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Review

Over-expression of RNA Helicases in Cancer

MOHAMED ABDELHALEEM

Division of Haematopathology, Department of Paediatric Laboratory Medicine, Hospital for Sick Children, University of Toronto, Canada

Abstract. *RNA helicases constitute a large group of essential enzymes involved in all aspects of RNA metabolism. With few exceptions, human RNA helicases of DDX and DHX gene families have not been well characterized. However, several of them have been shown to be dysregulated in cancer, including over-expression in various types of tumors. Although the exact contribution of RNA helicases to carcinogenesis has not been determined, their over-expression in cancer render them potential targets for novel anti-cancer agents. In this review, RNA helicases whose expression is up-regulated in cancer are highlighted.*

RNA helicases

RNA processing involves a sequence of highly regulated steps (*e.g.* transcription, splicing, transport, translation and decay). The involvement of RNA molecules in these steps is influenced by their tendency to form secondary structures and by their interaction with other RNA molecules and proteins (1,2). Conserved enzymes, called RNA helicases, utilize the energy derived from NTP hydrolysis to modulate the structure of RNA, and thus potentially influence all biological processes that involve RNA (3).

The amino acid sequence of an RNA helicase is characterized by the presence of a centrally located "helicase domain", consisting of eight motifs (4). The motifs have been suggested to contain the amino acids required for NTP hydrolysis, RNA binding and unwinding activities. Based on variations of the sequence of the motifs of the helicase domain, RNA helicases are classified into families (5). The two largest human RNA helicase gene families have been recently identified. The *DDX* and *DHX* gene families are named after the DEAD-box and DEAH box (where DEAD and DEAH represent the one-letter-code of the amino acids constituting motif II, the signature motif, of the helicase domain) (6). With few exceptions, the biochemical activities and biological functions of the majority of human RNA helicases are largely unknown.

Correspondence to: Mohamed Abdelhaleem, MD, PhD, FRCPC, Room 3691 Atrium, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8. Tel: (416) 813 6434, Fax (416) 813 6257, e-mail: mohamed.abdelhaleem@sickkids.ca

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Over-expression of RNA helicases in cancer

Several RNA helicases are dysregulated in cancer in the form of involvement in chromosomal translocation, down-regulation and over-expression (reviewed in reference 7). Although the exact role of helicases in carcinogenesis has not been clearly delineated, it is possible that dysregulation of the normal function of RNA helicases can potentially result in abnormal RNA processing with deleterious effects on the expression/function of key proteins. Table I summarizes the RNA helicases whose expression has been shown to be up-regulated in various types of cancer.

DDX1 is over-expressed in retinoblastoma and co-amplified with *MYCN* in neuroblastoma cell lines and primary tumor specimens (8-10). *DDX1* shows *in vitro* ATPase and RNA helicase activities (11). *DDX1* has been shown to be a nuclear protein, which interacts with a factor involved in the 3'-end processing of pre-mRNA (12). The role of *DDX1* over-expression in carcinogenesis is unknown. However, *DDX1* also interacts with heterogeneous nuclear-ribonucleoprotein K (hnRNPK), which is known to be involved in the regulation of transcription, translation, nuclear transport and signal transduction (11). Up-regulation of *DDX1* might result in disruption of these cellular process in which it participates.

DDX2A (eIF4A1) mRNA has been shown to be over-expressed in human melanoma (13) and hepatocellular carcinoma (14). Moreover, *DDX2A* was suggested to be associated with metastasis in early stage non-small cell lung cancer (15). *DDX2* (eIF4A) is the best characterized human RNA helicase in terms of structure and biochemical activity. *DDX2* is part of a molecular complex involved in translation

Table I. *Summary of the human RNA helicase up-regulated in cancer.*

RNA Helicase	Other Names	Over-expressed in tumor (References)
DDX1		Neuroblastoma and retinoblastoma (8-10)
DDX2	eIF4A	Melanoma (13) and hepatocellular carcinoma (14)
DDX5	p68	Colorectal cancer (19)
DDX6	*RCK*, p54	Colorectal cancer (23,24)
DHX9	RNA helicase A, Nuclear DNA helicase II	Lung cancer (28)
DDX43	*HAGE*	Several tumors (32)
DDX48	hNMP265, KIAA0111	Gastric cancer (34)
DDX53	*CAGE*	Solid tumors and precancerous conditions (35)

initiation (16), in which the function of eIF4A is to unwind the mRNA secondary structure in the 5' UTR to facilitate ribosome binding (17). Anti-sense mediated down-regulation of *DDX2A* in melanoma cell lines resulted in inhibition of cellular proliferation (50). This finding suggests that the over-expressed RNA helicase can be used as a potential therapeutic target for novel anti-cancer agents.

DDX5 is over-expressed and post-transcriptionally modified in colorectal tumors (19). The changes were present in both benign and malignant colorectal tumors, suggesting that changes in *DDX5* expression/modification represented an early event in tumor development (19). *DDX5* is functionally implicated in pre-mRNA splicing (20). Recent studies have shown that *DDX5* plays a role in the alternative splicing of the proto-oncogene c-*H-ras* (21).

DDX6, also known as the *RCK* gene, is fused in frame to the immunoglobulin heavy chain gene in t(11;14)(q23;q23), seen in lymphoma. Although *DDX6* mRNA and protein sizes were not altered as a result of the translocation, the expression of *DDX6* was elevated compared to normal lymphocytes (22). The exact role of *DDX6* in lymphoma has not been defined. However, *DDX6* over-expression has been observed in other types of tumors. Tumor cell lines originating from tissues that normally have low to undetectable levels of *DDX6* (such as brain, muscle and lung) strongly express *DDX6* at the protein level (22). *DDX6* is over-expressed in colorectal carcinomas and adenomas (23,24). Studies have suggested that *DDX6* might play a role at the protein translation level by modifying the mRNA structure to facilitate *c-myc* translation (25).

DHX9 (also known as RNA helicase A (26) and nuclear DNA helicase II (27)) has been shown to be over-expressed in lung tumors (28). A recent study has shown that *DHX9* is involved in the up-regulation of the expression of MDR1, the multidrug-resistant gene in cancer cells (29). *DHX9* links the C-terminus domain of breast cancer tumor suppressor protein, BRCA1, to RNA polymerase II (30). Over-expression of a *DHX9* peptide, containing the domain that binds BRCA1, resulted in inhibition of the normal function of BRCA1 and a phenotype characterized by pleomorphic nuclei and aberrant mitoses (31). This result suggests that upregulation of *DHX9* expression might interfere with the tumor suppressor activity of BRCA1.

Several other RNA helicases were originally identified based on their over-expression in cancer. *DDX43 (HAGE)* were identified as a novel RNA helicase up-regulated in a human sarcoma cell line (32). *DDX43* is also up-regulated in several tumors of various histological types (32). *DDX48*, which is highly homologous to *DDX2*, has been identified as one of a few genes up-regulated in a specific type of gastric cancer (33,34). *DDX53*, with an amino acid sequence closely related to *DDX43*, was up-regulated in solid tumor tissues and cell lines (35).

Could RNA helicases serve as targets for novel anti-cancer agents?

Helicases have been used as antiviral drug targets with varying degrees of success (36). The over-expression of several RNA helicases in cancer raises the question of whether they could serve as potential targets for novel agents. However, helicases are complex proteins, which are part of multi-protein complexes that regulate essential cellular processes. Therefore, much work lies ahead in trying to understand the normal function of helicases, their molecular interaction and their exact role in carcinogenesis.

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