.
29. Tang S, Xie Z, Wang P, Li J, Wang S, Liu W, Li M, Wu X, Su H, Cen S, *et al*: LncRNA-OG promotes the osteogenic differentiation of bone marrow-derived mesenchymal stem cells under the regulation of hnRNPK. Stem Cells 37: 270-283, 2019.
30. Li J, Chen Y, Xu X, Jones J, Tiwari M, Ling J, Wang Y, Harismendy O and Sen GL: HNRNPK maintains epidermal progenitor function through transcription of proliferation genes and degrading differentiation promoting mRNAs. Nat Commun 10: 4198, 2019.
31. Ren D, Sun Y, Zhang D, Li D, Liu Z, Jin X and Wu H: SGLT2 promotes pancreatic cancer progression by activating the Hippo signaling pathway via the hnRNPK-YAP1 axis. Cancer Lett 519: 277-288, 2021.
32. Bampton A, Gatt A, Humphrey J, Cappelli S, Bhattacharya D, Foti S, Brown AL, Asi Y, Low YH, Foiani M, *et al*: HnRNP K mislocalisation is a novel protein pathology of frontotemporal lobar degeneration and ageing and leads to cryptic splicing. Acta Neuropathol 142: 609-627, 2021.
33. Meng Y, Zhao Q, An L, Jiao S, Li R, Sang Y, Liao J, Nie P, Wen F, Ju J, *et al*: A TNFR2-hnRNPK axis promotes primary liver cancer development via activation of YAP signaling in hepatic progenitor cells. Cancer Res 81: 3036-3050, 2021.
34. Toki N, Takahashi H, Sharma H, Valentine MNZ, Rahman FM, Zucchelli S, Gustincich S and Carninci P: SINEUP long non-coding RNA acts via PTBP1 and HNRNPK to promote translational initiation assemblies. Nucleic Acids Res 48: 11626-11644, 2020.
35. Chen Y, Wu J, Zhang S, Gao W, Liao Z, Zhou T, Li Y, Su D, Liu H, Yang X, *et al*: Hnrnpk maintains chondrocytes survival and function during growth plate development via regulating Hif1α-glycolysis axis. Cell Death Dis 13: 803, 2022.
36. Braems E, Bercier V, Van Schoor E, Heeren K, Beckers J, Fumagalli L, Dedeene L, Moisse M, Geudens I, Hersmus N, *et al*: HNRNPK alleviates RNA toxicity by counteracting DNA damage in C9orf72 ALS. Acta Neuropathol 144: 465-488, 2022.

37. Sun XL, Wang ZL, Wu Q, Jin SQ, Yao J and Cheng H: LncRNA RMST activates TAK1-mediated NF-κB signaling and promotes activation of microglial cells via competitively binding with hnRNPK. IUBMB Life 71: 1785-1793, 2019.
38. Chen CC, Yang JH, Fu SL, Lin WJ and Lin CH: Arginine methylation of hnRNPK inhibits the DDX3-hnRNPK interaction to play an anti-apoptosis role in osteosarcoma cells. Int J Mol Sci 22: 9764, 2021.
39. Zhou W, Jie Q, Pan T, Shi J, Jiang T, Zhang Y, Ding N, Xu J, Ma Y and Li Y: Single-cell RNA binding protein regulatory network analyses reveal oncogenic HNRNPK-MYC signalling pathway in cancer. Commun Biol 6: 82, 2023.
40. Xie M, Wang C, Sun Y, Mao Q, Sun S, Wu M, Zhu J, Li W and Jiang Z: Maimendong and Qianjinweijing Tang combined with cisplatin suppressed lung cancer through targeting lncRNA-p21. J Ethnopharmacol 322: 117547, 2024.
41. Kawasaki Y, Komiya M, Matsumura K, Negishi L, Suda S, Okuno M, Yokota N, Osada T, Nagashima T, Hiyoshi M, *et al*: MYU, a target lncRNA for Wnt/c-Myc signaling, mediates induction of CDK6 to promote cell cycle progression. Cell Rep 16: 2554-2564, 2016.
42. Xia A, Yuan W, Wang Q, Xu J, Gu Y, Zhang L, Chen C, Wang Z, Wu D, He Q, *et al*: The cancer-testis lncRNA lnc-CTHCC promotes hepatocellular carcinogenesis by binding hnRNP K and activating YAP1 transcription. Nat Cancer 3: 203-218, 2022.
43. Huarte M, Guttman M, Feldser D, Garber M, Koziol MJ, Kenzelmann-Broz D, Khalil AM, Zuk O, Amit I, Rabani M, *et al*: A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. Cell 142: 409-419, 2010.
44. Lin N, Chang KY, Li Z, Gates K, Rana ZA, Dang J, Zhang D, Han T, Yang CS, Cunningham TJ, *et al*: An evolutionarily conserved long noncoding RNA TUNA controls pluripotency and neural lineage commitment. Mol Cell 53: 1005-1019, 2014.
45. Li D, Wang X, Mei H, Fang E, Ye L, Song H, Yang F, Li H, Huang K, Zheng L and Tong Q: Long noncoding RNA pancEts-1 promotes neuroblastoma progression through hnRNPK-mediated β-catenin stabilization. Cancer Res 78: 1169-1183, 2018.
46. Xi Z, Huang H, Hu J, Yu Y, Ma X, Xu M, Ming J, Li L, Zhang H, Chen H and Huang T: LINC00571 drives tricarboxylic acid cycle metabolism in triple-negative breast cancer through HNRNPK/ILF2/IDH2 axis. J Exp Clin Cancer Res 43: 22, 2024.
47. Wang Z, Chen J, Sun F, Zhao X, Dong Y, Yu S, Li J and Liang H: LncRNA CRLM1 inhibits apoptosis and promotes metastasis through transcriptional regulation cooperated with hnRNPK in colorectal cancer. Cell Biosci 12: 120, 2022.
48. Ji L, Li X, Zhou Z, Zheng Z, Jin L and Jiang F: LINC01413/hnRNP-K/ZEB1 axis accelerates cell proliferation and EMT in colorectal cancer via inducing YAP1/TAZ1 translocation. Mol Ther Nucleic Acids 19: 546-561, 2020.
49. Zhang Z, Zhou C, Chang Y, Zhang Z, Hu Y, Zhang F, Lu Y, Zheng L, Zhang W, Li X and Li X: Long non-coding RNA CASC11 interacts with hnRNP-K and activates the WNT/β-catenin pathway to promote growth and metastasis in colorectal cancer. Cancer Lett 376: 62-73, 2016.
50. Gu P, Chen X, Xie R, Xie W, Huang L, Dong W, Han J, Liu X, Shen J, Huang J and Lin T: A novel AR translational regulator lncRNA LBCS inhibits castration resistance of prostate cancer. Mol Cancer 18: 109, 2019.
51. Pintacuda G, Wei G, Roustan C, Kirmizitas BA, Solcan N, Cerase A, Castello A, Mohammed S, Moindrot B, Nesterova TB and Brockdorff N: hnRNPK recruits PCGF3/5-PRC1 to the Xist RNA B-repeat to establish polycomb-mediated chromosomal silencing. Molecular Cell 68: 955-969.e10, 2017.
52. Gao T, Liu X, He B, Nie Z, Zhu C, Zhang P and Wang S: Exosomal lncRNA 91H is associated with poor development in colorectal cancer by modifying HNRNPK expression. Cancer Cell Int 18: 11, 2018.
53. Peng W, Zhang C, Peng J, Huang Y, Peng C, Tan Y, Ji D, Zhang Y, Zhang D, Tang J, *et al*: Lnc-FAM84B-4 acts as an oncogenic lncRNA by interacting with protein hnRNPK to restrain MAPK phosphatases-DUSP1 expression. Cancer Lett 494: 94-106, 2020.
54. Xu W, Wu Y, Fang X, Zhang Y, Cai N, Wen J, Liao J, Zhang B, Chen X and Chu L: SnoRD126 promotes the proliferation of hepatocellular carcinoma cells through transcriptional regulation of FGFR2 activation in combination with hnRNPK. Aging (Albany NY) 13: 13300-13317, 2021.
55. Li L, Yan S, Zhang H, Zhang M, Huang G and Chen M: Interaction of hnRNP K with MAP 1B-LC1 promotes TGF-β1-mediated epithelial to mesenchymal transition in lung cancer cells. BMC Cancer 19: 894, 2019.
56. Zhang M, Wu J, Zhong W, Zhao Z and He W: DNA-methylation-induced silencing of DIO3OS drives non-small cell lung cancer progression via activating hnRNPK-MYC-CDC25A axis. Mol Ther Oncolytics 23: 205-219, 2021.
57. Xu L, Zhang T, Huang W, Liu X, Lu J, Gao X, Zhang YF and Liu L: YAP mediates the positive regulation of hnRNPK on the lung adenocarcinoma H1299 cell growth. Acta Biochim Biophys Sin (Shanghai) 51: 677-687, 2019.
58. Avar M, Heinzer D, Thackray AM, Liu Y, Hruska-Plochan M, Sellitto S, Schaper E, Pease DP, Yin JA, Lakkaraju AK, *et al*: An arrayed genome-wide perturbation screen identifies the ribonucleoprotein Hnrnpk as rate-limiting for prion propagation. EMBO J 41: e112338, 2022.
59. Swiatkowska A, Dutkiewicz M, Machtel P, Janecki DM, Kabacinska M, Żydowicz-Machtel P and Ciesiołka J: Regulation of the p53 expression profile by hnRNP K under stress conditions. RNA Boil 17: 1402-1415, 2020.
60. Mucha B, Qie S, Bajpai S, Tarallo V, Diehl JN, Tedeschi F, Zhou G, Gao Z, Flashner S, Klein-Szanto AJ, *et al*: Tumor suppressor mediated ubiquitylation of hnRNPK is a barrier to oncogenic translation. Nat Commun 13: 6614, 2022.
61. Wu L, Zhu X, Song Z, Guo M, Liang J and Yan D: FGD5-AS1 facilitates glioblastoma progression by activation of Wnt/β-catenin signaling via regulating miR-129-5p/HNRNPK axis. Life Sci 256: 117998, 2020.
62. Strozynski J, Heim J, Bunbanjerdsuk S, Wiesmann N, Zografidou L, Becker SK, Meierl AM, Gouveris H, Lüddens H, Grus F and Brieger J: Proteomic identification of the heterogeneous nuclear ribonucleoprotein K as irradiation responsive protein related to migration. J Proteomics 113: 154-161, 2015.
63. Xia Y, Lv J, Jiang T, Li B, Li Y, He Z, Xuan Z, Sun G, Wang S, Li Z, *et al*: CircFAM73A promotes the cancer stem cell-like properties of gastric cancer through the miR-490-3p/HMGA2 positive feedback loop and HNRNPK-mediated β-catenin stabilization. J Exp Clin Cancer Res 40: 103, 2021.
64. Robinson H, Ruelcke JE, Lewis A, Bond CS, Fox AH, Bharti V, Wani S, Cloonan N, Lai A, Margolin D, *et al*: Caveolin-1-driven membrane remodelling regulates hnRNPK-mediated exosomal microRNA sorting in cancer. Clin Transl Med 11: e381, 2021.
65. Feng J, Li H, Li J, Meng P, Wang L, Liu C, Zhao S, Sun W and Zhang Y: hnRNPK knockdown alleviates NLRP3 inflammasome priming by repressing FLIP expression in Raw264.7 macrophages. Redox Rep 25: 104-111, 2020.
66. Sidhu R, Gatt A, Fratta P, Lashley T and Bampton A: HnRNP K mislocalisation in neurons of the dentate nucleus is a novel neuropathological feature of neurodegenerative disease and ageing. Neuropathol Appl Neurobiol 48: e12793, 2022.
67. Puvvula PK, Buczkowski S and Moon AM: hnRNPK-derived cell-penetrating peptide inhibits cancer cell survival. Mol Ther Oncolytics 23: 342-354, 2021.
68. Zhang J, Liu X, Lin Y, Li Y, Pan J, Zong S, Li Y and Zhou Y: HnRNP K contributes to drug resistance in acute myeloid leukemia through the regulation of autophagy. Exp Hematol 44: 850-856, 2016.
69. Qin W, Kong N, Wang C, Dong S, Zhai H, Zhai X, Yang X, Ye C, Ye M, Tong W, *et al*: hnRNP K degrades viral nucleocapsid protein and induces type I IFN production to inhibit porcine epidemic diarrhea virus replication. J Virol 96: e0155522, 2022.
70. Yang X, Wen Y, Liu S, Duan L, Liu T, Tong Z, Wang Z, Gu Y, Xi Y, Wang X, *et al*: LCDR regulates the integrity of lysosomal membrane by hnRNP K-stabilized LAPTM5 transcript and promotes cell survival. Proc Natl Acad Sci USA 119: e2110428119, 2022.
71. Zhang L, Zhang S, Fan Z, Jiang Z, Li S, Liu A and Sun J: D816V mutation of KIT specifically induces phosphorylation of HNRNPL and HNRNPK in COS-1 cells. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 39: 138-143, 2023 (In Chinese).
72. Shu B, Zeng P, Kang S, Li PH, Hu D, Kuang G, Cao J, Li X, Zhang M, An LK, *et al*: Syntheses and evaluation of new Quinoline derivatives for inhibition of hnRNP K in regulating oncogene c-myc transcription. Bioorg Chem 85: 1-17, 2019.
73. Liu W, Yang D, Sun C, Wang H, Zhao B, Zhou G and Yu L: hnRNP K is a novel internal ribosomal entry site-transacting factor that negatively regulates foot-and-mouth disease virus translation and replication and is antagonized by viral 3C protease. J Virol 94: e00803-20, 2020.

74. Chen J, Dai L, Zheng H, Liu G, Zhao Y and Wang J: Analysis of clinical features and genetic variant in a neonate with Au-Kline syndrome due to a de novo variant of the HNRNPK gene. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 40: 226-229, 2023 (In Chinese).
75. Malaney P, Benitez O, Zhang X and Post SM: Assessing the role of intrinsic disorder in RNA-binding protein function: hnRNP K as a case study. Methods 208: 59-65, 2022.
76. Wu HL, Li SM, Huang YC, Xia QD, Zhou P, Li XM, Yu X, Wang SG, Ye ZQ and Hu J: Transcriptional regulation and ubiquitination-dependent regulation of HnRNPK oncogenic function in prostate tumorigenesis. Cancer Cell Int 21: 641, 2021.
77. Zhu HQ, Liu XL, Li R, Du QF, Zhang S, Yao F and Liu Z: Preliminary study of proteins related to blast crisis in chronic myeloid leukemia. Zhonghua Zhong Liu Za Zhi 31: 655-659, 2009 (In Chinese).
78. Lu Y, Cheng J, Cai W, Zhuo H, Wu G and Cai J: Inhibition of circRNA circVPS33B reduces warburg effect and tumor growth through regulating the miR-873-5p/HNRNPK axis in infiltrative gastric cancer. Onco Targets Ther 14: 3095-3108, 2021.
79. Huang WS, Xu FM, Zeng QZ, Liu XH, Gao XJ and Liu LX: ERK1/2-mediated cytoplasmic accumulation of hnRNPK antagonizes TRAIL-induced Apoptosis through upregulation of XIAP in H1299 cells. Biomed Environ Sci 30: 473-481, 2017.
80. Han J, Nie M, Chen C, Cheng X, Guo T, Huangfu L, Li X, Du H, Xing X and Ji J: SDCBP-AS1 destabilizes β-catenin by regulating ubiquitination and SUMOylation of hnRNP K to suppress gastric tumorigenicity and metastasis. Cancer Commun (Lond) 42: 1141-1161, 2022.
81. Bakhmet EI, Nazarov IB, Gazizova AR, Vorobyeva NE, Kuzmin AA, Gordeev MN, Sinenko SA, Aksenov ND, Artamonova TO, Khodorkovskii MA, *et al*: HnRNP-K targets open chromatin in mouse embryonic stem cells in concert with multiple regulators. Stem Cells 37: 1018-1029, 2019.
82. Zhao W, Wang S, Qin T and Wang W: Circular RNA (circ-0075804) promotes the proliferation of retinoblastoma via combining heterogeneous nuclear ribonucleoprotein K (HNRNPK) to improve the stability of E2F transcription factor 3 E2F3. J Cell Biochem 121: 3516-3525, 2020.
83. Zhang J, Liu X, Yin C and Zong S: hnRNPK/Beclin1 signaling regulates autophagy to promote imatinib resistance in Philadelphia chromosome-positive acute lymphoblastic leukemia cells. Exp Hematol 108: 46-54, 2022.
84. Yokoi S, Ito T, Sahashi K, Nakatochi M, Nakamura R, Tohnai G, Fujioka Y, Ishigaki S, Udagawa T, Izumi Y, *et al*: The SYNGAP1 3'UTR variant in ALS patients causes aberrant SYNGAP1 splicing and dendritic spine loss by recruiting HNRNPK. J Neurosci 42: 8881-8896, 2022.
85. Harris D, Zhang Z, Chaubey B and Pandey VN: Identification of cellular factors associated with the 3'-nontranslated region of the hepatitis C virus genome. Mol Cell Proteomics 5: 1006-1018, 2006.
86. Shu H, Hu J and Deng H: miR-1249-3p accelerates the malignancy phenotype of hepatocellular carcinoma by directly targeting HNRNPK. Mol Genet Genomic Med 7: e00867, 2019.
87. Li Y, Chen H, Li S, Li Y, Liu G, Bai J, Luo H, Lan X and He Z: LncSSBP1 functions as a negative regulator of IL-6 through interaction with hnRNPK in bronchial epithelial cells infected with Talaromyces marneffei. Front Immunol 10: 2977, 2020.
88. Mukhopadhyay NK, Kim J, Cinar B, Ramachandran A, Hager MH, Di Vizio D, Adam RM, Rubin MA, Raychaudhuri P, De Benedetti A and Freeman MR: Heterogeneous nuclear ribonucleoprotein K is a novel regulator of androgen receptor translation. Cancer Res 69: 2210-2218, 2009.
89. Cho E, Che X, Ang MJ, Cheon S, Lee J, Kim KS, Lee CH, Lee SY, Yang HY, Moon C, *et al*: Peroxiredoxin 5 regulates osteogenic differentiation via interaction with hnRNPK during bone regeneration. bioRxiv: 2022.06.09.495435, 2022.
90. Gray C, Kelleher B, Grimaldi L and Mihailescu ME: A G-quadruplex structure within the 3'-untranslated region of hnRNP K affects its translation by controlling the accessibility of miR-1249-3p to its binding site. Biophys J 122 (Suppl 1): 360A-361A, 2023.
91. Miki Y, Iwabuchi E, Takagi K, Suzuki T, Sasano H, Yaegashi N and Ito K: Co-expression of nuclear heterogeneous nuclear ribonucleic protein K and estrogen receptor α in endometrial cancer. Pathol Res Pract 231: 153795, 2022.
92. Li M, Yang X, Zhang G, Wang L, Zhu Z, Zhang W, Huang H and Gao R: Heterogeneous nuclear ribonucleoprotein K promotes the progression of lung cancer by inhibiting the p53-dependent signaling pathway. Thorac Cancer 13: 1311-1321, 2022.
93. Iwabuchi E, Miki Y, Suzuki T, Hirakawa H, Ishida T and Sasano H: Heterogeneous nuclear ribonucleoprotein K is involved in the estrogen-signaling pathway in breast cancer. Int J Mol Sci 22: 2581, 2021.