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REVIEW

Aberrant hnRNP K expression: All roads lead to cancer

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ABSTRACT

The classification of a gene as an oncogene or a tumor suppressor has been a staple of cancer biology for decades. However, as we delve deeper into the biology of these genes, this simple classification has become increasingly difficult for some. In the case of heterogeneous nuclear ribonuclear protein K (hnRNP K), its role as a tumor suppressor has recently been described in acute myeloid leukemia and demonstrated in a haploinsufficient mouse model. In contrast, data from other clinical correlation studies suggest that hnRNP K may be more fittingly described as an oncogene, due to its increased levels in a variety of malignancies. hnRNP K is a multifunctional protein that can regulate both oncogenic and tumor suppressive pathways through a bevy of chromatin-, DNA-, RNA-, and protein-mediated activates, suggesting its aberrant expression may have broad-reaching cellular impacts. In this review, we highlight our current understanding of hnRNP K, with particular emphasis on its apparently dichotomous roles in tumorigenesis.

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Introduction

Over the past several decades, clinical and basic science studies have attempted to determine the critical genetic alterations that directly influence tumorigenesis. In doing so, it has been useful to categorize genes as either tumor suppressors (resulting from gene loss or inactivating mutations) or oncogenes (when gene products are overexpressed). This has allowed researchers and clinicians to delineate the functional and clinical consequences of many genetic alterations. However, these classifications do not always accurately reflect the reality of aberrant gene expression. As an example, the protein p53 was first thought to be an oncogene when it was originally discovered due to its increased stability when mutated.[1,2] However, once its cellular function was better understood, it was proven to be a potent tumor suppressor.[3] Recently, its role as an oncogene (or at least having oncogenic potential) has been reassessed following the discovery that stabilized mutant p53 does in fact confer gain-of-function phenotypes.[4,5] Such blurring of traditional oncogene/tumor suppressor roles is now becoming more accepted, as evidenced by similar observations in the TGF-β pathway.[6,7]

More recently, evidence has emerged that heterogeneous nuclear ribonucleoprotein K (hnRNP K) may be even harder to classify as a tumor suppressor or an oncogene. This is due to the fact that biochemical and *in vitro* studies have shown that hnRNP K has the capacity to regulate both tumor suppressive and oncogenic pathways, and both its overexpression and knockdown results in cell proliferation and apoptotic defects.[8-13] In support of its potential oncogenic functions, clinical association studies suggest that hnRNP K overexpression correlates with poor clinical outcomes and advanced disease status in a variety of malignancies, including melanoma, prostate, breast, lung, colorectal, hepatocellular, and esophageal cancers.[14-18] In contrast, other clinical studies suggest reduced hnRNP K expression, due to deletion of or mutations in the *HNRNPK* gene, may underpin the pathogenesis of acute myeloid leukemia (AML).[19-23] In the case of mutation, there are further questions concerning whether specific mutations inactivate the protein or potentially stabilize or confer gain-of-function phenotypes, reminiscent of mutations observed in the c-Myc protein and mutant p53 proteins, respectively.

Given the lack of consensus between the biochemical, *in vitro*, and clinical data, it is apparent that hnRNP K has more to its story than just a simple classification as either an oncogene or tumor suppressor. This review will highlight aspects of our current knowledge of hnRNP K's role in cancer biology, describe studies that have evaluated hnRNP K-dependent transcriptional and translational activities, examine the molecular consequence of *Hnrnpk* haploinsufficiency *in vivo*, and provide insight into future investigations using Hnrnpk mouse models.

HnRNP K-mediated transcriptional and translational activities regulate pathways involved in tumorigenesis

hnRNP K is an extremely versatile and multifunctional protein that influences transcription, translation, splicing, RNA stability, and chromatin remodeling through its capacity to stringently bind RNA and single-stranded (ss) DNA via its KH domains.[24] The roles that hnRNP K plays in these diverse cellular functions are well documented and have been reviewed

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elsewhere.[25,26] Here; however, we will highlight key points to emphasize its potential role in both oncogenic and tumor suppressive pathways.

At the transcriptional level, hnRNP K has been implicated in directly and indirectly regulating gene expression. With respect to cancer biology, hnRNP K directly mediates the expression of both oncogenes and tumor suppressors, such as *SRC, MYC, CDKN1A* (*p21), HDM2* (*Mdm2* in the mouse), and *EIF4E* through its direct binding to C-rich regions in the promoters of these genes.[9-12,27] In addition to this direct transcriptional gene regulation, hnRNP K is implicated in positively influencing gene expression through direct interaction with the TATA-binding protein (TBP) of the RNA polymerase machinery,[28,29] as well as negatively regulating gene expression through its interactions with *lincRNA-21*.[30,31] Furthermore, hnRNP K also plays a critical role in chromatin remodeling by acting as a scaffold protein that binds to DNA matrix attachment regions (MARs) and thus stabilizes the chromatin.[32] While this finding suggests that hnRNP K positively influences global transcription through its chromatin interactions, hnRNP K also interacts with and regulates the localization of the Polycomb repressive complex through its interaction with a core component, Eed.[33] Taken as a whole, hnRNP K appears to have conflicting activating and repressive influences on gene expression. On the one hand, hnRNP K has the ability to directly enhance or repress transcription of specific genes, while on the other hand, it can simultaneously enhance or diminish global gene expression. Thus, given its proposed role in regulating critical cellular pathways, any change in its expression may result in significant consequences.

In addition to transcriptionally regulating gene expression through its direct interaction with DNA, hnRNP K also binds to mRNA transcripts and translationally regulates protein expression. Similar to its conflicting roles in both positively and negatively regulating transcription, hnRNP K has the capacity to activate or inhibit the translation of some mRNA transcripts. For example, hnRNP K has been shown to positively stimulate *MYC* translation,[8,34,35] while it inhibits the translation of *15-LOX*, a key regulator of erythroid differentiation.[36,37] Collectively, these duplicitous and opposing mechanisms of gene regulation present a complex situation, whereby hnRNP K may play a critical balancing act between its roles in directly and globally activating and repressing gene expression, and simultaneously controlling translation of mRNA transcripts. Thus, it is easy to envision scenarios where small changes in hnRNP K expression (either increased or decreased) could result in drastic cellular defects that impact oncogenic or tumor suppressor pathways and directly impact tumorigenesis.

Biochemical and *in vitro* evidence for a direct role of HnRNP K in tumorigenesis

Two of the classic tumor suppressor and oncogenic pathways directly impacted by hnRNP K-mediated transcriptional and translational activities are the p53/p21 and c-Myc pathways, respectively.[9-11] Biochemical experiments performed nearly a decade ago provided the first evidence that hnRNP K may play a pivotal role in tumor suppression. In these studies, hnRNP K was shown to be phosphorylated by ATM and ATR following DNA damage, which directly resulted in activation of *p21*.[10,11] Building on these findings, hnRNP K was later shown to be sumoylated in an ATR-dependent manner following UV-irradiation, resulting in enhanced p53-dependent transcriptional activation of *p21*.[38,39] These results indicate that hnRNP K may act as a putative tumor suppressor and suggest that its loss may directly impact tumor formation. Interestingly, hnRNP K has recently been shown to also negatively impact the translation of the *p21* transcript by binding to its 3′ UTR, although this effect was demonstrated in the context of neuronal differentiation.[40] These observations suggest that within tissue-specific contexts, hnRNP K may have the capacity to either suppress or promote tumorigenesis through a single pathway; however, detailed *in vivo* studies are needed to test the veracity of such a notion.

In addition to controlling tumor suppressive programs, hnRNP K has also been shown to influence the expression of oncogenic pathways.[26] As a classic example, hnRNP K directly interacts with C-rich regions in the *MYC* promoter, leading to increased c-Myc expression.[9] In addition, hnRNP K is also thought to translationally regulate c-Myc expression by binding to these same C-rich regions in the 5′ UTR of the *MYC* transcript to promote ribosomal loading and further drive c-Myc expression.[8] The transcriptional and translational hnRNP K-mediated regulation of c-Myc suggest that hnRNP K overexpression may result in oncogenic phenotypes, and perhaps most importantly, implicates hnRNP K as a potential driver of c-Myc-dependent malignancies when the *MYC* gene is not amplified or translocated.

Clinical evidence for a role of aberrant HnRNP K in tumorigenesis

Much of the clinical data regarding hnRNP K's role in tumorigenesis originates from pathologic and immunohistochemical analyses of archived patient samples. These studies revealed that increased hnRNP K expression associated with poor clinical status in melanoma, prostate, breast, lung, colorectal, hepatocellular, and esophageal cancers.[14-18] Given the myriad of tumor types that overexpress hnRNP K in these studies and its correlation with disease prognosis, these data suggest that hnRNP K may have oncogenic functions when overexpressed.

However, in contrast to hnRNP K's putative oncogenic roles, *HNRNPK* is one of 6 genes that maps to the minimally deleted region of the 9q21.32 locus, which is thought to harbor a haploinsufficient tumor suppressor in patients with acute myeloid leukemia (AML).[19-21,23] Furthermore, TCGA recently demonstrated that *HNRNPK* mutations have the capacity to act as driving events in AML.[22] However, it is currently unknown if these *HNRNPK* mutations confer gain-of-function or haploinsufficient phenotypes.

Therefore, to more fully evaluate how hnRNP K expression contributes to the pathogenesis of AML, we examined *HNRNPK* expression in AML patients with diploid karyotypes that carried a 9q21.32 deletion. To this end, we developed a dual-color fluorescence in situ hybridization (FISH) assay using bacterial artificial chromosomes containing the entire *HNRNPK* gene (RP11- 101L4) and a control probe to the 9p region (RP11-19G1). Using this FISH assay, we observed that *HNRNPK* is specifically lost in a subset of malignant

haematopoietic cells isolated from the bone marrows of *de novo* AML patients but not in healthy controls (Fig. 1). Additionally, qRT-PCR analyses revealed that deletion of the 9q21.32 locus significantly reduced *HNRNPK* expression in patients with AML.[41] Critically, 8 of 12 patients had deletion of this 9q21.32 region as their sole karyotypic abnormality, suggesting reduced *HNRNPK* expression directly contributes to the pathogenesis of AML.

An *in vivo* model of *Hnrnpk* haploinsufficiency

To directly examine if *HNRNPK* is, in fact, the haploinsufficient tumor suppressor residing at the 9q21.32 locus, our laboratory generated an *Hnrnpk* haploinsufficient mouse model and recently published a manuscript that examines the role of *Hnrnpk* haploinsufficiency *in vivo*.[41] Using mouse embryo fibroblasts (MEFs) and haematopoietic stem progenitor cells (HSPCs) in cytokine-dependent colony formation assays, we determined that reduced hnRNP K expression directly resulted in an increase in cellular proliferation. Molecularly, this increased proliferation was directly attributed to hnRNP K's inability to transcriptionally activate *p21* when its levels were reduced, supporting the notion that hnRNP K has tumor suppressive functions.

In addition to the increased proliferation observed in colony formation assays and in the bone marrow of these mice, *Hnrnpk* haploinsufficiency also contributed to defects in myeloid differentiation. Similar to the hnRNP K-mediated effects on p21, reduced hnRNP K expression also directly impacted the expression of critical myeloid differentiation factors *C/EBP*-α and -*β*. Molecular analyses revealed that reduced hnRNP K levels dampened its ability to transcriptionally regulate the expression of these genes. Interestingly, only the C/EBPα p42 isoform, but not p30, was significantly downregulated in $Hnrnpk^{+/-}$ mice. This lack of expression of the p42 isoform partially explains the myeloproliferative phenotype developed by $Hnrnpk^{+/-}$ mice, as previous studies have identified the p42 isoform as a critical myeloid tumor suppressor that significantly alters myelopoiesis. Given hnRNP K's role in translation and the fact that both the p30 and p42 isoforms are translated from the same mRNA, we hypothesized that hnRNP K may influence the expression of specific C/EBPα isoforms. This notion is supported by our finding that hnRNP K directly interacts with the *C/EBPα* transcript in human leukemic cell lines and in wild type mice. Importantly, these interactions were significantly reduced in bone marrow cells isolated from *Hnrnpk* haploinsufficient mice. Together, these clinical and animal model data suggest that reduced hnRNP K contributes to these leukemic phenotypes through its direct regulation of the p53/p21- and C/EBP- pathways and support the hypothesis that *HNRNPK* is the haploinsufficient tumor suppressor at the 9q21.32 locus (Fig. 2A and B).

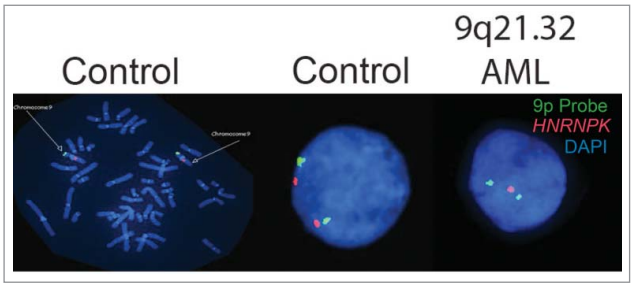

Figure 1. The *HNRNPK* gene is lost in a subset of *de novo* AML patients. (Left) Functional validation of the control probe (RP11-19G1, green) to the distal arm of chromosome 9p and *HNRNPK* probe (RP11-101L4, red) to the 9q21.32 locus using metaphase FISH on haematopoietic cells from healthy donors. DAPI is used as a counterstain to denote the DNA (chromosomes). (Middle). Nuclei of an interphase haematopoietic cell isolated from the bone marrow of a healthy donor indicating two *HNRNPK* alleles on chromosome 9 (two red/2 green). DAPI is used as a counterstain to denote the nucleus. (Right). Nuclei of an interphase haematopoietic cell isolated from the bone marrow of a *de novo* AML patient with haploinsufficient loss of the *HNRNPK* gene (one red/2 green). DAPI is used as a counterstain to denote the nucleus.

Reduced hnRNP K expression impacts developmental processes

With the multitude of pathways and cellular programs influenced by hnRNP K, it is easy to envision how alterations in its expression influence tumorigenesis. However, other striking phenotypes observed in haploinsufficient *Hnrnpk* mice were not related to increased cancer risk, but rather developmental defects.[41] *Hnrnpk* haploinsufficiency resulted in mice being born at a sub-mendelian ratio, extreme runtedness, a propensity for facial malformations, and a significant neonatal lethal phenotype. Analogous to our observations in mice, pediatric patients with germline *HNRNPK* mutations (c.953 + 1dup and c.257G > A; respectively) have been recently described.[42] These mutations result in haploinsufficient loss of wild type hnRNP K expression, and have been identified as causal events in the development of a syndrome consisting of craniofacial malformations, intellectual disability, and skeletal and connective tissue abnormalities. Furthermore, studies in *Xenopus laevis* have shown that antisense morpholino-mediated loss of hnRNP K expression also results in neuronal development defects.[43] However, perhaps the most striking evidence that hnRNP K is required for development stems from our observation that bi-allelic loss of *Hnrnpk* results in an embryo lethal phenotype prior to day 13.5 (E13.5).[41] Given that hnRNP K has been previously shown to transcriptionally regulate Mdm2 expression,[10,11] we postulated that bi-allelic *Hnrnpk* loss may potentially result in an embryo-lethal phenotype that is similar to loss of Mdm2 (i.e; an inability to negatively regulate p53-dependent apoptosis *in utero*).[44] However, when we generated $Hnrnpk^{+/-}$;$Trp53^{+/-}$ mice and then performed sibling matings, we did not rescue the *Hnrnpk*-null embryo-lethal phenotype. These initial observations suggest that hnRNP K's influence on embryonic development primarily resides in its impact on cellular programs outside of the p53 pathway.

Summary and future directions

Based on recent studies, there is now accumulating evidence that hnRNP K plays a critical role in regulating many fundamental cellular process that directly impact human diseases, such as tumorigenesis and congenital defects. In the context of malignancies, the impact that aberrant hnRNP K expression has on disease progression is complex, as there is evidence that hnRNP K has both oncogenic and tumor suppressive functions.

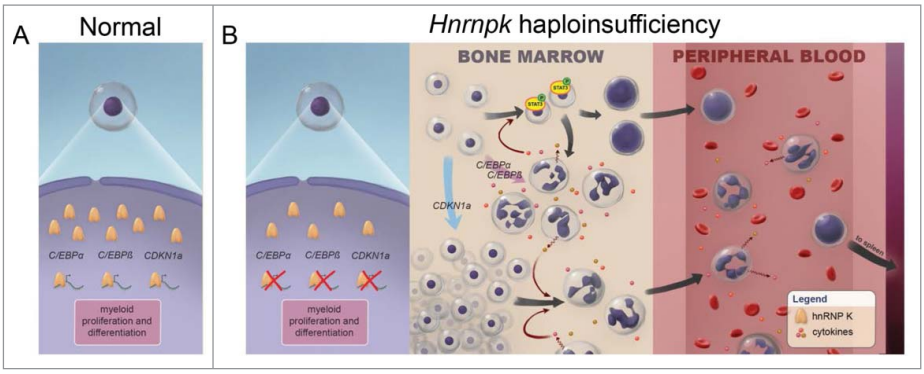

Figure 2. *Hnrnpk* haploinsufficiency results in proliferative and differentiation defects in the haematopoietic compartment. A. Under normal conditions, hnRNP K is required to maintain a homeostatic balance in haematopoietic development through its regulation of *p21, C/EBP-α*and *β*. B. (Left) *Hnrnpk* haploinsufficiency results in reduced hnRNP K expression and diminished p21, C/EBP-α and β levels. (Middle) In the bone marrow, reduced hnRNP K allows for expansion of the haematopoietic compartment, increased cytokine expression, and activation of Stat-3 signaling. (Right) Cells from the hyperproliferative bone marrow are mobilized and extravasate from the marrow into the periphery.

However, determining its precise impact on cancer risk is complicated by the fact that hnRNP K is capable of both strengthening and attenuating diametrically opposed oncogenic and tumor suppressive pathways. With the development of an *Hnrnpk* haploinsufficient mouse model, we have made initial strides in examining the tumor suppressive functions of hnRNP K and delineated the importance of reduced hnRNP K expression in cancer development through the p53/p21- and C/EBP-pathways.[41] As a result, this model system could become an effective pre-clinical platform to test therapies for patients with AML who harbor a 9q21.32 deletion. In these studies, standard frontline therapies could be used in combination with agents that antagonize the Mdm2-dependent degradation of p53, such as Nutlin-3, DS-3032b, or RG7112 in order to "re-engage" the p53 pathway.

In addition to its tumor suppressive functions, there are also clinical association studies, as well as biochemical and *in vitro* studies that strongly suggest hnRNP K may also serve as an oncogene when overexpressed.[14-18] However, to directly test this notion, there is an absolute need for the development of transgenic animal models that overexpress wild-type hnRNP K. We have currently undertaken this task by generating tissue-specific *Hnrnpk* transgenic mice. These model systems will directly test whether hnRNP K is a bona fide oncogene and will be useful in identifying the genes and cellular programs critical for tumorigenesis when hnRNP K is overexpressed. Similar to the *Hnrnpk* haploinsufficient mouse model, these mice will be instrumental in testing and developing hnRNP K overexpression-dependent therapies.

The challenge that remains (and will be central in our functional evaluation of *HNRNPK* mutations) is the generation of mutant knock-in *Hnrnpk* mouse models. This endeavor may prove a difficult task, as unlike the hotspot mutations observed in genes like *Tp53, IDH1*, and *KRAS*, the *HNRNPK* mutation spectrum (in cancers and in pediatric patients) is significantly more heterogeneous.[45] Thus, there is currently no clear indication as to which alteration is "the" critical mutation to initially examine. As such, there is a need for stringent biochemical and *in vitro* studies using mutant hnRNP K in order to guide future *in vivo* studies of mutant hnRNP K.

Even though numerous studies have examined the functional importance of hnRNP K since its discovery nearly a generation ago,[46] there remains much work to be done in order to fully understand the role of hnRNP K in human malignancies.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Author contributions

M.G., M.J.H, X.Z, and S.M.P. wrote the manuscript. X.Z. generated artwork. C.B.-R. and P.H. performed and analyzed pathologic and karyotype analyses. All authors reviewed and accepted the manuscript.

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