REVIEW

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DEAD box RNA helicase functions in cancer

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Members of the DEAD box family of RNA helicases are known to be involved in most cellular processes that require manipulation of RNA structure and, in many cases, exhibit other functions in addition to their established ATP-dependent RNA helicase activities. They thus play critical roles in cellular metabolism and in many cases have been implicated in cellular proliferation and/or neoplastic transformation. These proteins generally act as components of multi-protein complexes; therefore their precise role is likely to be influenced by their interacting partners and to be highly context-dependent. This may also provide an explanation for the sometimes conflicting reports suggesting that DEAD box proteins have both pro- and anti-proliferative roles in cancer.

Introduction

DEAD box RNA helicases play key, and often essential, roles in RNA metabolism and generally function as components of large multi-protein complexes. Members of this family share a conserved core containing nine conserved motifs, including the characteristic D-E-A-D motif; these motifs confer the ATP hydrolysis and RNA unwinding activities that have established them as RNA helicases. However, it is clear that many DEAD box proteins are multifunctional and have additional diverse roles that are conferred by their distinct N- and C-terminal domains and dependent on their interactions with partner proteins. There have been numerous reports indicating that DEAD box proteins are involved in processes that are key to cellular proliferation and/or neoplastic transformation; therefore, it is not surprising that deregulation of expression or function of these proteins has been implicated in cancer development or progression.[1]

In this review I shall focus on the DEAD box proteins DDX1, DDX3, DDX6, DDX5 and DDX17, proteins for which there is a significant body of evidence for their involvement in cancer development. Interestingly, all of these proteins have been suggested to have both oncogenic and tumor-suppressive roles in cancer and there have been often conflicting reports on their role in cancer development. However the data presented to date suggest that their precise function may be highly tumor- and/or context- dependent, and may be influenced by their interacting partners. I shall review the multiple functions that have been attributed to these proteins and discuss how these can act to promote or inhibit tumor development in different contexts. These are summarized in **Table 1**.

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DDX1

DDX1 amplification and potential role in cancer. One of the first indications that DDX1 may be involved in tumor development came from reports that it is co-amplified with the *MYCN* gene in retinoblastomas and neuroblastomas.[2-5] The finding that co-amplification of *DDX1* and *MYCN* was more frequent in higher stages of neuroblastoma and was associated with a significant reduction in disease-free survival compared with those with only *MYCN* amplification[3,6] suggested that DDX1 has oncogenic properties. This idea is supported by a more recent study of breast cancer gene expression and tissue microarrays, which showed that *DDX1* RNA overexpression and elevated cytoplasmic DDX1 protein are associated with early recurrence and suggested that DDX1 may be an independent prognostic marker for early recurrence in breast cancer.[7]

However, there have been several conflicting reports concerning the role of DDX1 in tumor development. For example, in one report high DDX1 expression in neuroblastoma was associated with better survival,[8] while a recent study showed that DDX1 expression was associated with improved local relapse-free-, distant metastasis-free- and overall survival in patients diagnosed with early-stage node-negative breast cancer,[9] suggesting a possible tumor suppressor role for DDX1. However, De Preter and colleagues found no evidence of any effect of DDX1 amplification on prognosis of patients with MYCH-amplified neuroblastomas,[10,11] while other reports suggested that the prognostic effect of *DDX1* amplification/overexpression on MYCN is different between different subgroups,[12,13] providing a possible explanation for the different results obtained from the various studies. Although most reports indicate an oncogenic role for DDX1 in tumor development, much of the evidence is circumstantial rather than mechanistic. Therefore, its precise function may depend both on the cancer type (or even subtype), treatment administered to patients, as well as context: i.e., the expression of other factors that may influence both DDX1 function and, independently, the treatment chosen for the specific cancer (e.g., Estrogen Receptor status in breast cancer).

DDX1 functions. Apart from the well-documented functions in the replication of several viruses, most notably HIV (reviewed in ref. 14), DDX1, like many other DEAD box proteins, is found to be a component of several cellular protein and ribonucleoprotein complexes.

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Table 1. The multiple functions attributed to the DEAD box proteins DDX1, DDX3, DDX6, DDX5 and DDX17, and their potential in tumor development

Protein*	Function	Targets/context	Importance in cancer
DDX1	Viral replication, nuclear export of viral RNAs	Export of HIV RNA, JC virus and HCV replication[14]	Co-amplified with *MYCN* in neuroblastoma and retinoblastoma[2-6] Overexpressed in breast cancer[7] and testicular carcinoma[22] Cell migration and anchorage- independent growth[19,22] *Most reports suggest oncogenic properties but some imply tumor-suppressive roles in some contexts.*[3-13]
	3'end processing of mRNAs	Associated with cleavage stimulating factor in HeLa cells[16]	
	RNA Transport / RNA clearance	Associated with RNA transporting granules (with DDX3) in neuronal dendrites[15] RNA clearance from DNA strand break sites in HeLa cells[17]	
	Cytoskeletal reorganization / cell migration	Cellular elongation and migration in monocytes[19] Anchorage independent growth in testicular germ cell tumor cell line[22]	
	Transcription	Activation of stem cell-associated genes (e.g., *Cyclin D2*) in testicular germ cell tumors[22]	
DDX3, DDX3X, DBX (Ded1p)	Viral replication, nuclear export of viral RNAs	HIV, HBV, HCV: potential drug target[23,24]	*Both oncogenic and tumor suppressor roles suggested in HCC and breast cancer*[42-51] Overexpression in HCC,[43] promotes anchorage independent growth[43] and cell cycle progression,[44] inhibits apoptosis[46,47] Reduced expression in some HCC,[49] inhibits cell cycle progression through activation of *$p21^{WAF1}$* transcription in HCC and lung cancer[40,49,50] Stimulates migration/invasion[42] *Context-dependent regulation of RNA export and translation could have important implications in tumor cell growth.*
	Pre-mRNA splicing	DDX3 and the yeast homolog, Ded1p, associated with mRNPs and spliceosomes but no direct evidence for functional role[26-28]	
	RNA export	Export of unspliced or partially spliced HIV transcripts[29] Associated with RNA transporting granules (with DDX1) in dendrites[15] and with the mRNP export receptor TAP[30]	
	Translation	Can both promote and repress translation initiation: associates with P-bodies, ATP hydrolysis allows release from P-bodies and translation initation[32-37]	
	Transcription	Activation of IFNβ, *$p21^{WAF1}$*, Snail; inhibition of E-cadherin transcription[38-42,60]	
	EMT, cell migration/invasion	DDX3 overexpression induces EMT and motility/invasiveness in MCF10 breast cancer cells[42]	
DDX6, Rck/p54 (Xp54; p47; ME31B; Dhh1p)	mRNP export, translational repression in development	Associated with cytoplasmic mRNP storage particles and translational repression in *Drosophila* and *Xenopus* oocytes;[58,65] Developmental roles in many species[57-62]	Overexpression in several cancers[53-56] Stimulation of cell cycle progression and proliferation[70-74] *Aberrant regulation of RNA export, RNA degradation and translation could have important implications in tumor cell growth* *Most reports suggest oncogenic properties*[70-74] *but some imply tumor-suppressive roles in certain contexts*[69,75]
	RNA degradation/ Translation repression	Associated with P-bodies and translational repression in HeLa cells[66,70] and yeast[69] Associated with RISC in HeLa cells, important for miRNA induced translation repression[67] Dhh1p associated with decapping and deadenylase complexes in yeast,[68,69] can promote mRNA degradation[71]	
	Cell cycle progression/proliferation	Dhh1p important for recovery from DNA damage-induced G1/S cell cycle arrest in yeast DDX6 required for S-phase progression and cell viability in HeLa and LoVo cells,[73,74] and proliferation in xenograft models[74] (*siRNA studies*) In contrast, DDX6 or Dhh1p *overexpression* inhibits cell growth[75,69]	

*Alternative names, including homologs in species other than human, are also shown. Homologs are shown in brackets.

3' end processing of pre-mRNAs. DDX1 is predominantly nuclear in many cells in which the *DDX1* gene is not amplified, while it is present in both the nucleus and cytoplasm in cells in which the gene is amplified/overexpressed (reviewed in ref. 14). However it has also been reported in the cytoplasm in some cell lines (e.g., neurons, see ref. 15 and below). Apart from showing a general punctate nucleoplasmic distribution, DDX1 is also found in discrete nuclear foci and is associated with the cleavage stimulation factor CstF-64, suggesting a role in 3'-end polyadenylation and cleavage of pre-mRNAs.[16] Additionally DDX1

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Table 1. The multiple functions attributed to the DEAD box proteins DDX1, DDX3, DDX6, DDX5 and DDX17, and their potential in tumor development (continued)

Protein*	Function	Targets/Context	Importance in Cancer
DDX5, p68 DDX17, p72	Transcription	DDX5 coactivates ERα[97], p53,[100] MyoD,[99] AR,[84] Runx2[98], NF-κB[87] DDX5 required for p53 DNA damage response[100] and activation of *selective* p53 target genes[101] DDX17 coactivates ERα and required for activation of ERα target genes[85] DDX5/DDX17 activate transcription of both pro- proliferation and anti-proliferative genes,[84-104] regulate promoter switching[110]	DDX5/DDX17 aberrantly expressed/modified in a range of cancers[83-89] DDX5/DDX17 coactivate transcription factors that play important roles in tumor development[84-110] DDX5 activates transcription of genes important for DNA replication. DDX5 stimulates EMT and DDX5/DDX17 modulate cell migration DDX5 *selectively* activates p53-dependent *p21*^{WAF1} induction; influences cell cycle arrest/apoptosis decision[101] *Deregulation of splicing/alternative splicing and miRNA biogenesis play important roles in tumor development* *Several reports suggest oncogenic roles for DDX5/DDX17, but also evidence for context-dependent tumor suppressor roles*[1,84-108]
	Pre-mRNA splicing/ alternative splicing	DDX5/DDX17 associated with spliceosomes, required for pre-mRNA splicing[111-113] Alternative splicing and exon skipping[114-118]	
	RNA clearance, nuclear export	DDX5 implicated in RNA clearance from chromatin and export[18,31]	
	miRNA biogenesis	DDX5 /DDX17 components of Drosha complex, implicated in miRNA processing of subsets of miRNAs[119-124]	
	Ribosome biogenesis	DDX5/DDX17 implicated in rRNA processing (knock-out mice)[79] DDX5/DDX17 required for ribosome biogenesis in HeLa cells[94]	
	EMT, cell migration	DDX5 regulates PDGF-induced EMT[88] DDX5/DDX17 modulate cell migration through NFAT5 regulation[108]	

*Alternative names, including homologs in species other than human, are also shown. Homologs are shown in brackets.

was also found to interact with poly(A) RNA and with heterogeneous nuclear ribonucleoprotein K (hnRNP K) a protein that is involved in multiple stages of mRNA biogenesis/metabolism including chromatin remodeling, transcription regulation, pre-mRNA processing, nuclear transport and translation. These findings are consistent with the idea that at least one of the functions of DDX1 is in 3' end processing of pre-mRNAs; however to date there is no evidence for a direct role in this process.

RNA transport/clearance. DDX1, together with DDX3 and DDX5 (see below), was identified as a protein associated with kinesin KIF5 in an RNA-transporting granule[15] in neuronal dendrites, suggesting a potential role in RNA transport. In this respect the association of DDX1 with hnRNP K would also support a role for DDX1 in RNA transport. Furthermore, a study demonstrating the re-distribution of DDX1 to ionizing radiation-induced foci and its co-localization with γ-H2AX and phosphorylated ATM, coupled with its ability to unwind DNA-RNA hybrids, suggest a possible role for DDX1 in RNA clearance from double strand break sites.[17] This is interesting because a RNA clearance role has also been implicated for DDX5 (see below).[18] Furthermore, the idea that DDX1 functions in RNA clearance from DNA double strand break sites implies a role in transcription-coupled repair, which may in turn have implications for DDX1 function in tumor development.

Cytoskeletal reorganization/cell migration. A potential role for DDX1 in cell motility has emerged from reports identifying DDX1 in (1) complexes with LRFN4, a neuronal transmembrane protein that is also expressed in monocytes and signals cytoskeletal reorganization and morphological cell elongation,[19] and (2) in proteomic analysis of the pseudopodial fractions of invasive variants of Moloney sarcoma virus- transformed Madin-Darby canine kidney cells. Although they do not specifically demonstrate that DDX1 is functionally involved in cell motility these observations are important since cell migration and/or invasion are key steps in tumor invasion and metastasis.

Interestingly, in one of these reports,[19] the complex containing DDX1 also contained several 14–3-3 proteins, which have been found to be involved in signal transduction, cell cycle control and apoptosis. Other studies also identified DDX1 as a component of 14–3-3-containing complexes[20,21] consistent with the idea that DDX1 may play a part in multiple cellular processes that are implicated in tumor development or progression.

Transcription: Transcriptional activation of stem cell associated genes. One of the strongest pieces of evidence linking DDX1 with tumor development comes from a study showing that it is required for transcriptional activation of stem cell associated genes (including *cyclin D2*) that are implicated in testicular germ cell tumors.[22] In this study, siRNA knockdown of DDX1 resulted in a striking inhibition in their anchorage-independent growth and an abrogation of their ability to form tumors in nude mice, indicating that DDX1 is critical for tumorigensis and highlighting potential mechanisms by which deregulation

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of DDX1 could play a crucial role in cancer development and/or progression.

DDX3

In recent years DDX3 has gained much attention due to its role in the replication of viruses that are of global health importance (including HIV, HBV, HCV) and there are major efforts aimed at developing strategies to target DDX3 therapeutically (reviewed in refs. 23, 24), including, most recently, small molecule inhibitors that target the DDX3 RNA binding site as a potential anti-HIV therapy.[23] However, numerous studies have demonstrated that DDX3 and its yeast homolog (Ded1p) function in multiple cellular processes involved in the regulation of gene expression (reviewed in refs. 23, 25). These include transcription, pre-mRNA splicing and mRNA export and translation, functions that are often associated with several other DEAD box proteins. Additionally, DDX3 has also been implicated in cell cycle regulation and apoptosis, consistent with it being important in cancer development. Interestingly, however, as appears to be the case for the other DEAD box proteins discussed here, there are reports suggesting both oncogenic and tumor suppressor functions for DDX3.

DDX3 functions. DDX3 (also known as DDX3X, DBX) has been variously described to be a nuclear protein, a cytoplasmic protein, and as a protein that shuttles between the nucleus and the cytoplasm, consistent with its described nuclear and cytoplasmic functions.

Pre-mRNA splicing/RNA export. Although initial studies suggested that the yeast Ded1p was involved in pre-mRNA splicing, its role in this process remains unclear. Nevertheless, Ded1p and the human DDX3 were found to associate with mRNPs and spliceosomes,[26-28] but whether DDX3/Ded1p is actively involved in splicing or whether it functions in export of spliced mRNAs remains to be fully elucidated.

DDX3 was first shown to be important for the export of unspliced or partially spliced HIV transcripts[29] and subsequently was found to associate with the major nuclear mRNA export receptor, Tip-associated protein (TAP), with mRNPs[30] and with RNA transporting granules,[15] shuttling from the nucleus to the cytoplasm. These studies suggest that DDX3 is unlikely to be involved in general mRNA export; instead it may be involved in the export of viral RNAs and specific subsets of cellular mRNAs and may subsequently also be important in regulating the translation of these mRNAs. Interestingly, DDX3 was recently shown to interact with another DEAD box helicase, DDX5, (see below) and suggested to influence DDX5 shuttling during mRNP export.[31]

Translation. Perhaps the best studied function for DDX3, and the yeast Ded1p, is their role in translation. Work from several groups showed that the Ded1p promotes translation initiation[32,33] and, indeed, many studies have reported interactions between DDX3/Ded1p and proteins involved in translation initiation (reviewed in ref. 23). However there have been other conflicting results: for example, one study reported that DDX3 represses cap-dependent translation by binding and inhibiting eIF4E;[34] others suggested that DDX3 promotes translation of specific mRNAs that contain secondary structures in their 5'UTR through interaction with eIF4F.[30,35] Yet another study suggested that the yeast Ded1p can both repress and promote translation through its association with P-bodies (Processing bodies).[36] This was confirmed by data showing that Ded1p interacts with eIF4G to assemble a translationally repressed Ded1p-mRNA-eIF4F complex in P-bodies but subsequently, upon ATP hydrolysis, resolves the "stalled" mRNP and allows its exit from the P-bodies for translation initiation thus controlling the release (and translation) of specific mRNAs in an ATP-dependent manner.[37] Interestingly, the inhibitory effect on translation initiation through eIF4E inhibition did not appear to require helicase activity[34] while the resolving of the stalled mRNP requires ATP hydrolysis and, presumably, RNA unwinding.[37] Thus, the precise function of DDX3/Ded1p in translation might also be modulated by other factors or conditions in the cell (e.g., stress conditions). This could have important implications in cancer and might, at least in part, explain the different reports suggesting both oncogenic and tumor suppressor roles for DDX3 (see below).

Transcription: Transcriptional regulation of genes important in cancer. Several studies from different groups have reported that DDX3 can regulate transcription of genes that are important in cancer. These include activation of the Interferon-β (IFNβ),[38,39] the cell cycle arrest gene *p21*^{waf1}[40] and the transcription factor Snail[41] promoters, and repression of the E-cadherin promoter.[42] Chromatin Immunoprecipitation assays demonstrated that DDX3 is recruited to the IFNβ, E-cadherin and the *p21*^{waf1} promoters,[38-40,42] suggesting that DDX3 functions in transcriptional initiation. Similarly, the DDX3-dependent effect on Snail transcription in the presence of histone deacetylase (HDAC) inhibitors[41] is consistent with DDX3 being involved in initiation of Snail transcription.

Interestingly, DDX3 appears to work in subtly different ways in regulating transcription of these genes. For example activation of the IFNβ promoter appears to be independent of ATPase or RNA helicase activity,[38,39] while activation of the *p21*^{waf1} promoter requires ATPase, but not RNA helicase activity,[40] suggesting promoter- or context-dependent effects. Interestingly similar promoter-dependent differences have been observed for DDX5 (see below).

In terms of the role of DDX3 in cancer, stimulation of Snail[41] and repression of E-cadherin[42] would be consistent with DDX3 promoting epithelial-mesenchymal transition (EMT) since these genes play key roles in this process. EMT is one of the pre-requisites for cancer invasion and metastasis, suggesting an oncogenic role for DDX3. In contrast, its activation of the cell cycle arrest gene *p21*^{waf1}[40] and its activation of IFNβ[38,39] (which has been shown to inhibit angiogenesis, a process that is critical for cancer growth) would imply a growth-, or tumor-suppressor, role for DDX3. Thus, as discussed below, the precise role of DDX3 in cancer may be tumor and/or context-dependent and is also likely to be dependent on the availability of other factors that regulate transcription.

DDX3 in cancer: oncogene or tumor suppressor? *DDX3 as an oncogene.* The first suggestion that DDX3 can act as an oncogene

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came from a study of hepatocellular carcinoma (HCC), which reported overexpression of DDX3 mRNA in a panel of HCC tissues and showed that ectopic expression of DDX3 stimulated anchorage-independent growth of HCC cells, a hallmark of cell transformation.[43] These findings are supported by data from two reports showing that (1) overexpression of DDX3 repressed E-cadherin expression and increased motility in breast cancer cell lines;[42] and (2) was required for Snail expression, an inducer of EMT.[41]

Additionally, DDX3 has been shown to promote translation initiation of cyclin E1 thus facilitating G1/S transition and promoting cell growth;[44] this is consistent with an earlier report that Hamster tsEt24 cells, which harbor a temperature-sensitive mutation in DDX3, exhibit G1 arrest at the non-permissive temperature.[45] Other studies have suggested that DDX3 has an anti-apoptotic function. DDX3 was found to be important in blocking tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) mediated apoptosis by associating with the TRAIL receptor 2 (TRAIL-R2/DR5) and blocking apoptotic signaling;[46] this finding was supported by data showing that DDX3 siRNA knockdown increased TRAIL-R2- mediated apoptosis[47] and that breast cancer cell lines expressing low levels of DDX3 were more sensitive to antibodies targeting this receptor.[48]

Taken together the above data support the notion that DDX3 can enhance cell proliferation through cell cycle regulation, inhibit apoptosis, and promote cell transformation and migration. These are all consistent with DDX3 having a tumor-promoting or oncogenic role in the cell.

DDX3 as a tumor suppressor. However, there is also evidence that, at least in some contexts, DDX3 has a tumor suppressor function. In contrast to the first report of DDX3 overexpression in HCC,[43] a subsequent study showed a reduction of DDX3 expression in HCC from hepatitis B-positive but not hepatitis C-positive patients.[49] Moreover, the latter study also showed that siRNA knockdown of DDX3 in the non-transformed mouse cell line NIH3T3 results in enhanced cell proliferation and premature entry into S-phase, concomitant with downregulation of *p21^{waf1}* and upregulation of *cyclin D1*; these data clearly contrast with those indicating that DDX3 can promote G1/S transition and cell growth- see above.[44,45] Additionally, Chang and colleagues[49] reported that constitutive DDX3 siRNA knockdown in NIH3T3 cells results in an increase in *ras*-induced anchorage-independent growth and resistance to apoptosis induced by serum depletion; these data again conflict with those from the reports by Huang, Sun and colleagues.[43,47]

In another study, ectopic expression of DDX3 was found to inhibit cell growth, as seen by colony formation assays in a range of tumor cells, in a p21-dependent manner through transcriptional activation of the *p21^{waf1}* promoter.[40] Similarly, in a separate report, DDX3 was shown to synergistically stimulate p53-dependent transcription of *p21^{waf1}*; moreover DDX3 was positively associated with p21 expression in lung cancer and reduced expression of DDX3/p53 and p21 were found to associate with poor relapse-free survival.[50] Both these studies support a tumor suppressor role for DDX3, through activation of p21 expression. These data contrast with those from Botlagunta and colleagues,[42] which showed that DDX3 has no effect on p21 expression in breast cancer MCF-7 cells and high DDX3 levels were associated with low p21 levels in aggressive breast cancers.

To further complicate the picture, DDX3 was found to inhibit cell growth in the human hepatocellular carcinoma cell line HuH-7 through repressing cap-dependent translation by binding and inhibiting the translation initiation factor eIF4E.[34] This conflicts with the data from Lai and colleagues[44] and is consistent with observations that DDX3 can both stimulate and inhibit translation in a context-dependent manner.

It is not clear why alterations in DDX3 levels produce such opposing tumor-suppressing and proliferation- or tumor-promoting effects in different cell lines, although the effect may depend on the expression of other cellular factors in the different systems and/or the model systems/genes under study. In this respect, alterations in nucleo-cytoplasmic shuttling and therefore the cellular localization of DDX3 may be important since it could have profound effects on its function, depending on context. The reasons behind the discrepancies concerning DDX3 localization in the various reports remain unclear (reviewed in ref. 23), although one study did show an alteration of DDX3 subcellular localization from the nucleus to the cytoplasm in a high percentage of cutaneous squamous cell carcinoma.[40] This may also perhaps explain the conflicting reports showing an increase in DDX3 expression in some cases, and a decrease in others, being associated with cancer development and/or progression.

DDX6

DDX6 (also known as Rck/p54) was first suggested to be involved in tumor development through its cloning as a gene found at a chromosomal 11q23 breakpoint in the RC-K8 B-cell lymphoma line, when it was shown to be highly homologous to the *Drosophila* DEAD box gene *ME31B*.[51,52] Subsequent reports demonstrated that the DDX6 protein is overexpressed in glioblastoma, rhabdosarcoma and lung cancer cell lines as compared with normal tissue,[53] in colorectal tumors[54,55] and in cases of HCV-related chronic hepatitis and hepatocellular carcinoma.[56] All these implied an involvement of DDX6 in cancer development, although the precise mechanism of its contribution to cancer was unclear at the time.

DDX6 functions. Developmental functions have been suggested for DDX6 homologs in several organisms including the *Drosophila* ME31B,[57,58] the *Schizosaccharomyces pombe* Ste13,[59] the *Xenopus* Xp54,[60] the *Caenorhabditis elegans* Cgh-1[61] and the murine Rck/p54.[62] Further functional studies on these homologs have demonstrated that DDX6-like proteins play important roles in several cellular processes including mRNP assembly/export, RNA degradation and translational regulation (reviewed in ref. 63).

mRNP assembly and export: association with P-bodies, RNA degradation and translational repression. The *Xenopus* Xp54 was found to shuttle between the nucleus and cytoplasm in *Xenopus* oocytes; it was shown to be involved in the export of maternal mRNAs and to localize to mRNP storage particles in the cytoplasm.[64] Similarly the *Drosophila* ME31B[58] and the Clam

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homolog p47[65] were shown to associate with RNP complexes and to repress translation of oocyte mRNAs. A more recent study using both the *Xenopus* Xp54 and human DDX6 demonstrated that RNA helicase activity is required for translation repression.[66] However, while DDX6 helicase activity was required for P-body assembly in HeLa cells the C-terminal domain (outside the helicase core) was sufficient for translational repression;[66] and suggested that ATP-dependent conformational changes in DDX6 and modulation of its binding to protein partners may be crucial in regulating translation. This implies that DDX6 is multifunctional and has helicase-dependent and -independent functions that depend on interaction with other partners. This is reminiscent of the findings with DDX3 and DDX5, and may be a common property of many DEAD box proteins.

Interestingly, DDX6 has also been found to interact with the Argonaute proteins Ago1 and Ago2, associate with the RNA-induced silencing complex (RISC) and to be important for miRNA-induced, but not siRNA-induced, translational repression[67] suggesting a further mechanism by which DDX6 may repress translation.

Other studies have shown that Dhh1p, the *Saccahromyces cerevisiae* homolog of DDX6 functions in mRNA decapping and is associated with both decapping and deadenylase complexes[68,69] providing a mechanism by which it can regulate translation of mRNAs through RNA degradation. These findings are supported by recent data, which shows that the human DDX6 is bound to repressed mRNAs at multiple points and proposes that this binding aids their localization to P-bodies and the recruitment of decapping complexes.[70] Interestingly, Dhh1p was similarly shown to promote degradation of a specific mRNA (porin mRNA) in yeast through interaction via its C-terminal domain,[71] again suggesting that this function is helicase-independent (see above).

Regulation of cell cycle progression and proliferation: DDX6 as an oncogene. Several studies, with both the human DDX6 and the yeast Dhh1p, have indicated that this protein acts as a positive regulator of cell cycle progression: Dhh1p has been shown to be important for recovery from DNA-damage-dependent G1/S cell cycle arrest,[72] while two separate studies demonstrated that siRNA knockdown of DDX6 resulted in S-phase cell cycle arrest.[73,74]

Furthermore, these studies showed that siRNA knockdown of DDX6 resulted in a reduction in cell viability,[73] as well as an increase in cell apoptosis and a reduction in their ability to form tumors in xenograft models.[74] Additionally, overexpression of DDX6 was shown to increase expression of the oncogene *c-Myc*, consistent with the idea that it would have a positive effect on cell proliferation.[55]

Taken together, these findings suggest that DDX6 homologs play an important, evolutionarily conserved, positive role in cell cycle progression and proliferation, perhaps through regulating translation of specific mRNAs that play key roles in cell cycle progression. This would be consistent with the idea that DDX6 can act as an oncogene and is supported by the many reports showing that it is overexpressed in a wide range of cancers.[53-56]

Growth inhibitory/tumor suppressor roles for DDX6. In contrast to the above, there has been one report that overexpression of DDX6 results in an inhibition of cell growth and a reduction in anchorage-independent growth, a hallmark of malignant transformation.[75] Furthermore, overexpression of Dhh1p was found to inhibit cell growth in yeast, suggested to be through general repression of translation.[69] While these results suggest that DDX6 homologs in these contexts have a negative role on cell proliferation and conflict with those described above, the discrepancy could be due to the fact that most of the experiments showing a positive effect of DDX6 on cell proliferation used siRNA depletion of endogenous DDX6 while those showing a negative effect on proliferation relied on ectopic overexpression. Perhaps having the correct physiological amount of DDX6 in cells is critical and the precise function of DDX6 will depend on the levels of the protein in the cell as well as the availability of interacting partners.

DDX5 and DDX17

DDX5 (also known as p68) is one of the prototypic members of the DEAD box family of RNA helicases.[76] DDX5 and the highly related DDX17 (p72)[77] have been shown to function in multiple processes in the cell, including transcription, pre-mRNA and -rRNA processing, alternative splicing and miRNA processing, and there have been several reports showing that their expression is deregulated in a range of cancers. Furthermore, both DDX5 and DDX17 have been functionally implicated in tumor development: several reports have suggested oncogenic or pro-proliferation roles for these proteins while some have implied potential tumor suppressor roles (reviewed in ref. 78). Furthermore, it is clear that post-translational modification of DDX5 and DDX17 has profound effects on DDX5/DDX17 function and this may be critical to their role in cancer.

The *DDX5* and *DDX17* genes share a remarkable degree of homology.[77] DDX5 and DDX17 function in multiple cellular processes; however, although they appear to share some functional overlap in some contexts, several reports have shown that they also have specific non-redundant functions (reviewed in ref. 78), perhaps most clearly demonstrated by the results from DDX5 and DDX17 knockout mice.[79]

Expression and modification of DDX5 and DDX17 in cancer. In the original paper describing the discovery of DDX5,[81] the observation that exponentially growing cells appeared to have higher levels of the protein suggested that DDX5 may somehow be involved in cell proliferation. A subsequent report indicated that DDX5 expression was developmentally regulated and associated with organ maturation /differentiation but that, in cell lines, expression was induced by serum suggesting that the regulation of DDX5 expression is complex.[80]

The first report of aberrant DDX5 expression in cancer came from a study which showed that DDX5 was overexpressed and abnormally modified (by polyubiquitylation) in colorectal cancer.[81] This was followed by several other reports showing DDX5, and in several cases also DDX17, overexpression in a range of cancers including colon,[82,83] prostate,[84] breast,[85] cutaneous squamous cell carcinoma[86] and glioma.[87]

Phosphorylation of DDX5, in particular on Tyrosine593, has been reported to be associated with cellular transformation and

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tumor development[82] and to alter DDX5 localization and function. DDX5 phosphorylated on Y593 through the action of the Platelet-Derived Growth Factor (PDGF)-activated c-Abl kinase was found to be exported from the nucleus to the cytoplasm and to facilitate β-catenin nuclear import.[88] Furthermore it was shown to be important for PDGF-induced Epithelial-Mesenchymal Transition (EMT).[88] Similarly PDGF-induced phosphorylation of DDX5 was found to be important for β-catenin nuclear translocation and activation in prostate cancer cells.[89] Although some other studies reported that Y593 phosphorylation on DDX5 was not required for β-catenin nuclear localization,[83,90] it is clear that phosphorylation by c-Abl affects DDX5 function, at least in certain contexts, as shown by its effects on induction of *cyclin D1* and *c-Myc* expression,[91] *Snail1*[92] and Androgen Receptor target genes[84] (see below). Furthermore a double phosphorylation on Y593 and Y595 of DDX5 was found to impart resistance to apoptosis in gliobastoma cells treated with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL).[93]

Taken together these findings suggest that post-translation modification of DDX5 and DDX17 may play important roles in cancer development/progression and that DDX5/DDX17 have pro-proliferation/-transformation roles that can be modulated by post-translational modification. This idea is supported by reports showing that simultaneous depletion of both DDX5 and DDX17 results in an inhibition of both proliferation of cancer cells and of their ability to form tumors in xenograft mouse models,[83,94] and that DDX5 depletion inhibited transformation of RasV12 transformed *Arf*-deficient cells in vitro and in vivo.[95] It is also consistent with reports that DDX5 expression associates with higher grade in prostate and breast cancers,[84,85] gliomas[87] and metastatic cutaneous squamous cell carcinoma.[86] Furthermore, a recent report demonstrated that *DDX5* is amplified in a subset of breast cancers; in these cancers DDX5 is required for proliferation and inhibition of DDX5 sensitizes this subset of cancer cells to trastuzumab,[96] suggesting that DDX5 is oncogenic in certain cancers and could even be a therapeutic target.

However, in the study of Estrogen Receptor α (ERα)-positive breast cancers which showed the association of DDX5 with higher grade and markers of poor prognosis, but not significantly with survival, DDX17 was associated with better survival[85] suggesting that the role of DDX5 and DDX17 in cancer development and progression is more complex and is likely to be context-dependent, as discussed below.

DDX5 and DDX17 functions: oncogenes or tumor suppressors? *Regulation of transcription.* There is now a large body of evidence demonstrating that DDX5 and DDX17 act as coactivators of transcription factors that are themselves highly regulated and play important roles in cancer development. Much of the work to date in this area has been performed on DDX5, perhaps reflecting the higher availability of reagents; however it is clear that DDX17 also acts as a regulator of transcription, with some functions that are distinct from those of DDX5. Chromatin immunoprecipitation assays indicate that DDX5 and DDX17 are recruited to responsive promoters and act, at least in part, by modulating transcriptional initiation. Interestingly, DDX5/DDX17 RNA helicase activity appears to be required for transcriptional regulation in some, but not all, cases (reviewed in ref. 78), suggesting that the precise function of DDX5/DDX17 in transcription may be dependent on the promoter context and/or on other interacting factors.

Consistent with the idea that DDX5 has pro-proliferation or oncogenic roles in cancer, it has been shown to coactivate ERα,[97] Androgen Receptor (AR),[84] Runx2,[98] the NFκB transcription factor p50,[87] and to upregulate expression of *cyclin D1*, *c-Myc* consistent with β-catenin activation[88,91] as well as genes required for DNA replication.[96] Furthermore, DDX5 was found to activate transcription of the *Snail1* gene by displacing histone deacetylase from the *Snail1* promoter,[92] consistent with an involvement in EMT. Interestingly Y593 phosphorylation was found to be important for this function, as previously shown for DDX5 activation of AR,[84] underscoring the idea that phosphorylation of DDX5 can modulate its function.

On the other hand, anti-proliferative or tumor-suppressor functions have also been implied for DDX5 and DDX17. A pro-differentiation role was suggested by the finding that DDX5 and DDX17 coactivate the myogenic regulatory factor MyoD and are required for skeletal muscle cell differentiation.[99] DDX5 has also been shown to coactivate the p53 tumor suppressor and to be required for the p53-dependent DNA damage response.[100] However, such a role is likely to be context-dependent since a recent study demonstrated that while DDX5 is required for p53-dependent *p21^{waf1}* induction and cell cycle-arrest it is not required for apoptosis induction,[101] suggesting that in certain cases DDX5 could have a pro-survival role. Furthermore, the finding that DDX5 induces expression of the cell cycle arrest gene *p21^{waf1}*,[101] and conversely *cyclin D1* in a different context,[91] suggests that DDX5, under different conditions, could have opposing effects on cell cycle progression. These findings underscore the idea that DDX5 function is highly dependent on context and presumably, post-translational modification. Additionally, a recent study found that DDX5 coactivates the vitamin D receptor and enhances its response to the activated vitamin D ligand, calcitrol, again suggesting an anti-proliferative role for DDX5 and proposing a possible p53-independent way of inducing *p21^{waf1}* expression.[102]

Sumoylation and acetylation have also been shown to modulate DDX5/DDX17 function as transcriptional regulators.[103-105] It is also clear that both DDX5 and DDX17 can act as transcriptional repressors,[106,107] with sumoylation enhancing their repressor activity in some, but not all, contexts,[103,104] implying further context- and possibly tumor-dependent regulation of their function.

A further complexity is provided by the recent finding that DDX5/DDX17 have dual and opposing roles in regulating the pro-migration transcription factor NFAT5: they enhance NFAT5 transcriptional activity and increase cell migration but they also modulate alternative splicing of NFAT5 leading to the inclusion of exon 5, which includes a translation termination codon and leads to nonsense-mediated decay.[108] Thus DDX5/DDX17 can both enhance NFAT5 transcriptional activity and, by regulating its splicing, reduce its protein expression level.

Other functions for DDX5 and DDX17 in more global modulation of transcription have been described. These include: (1) transcriptional "insulation" by DDX5 through interaction with CTCF, a DNA binding protein involved in chromatin

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organization, to avoid inappropriate activation or repression of genes;[109] (2) Estrogen-regulated promoter switching by DDX5 and DDX17 to modulate ERα-mediated transcription;[110] and (3) RNA clearance from chromatin to allow gene deactivation and possibly RNA export.[18,31] These would have important implications for context-dependent functions for DDX5/DDX17 and may, at least in part, explain the conflicting reports implying both oncogenic and tumor suppressor roles for these proteins.

Splicing/alternative splicing. DDX5 and DDX17 have been shown to be associated with the spliceosome and to function in pre-mRNA splicing.[111-113] Perhaps more interesting in terms of their potential role in cancer development are the reports demonstrating that they can regulate alternative splicing. Of particular interest are the data showing that DDX5 and DDX17 can modulate alternative splicing that is regulated by steroid hormone receptors, with DDX5 enhancing AR-mediated exon skipping[84] and DDX17 (but not DDX5) inhibiting ERα/ERβ-mediated exon skipping.[114,115] Furthermore, DDX5 was found to modulate alternative splicing of the H-Ras proto-oncogene, enhancing skipping of the alternative D (IDX) exon and thus altering the balance in favor of the more oncogenic p21 H-ras isoform.[116,117]

Recently, in a mouse model of tumor progression, DDX5 and DDX17 were found to contribute to tumor cell migration and invasion by regulating alternative splicing of several DNA-binding factors, including the epigenetic chromatin regulator *macroH2A1* histone (*mH2A1*).[118] Interestingly either DDX5 or DDX17 depletion inhibited cell migration/invasion, with simultaneous depletion of both proteins having an enhanced effect.

This study also demonstrated that the mH2A1.1 and mH2A1.2 isoforms of mH2A have opposing effects on the transcription of the redox metabolism gene, superoxide dismutase *SOD3*, which inhibits cell migration. DDX5 and DDX17 favored expression of mH2A1.2, which inhibits expression of SOD3. Thus, through modulation of *mH2A1* alternative splicing, DDX5/DDX17 could regulate redox metabolism and cell migration/invasion, critical factors in cancer progression and metastasis. In this respect it is important to note that the same study found that a high level of the *mH2A1.2* isoform was associated with a shorter metastasis-free disease survival in breast cancer.[118]

miRNA biogenesis. A DDX5/DDX17 function that is gaining considerable interest is their role in miRNA biogenesis. Several studies have demonstrated that DDX5 and DDX17 are components of the Drosha micro-processor complex and are important for the processing of certain subsets of miRNAs. Perhaps the most clear-cut evidence for the role of DDX5/DDX17 in miRNA biogenesis comes from a study that showed that transgenic mice in which either DDX5 or DDX17 had been knocked out showed defects in the processing of certain, but not all, miRNAs; interestingly DDX5 and DDX5 knockouts were associated with embryonic and post-natal lethality respectively, with the double knockout resulting in earlier embryonic lethality.[79] Expression of certain miRNAs was reduced in both *DDX5*$^{-/-}$ and *DDX17*$^{-/-}$ embryos while for one miRNA tested (miR-214) expression was reduced in *DDX17*$^{-/-}$ but not *DDX5*$^{-/-}$ embryos. Taken together, these findings support the idea that DDX5 and DDX17 share some functions but also have other non-redundant functions in the cell. Interestingly, DDX5 was also shown to unwind the Let-7 miRNA precursor duplex and to be important for Let-7-mediated silencing,[119] providing another mechanism by which it can modulate miRNA biogenesis.

It is established that deregulated miRNA expression can contribute to cancer development and progression (reviewed in ref. 120). Interestingly, DDX5 and DDX17 have been reported to modulate the association of p53,[121] ERα,[122] TGF-β and bone morphogenic protein (BMP)-specific SMAD signal transducers[123] to the Drosha complex, and to regulate the processing of subsets of miRNAs that play key roles in cancer progression. However, DDX5 and DDX17 have been implicated in promoting the processing of both oncogenic and tumor/growth-suppressor miRNAs: DDX5 was found to promote processing of the oncogenic miR-21 via TGF-β/BMP[123] but also of several growth suppressing miRNAs that are modulated by p53 (including miR16-1, miR-143 and miR-145).[121] On the other hand, in a different context, DDX5 and DDX17 appear to enhance ERα-mediated inhibition of miR16-1, miR-143 and miR-145 processing.[122] Such apparently opposing roles highlight the context dependence of DDX5/DDX17 function; e.g., expression of p53 and/or ERα. Furthermore, in basal breast cancer cells, DDX5 was found to regulate expression of several miRNAs including miR-21, miR-182 and Let-7 family miRNAs;[124] interestingly, siRNA knockdown of DDX5 or miR-182 inhibition resulted in actin cytoskeleton reorganization suggesting a role for DDX5 in cellular invasion through miR-182 regulation.

Ribosome biogenesis: rRNA processing. An additional finding from the DDX5/DDX17 knockout mouse study that described a role in Drosha miRNA processing was that *DDX17*$^{-/-}$ mouse embryo fibroblasts exhibited a reduced cell proliferation and an increase in cell death;[79] moreover in both *DDX5*$^{-/-}$ and *DDX17*$^{-/-}$ embryos there was a reduction of 5.8S rRNA expression, suggesting additional roles for DDX5 and DDX17 in rRNA processing. These findings are consistent with results obtained from DDX5/DDX17 siRNA knockdown from HeLa cells[94] and from DDX5 siRNA knockdown in Mouse Embryo Fibroblasts study.[95] The latter study also showed that DDX5 enhanced both the transcription of the 47S pre-rRNA and processing, underscoring the multi-functional roles of DDX5/DDX17. Furthermore, given that aberrant ribosome biogenesis can have profound effects on metabolism and cancer development/progression, these findings could have important implications for the potential role of DDX5 and DDX17 in cancer.

DEAD box RNA helicases in cancer: Is it all context? It is clear that DEAD box RNA helicases generally function as components of multi-protein complexes and that they do not act by simply unwinding RNA duplexes; indeed several have been shown to act as RNPases or to exhibit RNA annealing activity (reviewed in ref. 125). Furthermore, while DEAD box proteins clearly have ATP-dependent functions through their shared helicase core domain, they have additional ATP-independent roles that are presumably conferred through their interaction with protein partners via their non-conserved N- and C-terminal domains. This would allow DEAD box proteins to integrate different processes in RNA metabolism: for example they could couple transcription, RNA processing and RNA export through

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ordered and regulated interactions with different protein partners. Such multi-functionality would, however, be highly context-dependent and would depend on the availability of interacting partners.

There are several key issues that need to be addressed regarding the precise mechanism(s) of action of DEAD box proteins. For example, it is established that several of these proteins act as transcriptional co-regulators, modulating transcriptional initiation through their interactions with components of the transcription machinery at responsive promoters, although there is no evidence that they directly bind chromatin. However, it is unclear what determines whether they act as co-activators or co-repressors. Furthermore, the mechanisms by which they might couple transcriptional initiation to post-transcriptional processes remain to be elucidated: it is not known whether these proteins bind the nascent RNAs and then act as 'adaptor' molecules to recruit splicing or export factors to facilitate these processes. In this respect it would also be interesting to examine the importance of helicase activity in these events since it appears to be required for some but not all the reported functions. Similarly, the precise roles of DEAD box proteins in other processes, e.g., regulation of translation or miRNA biogenesis, are not fully understood and much of the evidence relies on their association with the respective protein complexes and the effects of overexpression or siRNA knockdown studies.

As discussed above, several DEAD box proteins are aberrantly expressed in cancer tissues as compared with matched normal tissue and in some cases (e.g., DDX5) they also appear to be differentially post-translationally modified, supporting the idea that alterations in protein levels or modification can impact on their role in cell proliferation and/or transformation. However, the precise role of DEAD box proteins will clearly also depend on their interacting partners, the expression and/or function of which may also be independently altered during cancer development. In this respect, changes in post-translational modification of DEAD box proteins will also influence their interactions with partners and their impact on different cellular processes, adding further complexity. Thus a given DEAD box protein could have a growth promoting or pro-proliferation role in some contexts and a growth- or tumor-suppressing role in others. This context dependence would clearly have profound implications for the consideration of DEAD box proteins as possible biomarkers or therapeutic targets in cancer. Therefore, before choosing to therapeutically target a specific DEAD box protein it will be important to consider the type, or indeed subtype, of cancer and the expression of other interacting partners, since the therapy could have opposing effects in different contexts. There is clearly much work to be done in this area.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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