Role and molecular mechanism of heterogeneous nuclear ribonucleoprotein K in tumor development and progression (Review)

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Abstract. Heterogeneous nuclear ribonucleoprotein K (hnRNP K) is a member of the hnRNP family, which exists in the nucleus and the cytoplasm simultaneously. It is a multifunctional protein that can participate in a variety of regulatory progressions of gene expression and signal transduction, such as chromatin remodeling, transcription, RNA alternative splicing and translation. hnRNP K not only directly binds to the kinases, but also recruits the associated factors regarding transcription, splicing and translation to control gene expression, and therefore, it serves as a docking platform for integrating transduction pathways to nucleic acid-directed processes. Numerous studies also show that abnormal expression of hnRNP K is closely associated with the tumor formation. This protein is overexpressed in numerous types of cancer and its aberrant cytoplasmic localization is also associated with a worse prognosis for patients. These results consistently indicate that hnRNP K has a key role in cancer progression. To understand the hnRNP K pathophysiological process in tumor disease, the previous research results regarding the association between hnRNP K and tumors were reviewed.

Contents

1. Introduction

RNA-binding proteins are the proteins that have similar characteristics and intracellular distribution, and are termed heterogeneous nuclear ribonucleoproteins (hnRNPs) (1). Their role is in sharp contrast with the roles of small nuclear ribonucleoproteins (snRNPs) and mRNA proteins (mRNPs). Thus far, ~20 types of hnRNPs have been identified, ranging from A1 to U. A large number of studies have shown that these proteins have a significant role in the progression of gene regulation, including DNA repairing, telomerase extending, signal transduction, and transcriptional and translational levels (2). Of which, hnRNP K is one type of DNA and RNA-binding protein involved in various regulatory progressions by means of protein-protein interaction (3).

The relative molecular weight of hnRNP K is ~66 kDa, which is comprised of three DNA-RNA binding homology domains (KH1, KH2 and KH3), a K-protein-interactive region (KI) and a C-terminal protein kinase-binding domain (4). Each of these three KH domains contains 65-70 amino acids, two of them located at the N-terminus, and the remaining one at the C-terminus. KH domains have evolutionarily conserved features making the KH domain with the same number of amino acids or the same amino acid sequence exhibit similar functions in different tissues. The typical function of KH domains is to recognize and bind to RNA and single-stranded DNA. The KI domain lies between KH2 and KH3, which specifically exists in hnRNP K. This domain is responsible for regulating the interaction between hnRNP K and other proteins in the nucleus and cytoplasm. The KI region contains the proline-rich docking sites, such as RXXPXXP and PXXPXR, which interact particularly with SH3 domains of the Src-family signals. Furthermore, hnRNP K contains a

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nuclear-localization signal with the function of mediating its transport from the cytoplasm to the nucleus (5,6). Therefore, it acts as a nucleocytoplasmic shuttling protein to regulate gene expression by the nuclear pore complex with the help of a nuclear shuttling domain (7) (Fig. 1).

According to previous results, there is a close association between tumors and hnRNP K; it often shows a high expression state in a variety of tumors, such as prostate cancer, colon cancer, nasopharyngeal cancer, oral squamous cell carcinoma, leukemia and breast cancer. hnRNP K is able to interact with multiple molecular partners and is involved in a number of gene regulation steps (7-9) (Table I). hnRNP K is specific for hnRNP family members, and compared with other hnRNP proteins, has different structural characteristics (KH domain and DNA binding sites), so that it can participate in numerous cellular processes in the nucleus and cytoplasm. Of note, in addition to having the same functions with other hnRNPs, such as mRNA splicing and the cytoplasmic transport of mRNA, it can regulate DNA transcription, RNA processing and RNA translation, particularly with regards to the process of oncogene expression (2). All these features make it exhibit multiple roles in the cell cycle, inhibition of apoptosis and tumor metastasis. The present review assessed certain studies from the perspective of the role and molecular mechanisms of hnRNP K in promoting tumors, providing a more in-depth and comprehensive understanding of the function of hnRNP K, and information for future investigations to further explore its role in the tumor progression.

2. hnRNP K as a transcription factor to promote tumors

hnRNP K can be a transcription factor to promote the expression of certain oncogenes (10,11), which combines the upstream pyrimidine-rich regions of promoters. *In vivo* it is able to interact directly with transcription machinery-related factors, such as the TATA box-binding protein (TBP), a subunit of the eukaryotic transcription factor TFIID, the RNA polymerase and others (12). These factors act synergistically to promote the transcription process by the way of protein-protein interaction.

There are CT repetitive sequences in the promoter region of c-myc, known as the CT element (13). It is comprised of four consecutive repeated CCCTCCCCA sequences and a fifth repeat sequence, which is separated by a 9-base pair long sequence located downstream of the first four sequences. Pioneer studies have shown that the N-terminus of hnRNP K contains 35-amino acid residues that are necessary for trans-activating the CT element. When hnRNP K recognizes the CT element of the c-Myc promoter region in a specific-binding manner, it can recruit and interact with TBP and RNA polymerases to upregulate the expression of c-Myc. For example, it was found that c-myc and hnRNP K simultaneously increased in breast cancer (14). Following further exploration of hnRNP K, hnRNP K promoted transcription of c-myc in a CT element-dependent manner in these tumors, and subsequently c-Myc stimulated cell proliferation and inhibited apoptosis during the progression of malignant transformation.

Activation or overexpression of c-Src, a non-receptor tyrosine kinase of numerous signal pathways, has been associated with a host of malignant cancers (15,16). c-Src expression is regulated by the housekeeping-like *SRC*1A promoter in numerous tissues (17). There are three substantial polypurine/polypyrimidine (TC1, TC2 and TC3) tracts within this promoter that have a role in enhancing transcriptional activity. In addition, hnRNP K was shown to regulate the *SRC*1A promoter cooperatively with the transcription factor Sp1 (18,19). The study by Ritchie *et al* (20) proposed that hnRNP K recognizes and binds to TC1 and TC2 of the promoter region at first, which facilitates double strands to separate and become a single strand, leading to the affinity of hnRNP K with the increase in single-stranded DNA, followed by hnRNP K recruiting the basal transcriptional machinery, TBP and TFIID. The intact TC3 tract is capable of binding the single-stranded form with a high affinity to retain promoter activity. This series of processes promotes the transcription complex formation, so as to upregulate the expression of src.

3. hnRNP K interaction with nuclear matrix proteins to promote tumors

Nuclear matrix (NM) is a fibrin protein-based grid system present in the eukaryotic nucleus, excluding the nuclear membrane, laminin, chromatin and nucleolus. This dynamic complex mainly contains a variety of proteins and a small amount of RNA and DNA. NM has an important role in gene regulation process, such as chromatin remodeling, DNA replication and transcription and RNA processing (21). hnRNP K activates at the chromatin level, exhibiting a transient recruitment to multiple sites within each of the inducible gene loci, including the promoter and transcribed regions (22). hnRNP K is abundant in the NM, which has a role in stabilizing the NM network. Furthermore, hnRNP K as one type of NM protein can bind to the NM attachment region (MAR) sequences, and is located in interchromatin granule clusters (23). MAR is a class of DNA sequence, which exists in eukaryotic cellular chromatins and specifically recognizes the NM (24,25). When MAR binds to NM, it creates a position segmentation effect and maintains each transcription unit relatively independent from each other to be free of interaction with the surrounding chromatins. As a consequence of the anchoring of MAR sequences to NM, chromatin fibers are organized into topologically isolated loops to regulate the progression of gene transcription and translation, and removal of gene silencing resulted from the position effect. It is the position of a gene within the loop that determines its activity (26). As hnRNP K is the constituent of NM, chromatin remodeling and the transcription process of gene expression will be affected accordingly if the NM internal structure is altered or the interaction between NM and MAR sequences is repressed, with the original normal regulatory process affected as well. In prostate cancer cells (27), phosphorylated AKT can promote the phosphorylation of hnRNP K. The effect of hnRNP K stabilizing AR will be weakened in succession, which is co-located with the AR in the NM at first. In turn, phosphorylated hnRNP K inhibits the expression of AR after it recognizes DNA-MAR sequences in the nucleus, which makes the androgen-sensitive prostate cancer cells convert to androgen-insensitive cancer cells and increases the risk of a poor prognosis in patients who have received androgen-deprivation therapy.

Table I. hnRNP K interacts with diverse groups of molecular partners to regulate gene expression and signal transduction.

Process	Protein partner	Regulated gene
Transcription	General factors: TBP and HMGB1 Activators: Pura, Sox10 and C/EBPb Repressors: Zik1, Kid1 and MZF-1	c-Myc, c-Src, thymidine kinase eIF4E, CHRNA4 and CD43
Chromatin remodeling	Eed, DNA-methyltransferase, scaffold attachment factor B and MARs	AR
RNA processing	hnRNP E2, I, K, L and U 9G8, SRp20, YB-1 and Sam68	β-tropomyosin, renin
Translation	EF-1α	c-Myc, 15-lipoxygenase, human papilloma virus type 16, eIF4E and p21
Signal transduction	Src, Lyn, Fyn, Lck, Itk, PKCα, PKCδ, PKCε, ERK1/2, JNK, Vav and PRMT1	

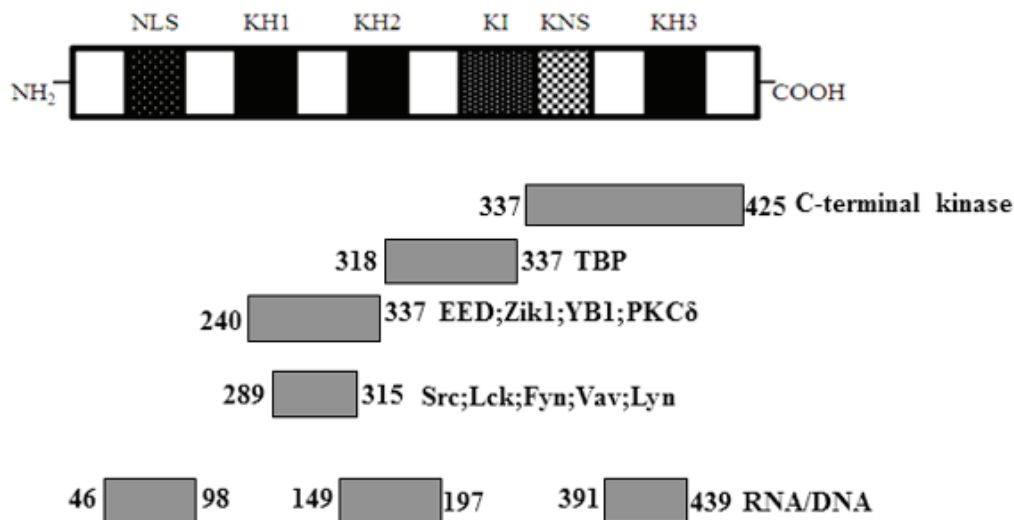hnRNP K, heterogeneous nuclear ribonucleoprotein K.

Figure 1. Diagrammatic illustration of the K protein. The rectangles represent K homology domains (KH), K interactive region (KI), nuclear localization signal (NLS), nuclear shuttling domain (KNS) and domains that recruit protein and RNA partners. The numbers indicate the positions of amino acid (aa) residues. NLS in aa 1-40; KH 1 in aa 46-98; KH 2 in aa 149-197; KH 3 in aa 391-439; KI domain in aa 240-337; and KNS in aa 338-361.

4. Involvement of hnRNP K in RNA alternative splicing (AS) to promote tumors

AS is an essential mechanism in post-transcriptional regulation, which is a crucial step of the gene expression process in eukaryotes (28). It is a major cause for protein diversity and has critical roles in differentiation, development and disease. Thus, a gene may encode a variety of proteins. Therefore, its regulation is associated with cancer. It has been confirmed that hnRNP K is involved in certain important splicing process by interacting with Sam68, TAF15, YB1, 9G8 and SRp20 (12). Of note, it participates in the expression of apoptosis-related genes by AS to promote the tumor formation. The mammalian B-cell lymphoma 2 (Bcl-2) family can be classified into the multi-motif Bcl-2 proteins that bear multiple BH motifs with pro-survival (Bcl-2, Bcl-xL, Bcl-w, myeloid leukemia-1, A1 and Bcl-B) and pro-apoptotic (Bcl-xS, Bcl-2-associated X protein and Bcl-2

homologous antagonist/killer) activity (29). hnRNP K can regulate the Bcl-2 AS process and inhibit Bcl-xS generation, which results in a reduction of apoptosis in tumor cells (30). In the event of AS, U1 snRNA identify the pre-mRNA 5' splicing site in a nucleotide complementary manner while U2AF recognizes and combines the upstream pyrimidine-rich region of the 3' splicing site and promotes U2 snRNP and the U4, U5 and U6 snRNP trimer to bind together to form a 60S spliceosome where a transesterification reaction occurs, leading to the generation of different isoforms at different sites (31,32). Furthermore, there is a B1 splicing-regulatory region existing in the 5' splicing site of Bcl-xS. hnRNP K can bind to the pyrimidine-rich region of B1 to inhibit the production of the Bcl-xS isoform. Simultaneously, hnRNP K is able to interact with Sam68, which has a role in upregulating Bcl-xS expression to weaken its upregulation capacity. As a result, the apoptosis pathway is blocked, so that cancer cells survive to escape from
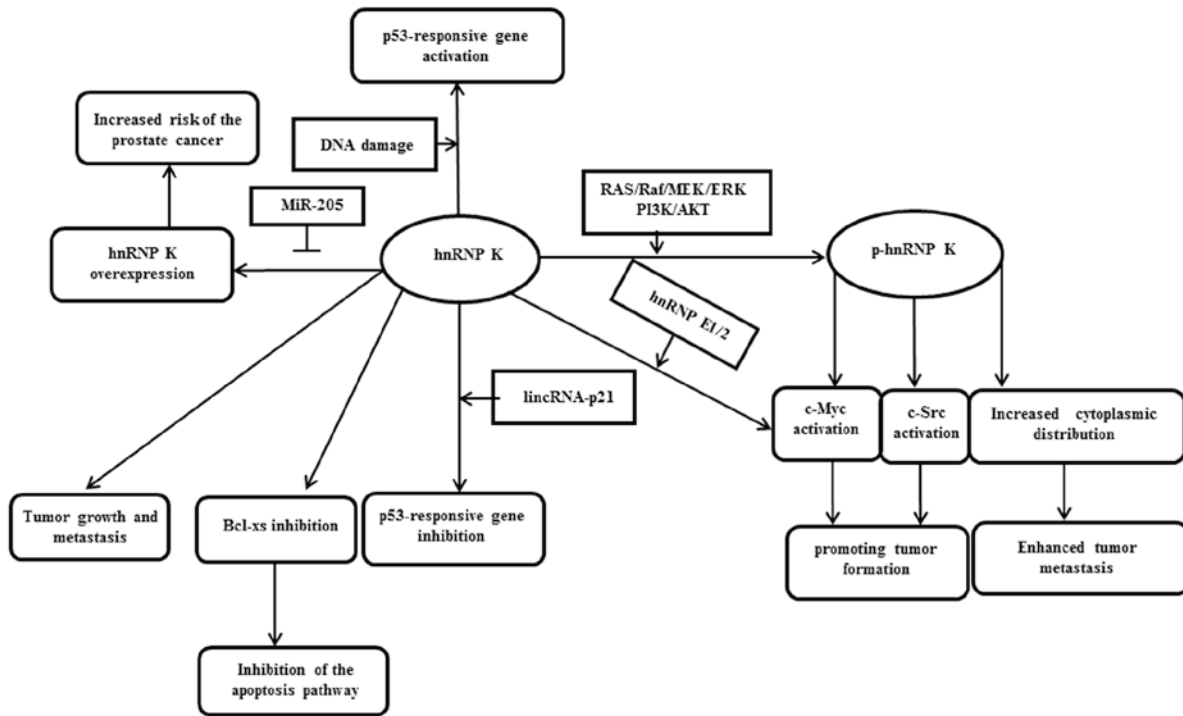
Figure 2. Signaling pathways of hnRNP K. The summary of the principal pathways regulated by hnRNP K, in which hnRNP K can drive cancer development and progression. hnRNP K, heterogeneous nuclear ribonucleoprotein K.

the apoptotic signals. Due to this advantage condition, tumor cells can be maintained in a safe environment and proliferate rapidly.

5. Involvement of hnRNP K in RNA translation to promote tumors

The translation mechanisms of hnRNP K action are the most intensively studied. It has been confirmed that hnRNP K can affect the tumor growth and development at the translational level as well. Bomsztyk et al (7) found that hnRNP K have a direct interaction with the translation elongation factor 1α, confirming its role in translational regulation. Following this, it was also found that hnRNP K could bind to the polypyrimidine sequence of translation initiation factor eIF4E (4EBE) to upregulate oncoprotein expression and promote certain malignant phenotype formations (33). In addition, hnRNP K can interact with the CU-rich region of p21 mRNA 3' untranslated region (UTR) to inhibit p21 translation and promote cell proliferation (34). When chronic myelogenous leukemia converts from the chronic phase to the acute phase (35), the expression product of B-cell surface receptor (BCR)/ABL, p210, can activates the tyrosine kinase activity of mitogen-activated protein kinase (MAPK)[Erk1/2] in a dose-dependent manner in the bone marrow and lymphocytes cells with the BCR/ABL gene. Subsequently, activated MAPK[Erk1/2] induces hnRNP K expression and stability increased. Stable hnRNP K binds to the myc mRNA internal ribosome entry site to stimulate translational activation and expression upregulation (3). The increased myc protein will facilitate leukocyte cell proliferation, colony formation and stimulate the occurrence of leukemia.

Table II. Heterogeneous nuclear ribonucleoprotein K expression in individual types of cancer and its association with prognosis in different types of cancer.

Type of cancer	Expression in tumor tissue[a]	Prognostic significance
Colorectal	Increased	Survival
Esophageal squamous cell	Increased	Poor prognosis
Hepatocellular	Increased	ND
Lung	Increased	ND
Melanoma	Increased	ND
Nasopharyngeal	Increased	Poor prognosis
Oral squamous cell	Increased	Poor prognosis
Prostate	Increased	Poor prognosis

[a]Expression was compared to normal or non-tumor tissue. ND, not determined.

6. hnRNP K interacts with signaling molecules to promote tumors

hnRNP K can cooperate with the Src tyrosine kinases family, tryptophan/threonine kinase PKCδ, Erk1/2, Vav and other molecules to regulate its interaction with the target proteins or gene sequences. As combination factors vary, the effect of the production of different signaling molecules is also significantly different (36). For example, Jeon et al (37) have demonstrated that hnRNP K can bind to the signal transducer

protein Vav to become involved in the BCR signaling pathway. Interaction of the Vav proto-oncogene product with hnRNP K regulates and promotes the process of cell transformation by the SH3 domain (38,39). In hepatocellular carcinoma (40), it can increase the expression of the protein kinase inhibitor CFLP (cellular FLICE-like inhibitory protein) that prevents pro-caspase-8 activation and X-linked inhibitor of apoptosis protein and maintain them at a high level to inhibit the classic caspase apoptosis pathway activation. In breast cancer (41), the epidermal growth factor receptor family can increase the expression of hnRNP K following activation by exogenous growth signals, and subsequently, the upregulated hnRNP K binds to and activates the c-myc promoter region to improve the expression of c-myc to accelerate the tumor formation process. In prostate cancer, hnRNP K participates in the AKT/hnRNP K/AR/β-catenin signaling pathway (42), which has a crucial impact on converting prostate cancer into a hormone-insensitive neuroendocrine (NE) differentiation phenotype. The presence of this phenotype indicates a poor prognosis for patient. Phosphorylated AKT is present at prostate cancer cells in three pathways mainly; following promotion of GSK3β phosphorylation, the phosphorylated GSK3β will be transported from the cytoplasm into the nucleus; the second pathway promotes the intracytoplasm AR to be phosphorylated and subsequently degraded by the proteasome pathway; the last promotes hnRNP K phosphorylation and enters into the nucleus. GSK3β and phosphorylated hnRNP K of common positioning within the nucleus bind to the AR sequence and repress AR expression, while increasing the expression of NE differentiation phenotype markers, neuron-specific enolase (NSE), simultaneously, which causes hormone-sensitive prostate cancer to become hormone-insensitive and NSE-independent prostate cancer phenotype, ultimately resulting in ineffective androgen-withdrawal therapy. In the cytoplasm of tumor cells, the activation of Ras and MEK can also make hnRNP K stably exist in the cytoplasm (43). Stabilized hnRNP K is able to activate ERK to promote upregulation of matrix metalloproteinase 3 (MMP3) and MMP10. These factors have an important role in promoting tumor metastasis. A succession of studies are now providing a mechanistic basis, highlighting and reinforcing that specific MMPs are key in tumor invasion and metastasis through their catalytic and non-catalytic roles, including modulating tumor cell motility, promoting invadopodia formation, interactions of MMPs with pro-invasive pathways, sensing matrix stiffness and induction and maintenance of epithelial-mesenchymal transition (44). Therefore, hnRNP K simultaneously provided favorable conditions for tumor invasion and metastasis when upregulating MMPs expression.

7. hnRNP K interacts with non-coding RNAs (ncRNAs) to promote tumors

In the human genome, ~90% is transcribed into ncRNAs. ncRNAs are diverse RNA transcripts that are not transcribed into proteins but have been shown to regulate the transcription, stability or translation of protein-coding genes (45,46). According to their size, they can be divided into long ncRNAs and short ncRNAs (microRNAs). ncRNAs are associated with numerous diseases, including a variety of

tumors (47). In addition, there is a close association between hnRNP K and ncRNAs, which may indicate that there is contact between hnRNPK and ncRNAs in tumors. Recently, Gumireddy et al (48) identified that a translational regulatory ncRNA (treRNA) was highly expressed in metastatic breast cancer and primary colon cancer through genome-wide computational analysis. It interacted with hnRNP K to promote tumor invasion and metastasis. treRNA can combine with hnRNP K, FXR1, puf60, SF3B3 and other factors to facilitate the formation of the treRNA-associated protein complex. This complex is able to directly or indirectly bind to the E-cadherin mRNA 3'UTR, and reduce translation efficiency of E-cadherin mRNA, and therefore E-cadherin expression decreased. Downregulated E-cadherin leads to a direct result of adhesion activity decrease between tumor cells. As a consequence, tumor cells shed from the primary tumor into the circulation system, and position in the new site. In addition, Qin et al (49) showed that hnRNP K is a target of miR-205. miR-205 has a complex regulatory role in tumor initiation and growth processes. It can inhibit or promote tumor formation depending on its binding targets and microenvironment. Furthermore, it was found that miR-205 can bind to the 3'UTR of hnRNP K to reduce hnRNP K expression (50). However, miR-205 is downregulated in prostate cancer, so its inhibition for hnRNP K is derepressed, which leads to promoting the state of tumors (51).

8. Conclusion

hnRNP K is an RNA/DNA-binding protein that is a target of multiple kinases or recruits factors involved in signal transduction and gene expression. Its abnormal expression can make the tumor formation risk increase significantly. In several tumors, the hnRNP K expression level progressively increases from normal to hyperplasia to carcinoma tissue, and it is often associated with tumor stage, indicating an asociation between hnRNP K expression and tumors progression (52,53). Inoue et al (54) have proved that hnRNP K has an important role in tumor invasion. They identified that hnRNP K is involved in tumor cell metastasis, and its cytoplasmic localization is essential for cell invasion and metastasis. Recently, it was also proved that if hnRNP K is overexpressed, cell malignancy and metastatic ability would be improved in vitro and in vivo. Furthermore, Hope and Murray (55) demonstrated in colon cancer that hnRNP K in addition to the high expression appeared with an abnormal cytoplasmic localization, and it correlated with lymph node metastasis, suggesting that it is a poor prognostic markers. Gao et al (43) have demonstrated that hnRNP K could induce the expression of certain genes involved in the cell extracellular matrix, cell motility and angiogenesis by cDNA microarray analysis and signaling pathway analysis. Therefore, regardless of the tumor type, the abnormal increase or cytoplasmic localization of hnRNP K may be regarded as a valid marker of poor prognosis (Table II). In summary, hnRNP K is involved in multiple cellular functions relevant to cancer development and progression (Fig. 2). The overexpressed hnRNP K in numerous tumors, as a multifunctional protein, may hopefully become a therapeutic target due to its role in promoting malignant transformation and tumor metastasis. If this hypothesis is true,

reasonable drugs and therapies can be designed to intervene with tumor growth according to the regulatory characteristics of hnRNP K. Further investigations are required.

Acknowledgements

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