REVIEW ARTICLE

The DEAD-box protein family of RNA helicases: sentinels for a myriad of cellular functions with emerging roles in tumorigenesis

Mohamed A. M. Ali[1]

Abstract

DEAD-box RNA helicases comprise a family within helicase superfamily 2 and make up the largest group of RNA helicases. They are a profoundly conserved family of RNA-binding proteins, carrying a generic Asp–Glu–Ala–Asp (D–E–A–D) motif that gives the family its name. Members of the DEAD-box family of RNA helicases are engaged in all facets of RNA metabolism from biogenesis to decay. DEAD-box proteins ordinarily function as constituents of enormous multi-protein complexes and it is believed that interactions with other components in the complexes might be answerable for the various capacities ascribed to these proteins. Therefore, their exact function is probably impacted by their interacting partners and to be profoundly context dependent. This may give a clarification to the occasionally inconsistent reports proposing that DEAD-box proteins have both pro- and anti-proliferative functions in cancer. There is emerging evidence that DEAD-box family of RNA helicases play pivotal functions in various cellular processes and in numerous cases have been embroiled in cellular proliferation and/or neoplastic transformation. In various malignancy types, DEAD-box RNA helicases have been reported to possess pro-proliferation or even oncogenic roles as well as anti-proliferative or tumor suppressor functions. Clarifying the exact function of DEAD-box helicases in cancer is probably intricate, and relies upon the cellular milieu and interacting factors. This review aims to summarize the current data on the numerous capacities that have been ascribed to DEAD-box RNA helicases. It also highlights their diverse actions upon malignant transformation in the various tumor types.

Keywords Carcinogenesis · Cellular processes · DEAD-box proteins · Oncogenes · RNA metabolism · Tumor suppressor genes

Introduction

Ribonucleic acid (RNA) helicases are profoundly conserved enzymes that utilize adenosine triphosphate (ATP) to bind or remodel RNA or ribonucleoprotein (RNP) complexes [1]. The DEAD-box protein family of RNA helicases belongs to superfamily 2 (SF2) and is by far the largest family of nucleic acid helicases [2]. The DEAD-box [a motif named after its amino acid sequence (Asp–Glu–Ala–Asp)] family of RNA helicases is characterized by the presence of several conserved motifs, including the signature DEAD sequence that gives the family its name. They are found in all three domains of life [3]. The most widely recognized function of DEAD-box proteins is to utilize cycles of ATP-binding and hydrolysis to catalyze conformational rearrangements of RNAs during their biogenesis or in the course of their cellular roles [4]. They have been appeared to play key, and frequently fundamental, roles in all aspects of cellular RNA metabolism that involve modulation of complex RNA structures or dissociation of enormous RNP complexes, e.g., transcription, RNA processing, RNA export, RNA degradation, ribosome biogenesis and translation [5]. Members of the DEAD-box family of RNA helicases share a profoundly conserved core containing twelve conserved motifs, including the signature DEAD motif; these motifs give the ATP hydrolysis and RNA-unwinding activities that have established them as RNA helicases [6]. How DEAD-box helicases achieve extraordinarily wide group of functional roles utilizing a virtually indistinguishable core has been a focal and longstanding inquiry in RNA biology. Emerging responses to this inquiry are multifaceted and incredibly influenced by the cellular milieu for any given DEAD-box helicase. So far, it is obvious that the molecular basis for the cellular role of

✉ Mohamed A. M. Ali
mohd_ali2@sci.asu.edu.eg

[1] Department of Biochemistry, Faculty of Science, Ain Shams University, Abbassia, Cairo 11566, Egypt

each enzyme lies in its biochemical capacity. Indeed, numerous DEAD-box proteins are multifunctional and have extra various functions in a scope of various cellular processes that are conferred by their distinct, less conserved, N- and C-terminal domains and dependent on their interactions with partner proteins [7].

DEAD-box proteins have been appeared to function as transcriptional co-regulators and regulators of post-translational modifications and are crucial in modulating numerous cellular signaling pathways [8]. Moreover, there have been various reports showing that DEAD-box proteins are implicated in processes that are key to cellular proliferation and/or malignant transformation; subsequently, it is not astonishing that dysregulation of expression or function of these proteins have possibly detrimental impacts on ordinary cellular homeostasis, and has ensnared in cancer development and/or progression. Indeed, DEAD-box helicases can function either as oncogenes or tumor suppressor genes in various cancer types [9–11]. To date, the data presented propose that the exact role of these proteins in cancer is probably tumor- and/or context dependent, and may be impacted by their interacting partners. Amassing evidence demonstrated that DEAD-box helicases can be viewed as promising targets for anticancer chemotherapy, but additionally that their utilization requires a more profound comprehension of the molecular mechanisms underlying their double function in cancer [12].

Here, I shall review the various functions that have been ascribed to the DEAD-box proteins and discuss how these proteins can act to boost or repress tumor development in various settings. I shall then portray the diverse DEAD-box helicase inhibitors accessible, illustrating the potential merits and possible caveats of their utilization as anticancer drugs.

The DEAD-box protein family of RNA helicases

RNA helicases are RNA-binding proteins that catalyze the ATP-dependent separation of RNA duplexes and the structural rearrangement of RNAs and RNP complexes in all aspects of RNA metabolism [13].

DEAD-box proteins constitute the largest family within the SF2 of helicases. The name "DEAD-box" originates from the single letter amino acid code Asp (D)–Glu (E)–Ala (A)–Asp (D) that is present in the profoundly conserved motif II (or Walker B motif) [14]. They are a ubiquitous protein family found in all realms of life, with more than 30 family members in humans (Table 1), and embroiled in nearly all events of RNA metabolism [5]. They participate in all cellular RNA-mediated processes by boosting RNA structural rearrangements to encourage folding and remodeling

transitions of RNAs and RNPs in an ATP-dependent way. Such dynamic rearrangements are essential for some, if not all, steps in the life of an RNA molecule [4].

Structural features of DEAD-box RNA helicases

The general architecture of the DEAD-box helicase family is very conservative. Members of the DEAD-box family contain a profoundly conserved helicase core that harbors the binding sites for ATP and RNA. The core is surrounded by variable auxiliary domains, which are believed to be crucial for the various functions of these enzymes [15] (Fig. 1).

The helicase core

All DEAD-box helicases share the profoundly conserved SF2 helicase core that comprises of two recombinase A (RecA, the bacterial recombination protein)-like domains, with at least 12 profoundly conserved sequence motifs (Q, I, Ia, Ib, Ic, II, and III in the N-terminal domain [domain 1, D1], and IV, IVa, V, Va, and VI in the C-terminal domain [domain 2, D2]) dispersed between the two RecA-like domains, where they line two inter-domain clefts that form the ATP- and RNA-binding sites, and contribute to ATP binding and hydrolysis, RNA binding and duplex unwinding [15]. The ATP interacts with residues from both domains, including residues from motifs Q, I, II and VI. Like the ATP-binding site, single-stranded RNA (ssRNA) binding to the helicase core includes interactions with residues from both helicase core domains, primarily from motifs Ia, Ib, Ic, IV, IVa and V. Obviously, residues in motifs III and Va are pivotal for shifting the state of ATP-binding to the RNA-binding site, and vice versa (Fig. 1). The network of interactions linking the ATP- and RNA-binding motifs is believed to be crucial for coupling ATP binding, hydrolysis, and product (adenosine diphosphate, ADP and inorganic phosphate, Pi) liberation to alterations in RNA affinity and bound RNA conformations [16].

The two helicase core domains are connected by an adaptable linker and can, thus, change their orientation to each other. Due to the separation of the helicase core domains by a comparatively long linker, DEAD-box helicases transit between the so-called "inactive open" and "active closed" conformations. In the absence of ATP and RNA, the DEAD-box helicase core adopts an open form, wherein the two helicase domains move freely as for each other and do not form inter-domain connections. Collaborative binding of ATP and RNA stimulates a switch from the pliable open conformation to the more inflexible closed form. In this compact form, a complicated interaction network is formed between the conserved motifs and the bound ATP and RNA. This

Table 1 Human DEAD-box RNA helicases

Symbol	Full name	Aliases	Cytogenetic location
DDX1	DEAD-box helicase 1	DBP-RB, UKVH5d	2p24.3
EIF4A1	Eukaryotic translation initiation factor 4A1	DDX2A, EIF-4A, EIF4A, eIF-4A-I, eIF4A-I	17p13.1
EIF4A2	Eukaryotic translation initiation factor 4A2	BM-010, DDX2B, EIF4A, EIF4F, eIF-4A-II, eIF4A-II	3q27.3
DDX3X	DEAD-box helicase 3 X-linked	CAP-Rf, DBX, DDX14, DDX3, HLP2, MRX102, MRXSSB	Xp11.4
DDX3Y	DEAD-box helicase 3 Y-linked	DBY	Yq11.221
DDX4	DEAD-box helicase 4	VASA	5q11.2
DDX5	DEAD-box helicase 5	G17P1, HLR1, HUMP68, p68	17q23.3
DDX6	DEAD-box helicase 6	HLR2, IDDILF, P54, RCK, Rck/p54	11q23.3
DDX10	DEAD-box helicase 10	Dbp4, HRH-J8	11q22.3
DDX17	DEAD-box helicase 17	P72, RH70	22q13.1
DDX18	DEAD-box helicase 18	Has1, MrDb	2q14.1
DDX19A	DEAD-box helicase 19A	DDX19-DDX19L, DDX19L	16q22.1
DDX19B	DEAD-box helicase 19B	DBP5, DDX19, RNAh	16q22.1
DDX20	DEAD-box helicase 20	DP103, GEMIN3	1p13.2
DDX21	DExD-box helicase 21	GUA, GURDB, RH-II/GU, RH-II/GuA	10q22.1
DDX23	DEAD-box helicase 23	PRPF28, SNRNP100, U5-100 K, U5-100KD, prp28	12q13.12
DDX24	DEAD-box helicase 24		14q32.12
DDX25	DEAD-box helicase 25	GRTH	11q24.2
DDX27	DEAD-box helicase 27	DRS1, Drs1p, HSPC259, PP3241, RHLP, dJ686N3.1	20q13.13
DDX28	DEAD-box helicase 28	MDDX28	16q22.1
DDX31	DEAD-box helicase 31	PPP1R25	9q34.13
DDX39A	DExD-box helicase 39A	BAT1, BAT1L, DDX39, DDXL, URH49	19p13.12
DDX39B	DExD-box helicase 39B	BAT1, D6S81E, UAP56	6p21.33
DDX41	DEAD-box helicase 41	ABS, MPLPF	5q35.3
DDX42	DEAD-box helicase 42	DDX42P, RHELP, RNAHP, SF3B8, SF3b125	17q23.3
DDX43	DEAD-box helicase 43	CT13, HAGE	6q13
DDX46	DEAD-box helicase 46	PRPF5, Prp5	5q31.1
DDX47	DEAD-box helicase 47	E4-DBP, HQ0256, MSTP162, RRP3	12p13.1
EIF4A3	Eukaryotic translation initiation factor 4A3	DDX48, Fal1, MUK34, NMP265, NUK34, RCPS, eIF-4A-III, eIF4A-III, eIF4AIII	17q25.3
DDX49	DEAD-box helicase 49	Dbp8, R27090_2	19p13.11
DDX50	DExD-box helicase 50	GU2; GUB; mcdrh; RH-II/GuB	10q22.1
DDX51	DEAD-box helicase 51		12q24.33
DDX52	DExD-box helicase 52	HUSSY19, ROK1	17q12
DDX53	DEAD-box helicase 53	CAGE, CT26	Xp22.11
DDX54	DEAD-box helicase 54	DP97	12q24.13
DDX55	DEAD-box helicase 55		12q24.31
DDX56	DEAD-box helicase 56	DDX21, DDX26, NOH61	7p13
DDX59	DEAD-box helicase 59	OFD5, ZNHIT5	1q32.1

configuration clarifies the robust excitation of ATP hydrolysis by RNA binding, the RNA-stimulated ATPase activity. Opening and closing of the two domains are believed to be important for the function of these enzymes [17].

DEAD-box proteins are commonly specific for ATPs for catalyzing duplex unwinding and for RNA-stimulated hydrolysis of the triphosphate [18]. This particularity is mainly given by the Q-motif, which sets up particular connections to adenine-specific functional groups; particularity for adenine nucleotides is given by a conserved glutamine in the Q-motif that hydrogen bonds with the Watson–Crick face of the base [19].

The RNA ties opposite the ATP-binding site, over the two helicase core domains [20]. The RNA-binding site is made out of a highly positively charged surface cleft, which can bind an ssRNA with five or more oligonucleotides. This RNA-binding area is supplemented by many extra positively charged residues, which can uphold the stabilization of the
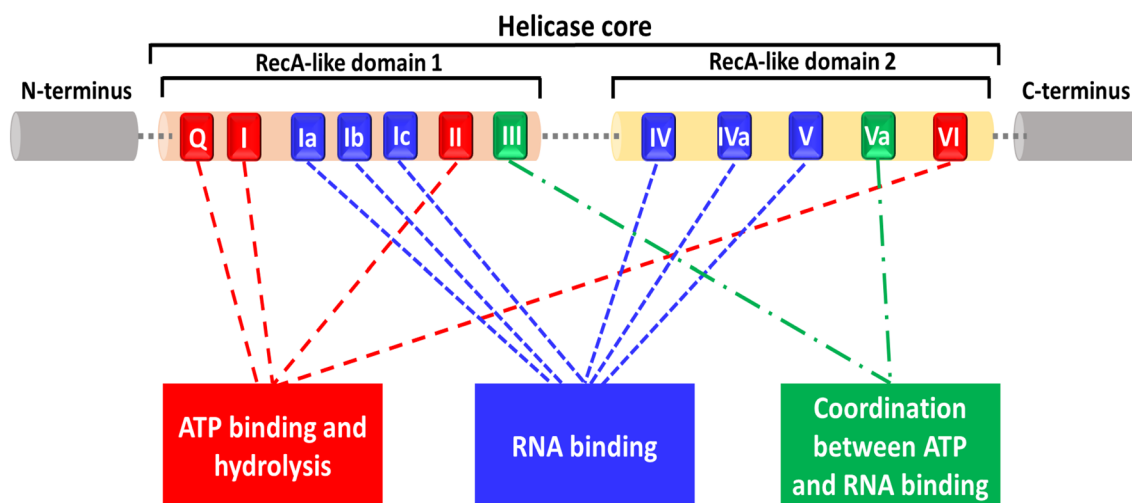
Fig. 1 Schematic representation showing domains and motifs common to the DEAD-box family of RNA helicases. The helicase core is composed of two RecA-like domains (domain 1 and domain 2), which contain conserved motifs involved in ATP binding and hydrolysis (red), RNA binding (blue), and communication between ATP-binding and RNA-binding sites (green). The variable N- and the C-terminus regions are also indicated (gray)

helicase–RNA complex [21]. The RNA-binding sites in the helicase core contact solely the sugar phosphate backbone of the RNA rather than the nucleotide bases, proposing that DEAD-box proteins bind to RNA substrates in a sequence-independent way [16]. Therefore, the residues in the helicase core give no known specificity for particular RNAs [22]. This is a merit for DEAD-box proteins that function as general RNA chaperones targeting several different RNAs [23].

The auxiliary domains

Even though DEAD-box helicases share a conserved core domain, variable N- and C-terminal regions contribute to the functional variety of this protein family. In the majority of DEAD-box helicases, the core is flanked by non-conserved C- and N-terminal extensions (Fig. 1), varying in length from a few to several hundred amino acids. These ancillary domains target the helicases to specific RNAs or proteins; the variety of these areas accounts for the vastness of function noted in this protein family. It is accordingly thought that these ancillary domains are crucial for the particular functions of a given DEAD-box helicase [1].

Cellular functions of DEAD-box proteins

DEAD-box proteins function throughout the lifetime of cellular RNAs from synthesis to unavoidable decay [1]. Because of their variety of binding and function, DEAD-box helicases possess focal and, in several cases, fundamental physiological roles in all facets of cellular RNA metabolism, including transcription, pre-mRNA splicing, microRNA

biogenesis, ribosomal RNA processing, ribosome biogenesis, RNA export, translation, and decay [24] (Fig. 2 and Table 2).

DDX1

DDX1 has been demonstrated to be implicated in diverse cellular processes, including mRNA processing, regulation of transcription and translation, RNA transport/clearance, and regulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcriptional activity.

### 3′-end processing of pre-mRNAs

In addition to its widespread dotted nucleoplasmic distribution, DDX1 is also found in discrete nuclear foci and is associated with the cleavage stimulation factor 64 kDa (CstF-64), proposing a role in 3′-end polyadenylation and cleavage of pre-mRNAs [25].

Regulation of transcription and translation

DDX1 has been shown to interact with poly(A) RNA and with the heterogeneous nuclear ribonucleoprotein K (hnRNP K), a multifunctional protein known to be embroiled in the regulation of transcription, translation, nuclear transport, and signal transduction [26].

RNA transport/clearance

DDX1, along with DDX3 and DDX5, has been recognized as a protein associated with kinesin family member 5 (KIF5)
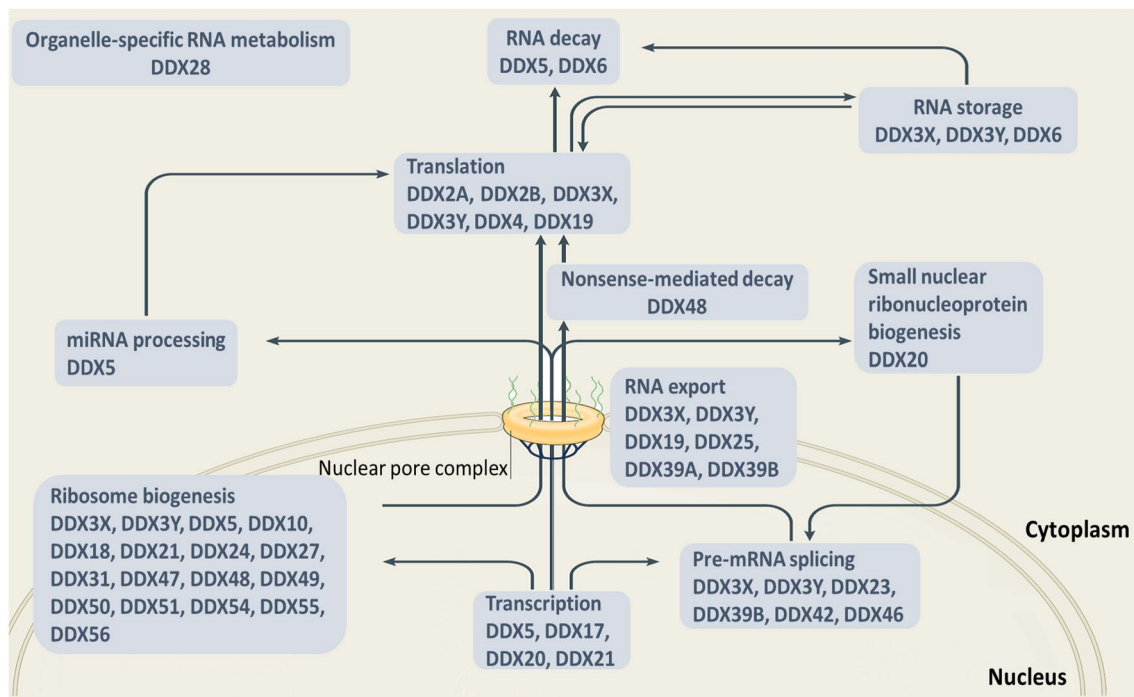
Fig. 2 Cellular processes involving DEAD-box proteins. RNA helicases of the DEAD-box family are involved in various different steps in RNA metabolism. In the nucleus, these include ribosome biogenesis, transcription and pre-mRNA splicing. In the cytoplasm, these include processes like miRNA processing, nonsense-mediated decay and translation, as well as organelle-specific RNA metabolism. At the interface between the nucleus and the cytoplasm, these enzymes are required for the directional transport of mRNA molecules. Human DEAD-box proteins that are involved in these processes are listed; many have been shown to be involved in several processes

in an RNA-transporting granule in neuronal dendrites, proposing a possible role in RNA transport [27].

An investigation demonstrating the re-distribution of DDX1 to ionizing radiation-induced foci and its co-localization with γ-H2AX (a phosphorylated variant of the H2A histone protein family) and phosphorylated ataxia telangiectasia mutated (ATM), combined with its capability to unwind RNA–DNA structures, propose a potential role for DDX1 in RNA clearance from DNA double-strand break locations, thereby facilitating the template-guided repair of transcriptionally active areas of the genome [28].

NF-κB-dependent transcription

DDX1 has been appeared to interact with the p65 subunit of NF-κB, thereby boosting NF-κB-dependent transcription, suggesting that DDX1 might function as a co-activator to promote NF-κB-mediated transcription activation [29].

DDX3

Various investigations have demonstrated that DDX3 functions in numerous cellular processes implicated in the regulation of gene expression. These include pre-mRNA splicing, mRNA export, transcription and translation [30].

Pre-mRNA splicing

DDX3 has been discovered to be associated with spliceosomes [31] and messenger ribonucleoproteins (mRNPs) [32], but whether DDX3 is effectively embroiled in splicing remains to be completely clarified.

mRNA export

DDX3 has been discovered to be associated with the major nuclear mRNA export receptor, Tip-associated protein (TAP), with mRNPs [33] and with RNA-transporting granules [27], shuttling from the nucleus to the cytoplasm. These reports propose that DDX3 is unlikely to be implicated in general mRNA export; rather it may be embroiled in the export of particular subclasses of cellular mRNAs and may, therefore, also be critical in regulating the translation of these mRNAs. Interestingly, DDX3 has been appeared to interact with another DEAD-box helicase, DDX5, and to affect its shuttling during mRNP export [34].

Transcription

Numerous investigations from various groups have revealed that DDX3 can regulate genes transcription. These include

Table 2 The multiple functions attributed to the DEAD-box proteins

DEAD-box protein	Function	Targets/context	References
DDX1	3′-end processing of pre-mRNAs	Associated with the cleavage stimulation factor CstF-64	[25]
	Regulation of transcription and translation	Interacts with poly(A) RNA and hnRNP K	[26]
	RNA transport/RNA clearance	Associated with kinesin KIF5 in RNA-transporting granules in neuronal dendrites	[27]
		Involved in RNA clearance from DNA double-strand break sites	[28]
	NF-κB-dependent transcription	Interacts with the p65 subunit of NF-κB	[29]
DDX3	Pre-mRNA splicing	Associated with mRNPs and spliceosomes	[31, 32]
	RNA export	Associated with the mRNP export receptor TAP	[33]
		Associated with RNA-transporting granules in neuronal dendrites	[27]
		Interacts with DDX5, thereby affecting its shuttling during mRNP export	[34]
	Transcription	Activation of IFNβ, p21waf1/cip1 and Snail transcription; inhibition of E-cadherin transcription	[35–37] [38]
	Translation	Can both promote and repress translation initiation	[39, 40]
DDX5 and DDX17	Transcription	DDX5 co-activates AR, Runx2, NF-κB, MyoD, p53 and vitamin D receptor	[43–45, 50, 51, 53]
		DDX5 up-regulates the expression of cyclin D1, c-Myc and genes required for DNA replication	[46–48]
		DDX5 activates the transcription of the Snail1	[49]
		DDX5 is required for p53 DNA damage response and activation of selective p53 target genes	[51, 52]
		DDX5/DDX17 can act as transcriptional repressors	[57]
		DDX5 and DDX17 can both enhance NFAT5 transcriptional activity and, by regulating its splicing, reduce its protein expression level	[58]
		DDX5 is involved in transcriptional insulation through interaction with CTCF	[59]
		DDX5/DDX17 regulate promoter switching to modulate ERα-mediated transcription	[60]
	Pre-mRNA splicing/alternative splicing	DDX5/DDX17 associate with spliceosomes, required for pre-mRNA splicing	[61, 62]
		DDX5/DDX17 regulate alternative splicing and exon skipping	[63–65]
	miRNA biogenesis	DDX5 /DDX17 implicated in miRNA processing of subsets of miRNAs	[66–70]
DDX6	Translation repression/RNA degradation	Required for P-body formation and translational repression	[71]
		Interact with Ago1 and Ago2; associated with RISC; important for miRNA-induced translation repression	[72]
		Associated with decapping and deadenylase complexes	[73]
		Can promote mRNA degradation	[74]
	Cell cycle progression/proliferation	Required for S-phase progression and cell viability in vitro	[75, 76]
		Required for proliferation in xenograft models	[76]
DDX21	Transcription	Interacts with c-Jun and acts as a co-factor for c-Jun-activated transcription	[77]
	rRNA processing	Implicated in 18 and 28 S rRNA production	[78]

activation of the interferon-β (IFNβ) [35], the cell cycle arrest gene p21waf1/cip1 [36] and the transcription factor Snail [37] promoters, and inhibition of the E-cadherin promoter [38]. It has been shown that DDX3 is recruited to the IFNβ, E-cadherin and the p21waf1/cip1 promoters [35, 36, 38], proposing that DDX3 functions in transcriptional

initiation. Likewise, the DDX3-dependent impact on Snail transcription in the presence of histone deacetylase (HDAC) inhibitors [37] is consistent with DDX3 being implicated in initiation of Snail transcription. Interestingly, DDX3 seems to work in subtly various manners in regulating transcription of these genes. For instance, activation of the IFNβ promoter

seems to be independent of ATPase or RNA helicase activity [35]; whereas, activation of the p21waf1/cip1 promoter requires ATPase, but not RNA helicase activity [36], proposing promoter- or context-dependent impacts.

Translation

Many studies have reported interactions between DDX3 and proteins implicated in translation initiation. Nevertheless, there have been other inconsistent data: for instance, one investigation revealed that DDX3 inhibits cap-dependent translation by binding and repressing eukaryotic translation initiation factor 4E (eIF4E) [39]; another one proposed that DDX3 boosts translation of particular mRNAs that contain secondary structures in their 5′-untranslated region (5′-UTR) via interaction with eukaryotic translation initiation factor 4F (eIF4F) [40]. Consequently, the exact function of DDX3 in translation might be modulated by other factors or conditions in the cell.

DDX5 and DDX17

DDX5 and the profoundly related DDX17 have been appeared to function in various processes in the cell, including transcription regulation, pre-mRNA splicing/alternative splicing, and miRNA biogenesis [41].

Regulation of transcription

There is currently an enormous body of evidence showing that DDX5 and DDX17 function as coactivators of transcription factors. To date, a significant proportion of the work in this area has been conducted on DDX5; nonetheless, plainly, DDX17 also functions as a regulator of transcription, with certain functions that are distinguished from those of DDX5. It has been shown that DDX5 and DDX17 are recruited to responsive promoters and function, partially, by modulating transcriptional initiation. Strikingly, DDX5/DDX17 RNA helicase activity seems to be required for transcriptional regulation in some, but not all, cases, proposing that the exact role of DDX5/DDX17 in transcription may be reliant on the promoter context and/or on other interacting factors [42]. DDX5 has been demonstrated to coactivate androgen receptor (AR) [43], Runt-related transcription factor 2 (RUNX2) [44], the NF-κB transcription factor p50 [45], and to up-regulate expression of cyclin D1, c-Myc consistent with β-catenin activation [46, 47] as well as genes required for DNA replication [48]. Furthermore, DDX5 has been shown to activate transcription of the Snail1 gene by displacing HDAC from the Snail1 promoter [49]. A pro-differentiation role has been proposed by the finding that DDX5 and DDX17 coactivate the myogenic regulatory factor myoblast determination protein 1 (MyoD) and are required for skeletal muscle cell differentiation [50]. DDX5 has also been found to coactivate the p53 tumor suppressor and to be required for the p53-dependent DNA damage response [51]. Nonetheless, such a function is most probably context-dependent since an earlier report showed that whilst DDX5 is needed for p53-dependent p21waf1/cip1 induction and cell-cycle arrest, it is not needed for apoptosis induction [52], proposing that, in specific cases, DDX5 could have a pro-survival role. Besides, the finding that DDX5 actuates expression of the cell cycle arrest gene p21waf1/cip1 [52], and on the contrary cyclin D1 in a different context [47], proposes that DDX5, under various conditions, could have opposing influences on cell cycle progression. These discoveries affirm the notion that DDX5 function is profoundly reliant on context and probably, post-translational modification. Moreover, a previous report demonstrated that DDX5 co-activates the vitamin D receptor and boosts its response to the activated vitamin D ligand, calcitriol, again proposing an anti-proliferative role for DDX5 and suggesting a potential p53-independent manner of stimulating p21waf1/cip1 expression [53]. Sumoylation and acetylation have additionally been demonstrated to modulate DDX5/DDX17 function as transcriptional regulators [54–56]. It is additionally obvious that both DDX5 and DDX17 can function as transcriptional repressors [57], with sumoylation promoting their repressor activity in some, but not all, contexts [54, 55], suggesting further context- and potentially tumor-dependent regulation of their function. A further intricacy is given by the finding that DDX5/DDX17 have double and contradicting roles in regulating the pro-migration transcription factor nuclear factor of activated T-cells 5 (NFAT5): they boost NFAT5 transcriptional activity and increase cell migration but they additionally modulate alternative splicing of NFAT5, resulting in the inclusion of exon 5, which includes a translation termination codon and results in nonsense-mediated decay [58]. Consequently, DDX5/DDX17 can both boost NFAT5 transcriptional activity and, by regulating its splicing, decrease its protein expression level. Different roles for DDX5 and DDX17 in more global modulation of transcription have been reported. These include: (1) transcriptional "insulation" by DDX5 via interaction with CCCTC-binding factor (CTCF), a DNA-binding protein implicated in chromatin organization, to avert improper activation or inhibition of genes [59]; and (2) estrogen-regulated promoter switching by DDX5 and DDX17 to modulate estrogen receptor alpha (ERα)-mediated transcription [60].

pre-mRNA splicing/alternative splicing

DDX5 and DDX17 have been demonstrated to be associated with the spliceosome and to function in pre-mRNA splicing [61, 62]. Probably, more striking are the reports showing that they can regulate alternative splicing. Exceptionally

compelling are the observations indicating that DDX5 and DDX17 can modulate alternative splicing that is regulated by steroid hormone receptors, with DDX5 enhancing AR-mediated exon skipping [43] and DDX17 (but not DDX5) repressing ERα/ERβ-mediated exon skipping [63]. Besides, DDX5 has been found to modulate alternative splicing of the H-Ras proto-oncogene, promoting skipping of the alternative intron-D-exon (IDX) exon, thereby omitting this exon from the H-Ras mRNA, and hence changing the balance in favor of the more oncogenic p21 H-ras isoform [64]. Formerly, DDX5 and DDX17 have been shown to contribute to tumor cell migration and invasion by regulating alternative splicing of multiple DNA-binding factors, including the epigenetic chromatin regulator macroH2A1 histone (mH2A1). Strikingly, either DDX5 or DDX17 depletion hindered cell migration/invasion, with synchronous depletion of both proteins possessing a boosted impact. This investigation additionally showed that the mH2A1.1 and mH2A1.2 isoforms of mH2A have opposing influences on the transcription of the redox metabolism gene, superoxide dismutase 3 (SOD3), which represses cell migration. DDX5 and DDX17 favored expression of mH2A1.2, which hinders expression of SOD3. Accordingly, via modulation of mH2A1 alternative splicing, DDX5/DDX17 could regulate redox metabolism and cell migration/invasion [65].

miRNA biogenesis

DDX5 has been appeared to unwind the Let-7 miRNA precursor duplex and to be critical for Let-7-mediated silencing [66], giving a mechanism by which it can modulate miRNA biogenesis. It has been confirmed that dysregulated miRNA expression can contribute to cancer development and progression [67]. Strikingly, DDX5 and DDX17 have been reported to modulate the association of p53 [68], transforming growth factor beta (TGF-β) and bone morphogenetic protein (BMP)-specific SMAD signal transducers [69] to the Drosha complex, and to regulate the processing of subclasses of miRNAs that play indispensable roles in cancer progression. Nonetheless, DDX5 and DDX17 have been embroiled in enhancing the processing of both oncogenic and tumor/growth suppressor miRNAs: DDX5 has been found to boost processing of the oncogenic miR-21 via TGF-β/BMP [69] but additionally of numerous growth-suppressing miRNAs that are modulated by p53 (including miR16-1, miR-143 and miR-145) [68]. Such obviously contradicting functions emphasize the context reliance of DDX5/DDX17 function. Moreover, in basal breast cancer cells, DDX5 has been shown to regulate the expression of many miRNAs, including miR-21, miR-182 and Let-7 family miRNAs; strikingly, small interfering RNA (siRNA) knockdown of DDX5 or miR-182 repression led to actin cytoskeleton reorganization, proposing a function for DDX5 in cellular invasion through miR-182 regulation [70].

DDX6

Translational repression and RNA degradation

It has been shown that DDX6 helicase activity is required for translation inhibition. Nevertheless, whilst DDX6 helicase activity has been demonstrated to be required for P-body assembly, the C-terminal domain has been discovered to be adequate for translational suppression, proposing that ATP-dependent conformational alterations in DDX6 and modulation of its binding to protein partners may be critical in regulating translation [71]. This suggests that DDX6 is multifunctional and has helicase-dependent and -independent roles that rely upon interaction with other partners. Strikingly, DDX6 has additionally been shown to interact with the Argonaute proteins Ago1 and Ago2, associate with the RNA-induced silencing complex (RISC), and to be pivotal for miRNA-induced, but not siRNA-induced, translational inhibition, proposing a further mechanism by which DDX6 may suppress translation [72]. It has been demonstrated that DDX6 roles in mRNA decapping, giving a mechanism by which it can regulate translation of mRNAs via RNA degradation [73]. This observation is upheld by prior findings, which demonstrate that the human DDX6 is bound to inhibited mRNAs at numerous points and suggests that this binding helps their localization to P-bodies and the recruitment of decapping complexes [74].

Regulation of cell cycle progression and proliferation

Multiple investigations have suggested that DDX6 functions as a positive regulator of cell cycle progression: two independent reports exhibited that siRNA knockdown of DDX6 led to S-phase cell-cycle arrest [75, 76]. Besides, these investigations indicated that siRNA knockdown of DDX6 brought about a decrease in cell viability [75], as well as an augmentation in cell apoptosis and a decrease in their ability to form tumors in xenograft models [76].

DDX21

DDX21 has been appeared to interact straightforwardly with the transcription factor c-Jun, and to partake in c-jun-mediated transcriptional activation of target genes [77]. DDX21 has additionally been recognized as a nucleolar protein regulating rRNA processing. Undoubtedly, knockdown of DDX21 has been shown to hinder 18S and 28S rRNA creation, and slowed down cell proliferation [78].

Relationships of DEAD-box RNA helicases with carcinogenesis

The DEAD-box RNA helicases play critical roles in various cellular processes that are ordinarily deregulated in cancers, including transcription, pre-mRNA processing/alternative splicing and miRNA processing [11]. Moreover, their capability to interact with a wide range of factors and function as multifunctional proteins can possibly affect numerous different processes [10]. There is compelling evidence to demonstrate that altered regulatory signaling pathways contribute to tumorigenesis, proliferation, invasion and metastasis of malignant cells. DEAD-box RNA helicases have been found to function as transcriptional co-regulators and regulators of post-translational modifications, and are important in modulating various cellular signaling pathways [8]. Accordingly, dysregulation of functionally various DEAD-box helicases can have injurious consequences on normal cellular homeostasis, and could have significant involvements in cancer development and progression [79]. Numerous DEAD-box RNA helicases have been discovered to be embroiled in cancer development because of their noted genomic amplification or deregulated expression. Also, a mounting number of these proteins have been demonstrated to be implicated in the regulation of, or the molecular interaction with, molecules involved in cellular proliferation or transformation. Additionally, other DEAD-box helicases participate in fusion transcripts resulting from cancer-associated chromosomal translocations. These observations bring up the inquiry of whether DEAD-box helicases can contribute to cancer development/progression [9].

DDX1

One of the primary signs that DDX1 might be implicated in tumor development originated from studies that it is overexpressed and co-amplified with the MYCN gene in neuroblastoma and retinoblastoma [80–83]. The observation that co-amplification of DDX1 and MYCN was more recurrent in higher stages of neuroblastoma and was associated with a considerable decrease in disease-free survival compared with those with only MYCN amplification [84] proposed that DDX1 has oncogenic properties. This thought has been upheld by a later investigation of testicular tumorigenesis, which indicated that DDX1 is a pivotal factor required for testicular tumorigenesis, slightly through the transcriptional activation of stem cell-associated genes localized on chromosome 12p [85]. Consistently, in an investigation of breast cancer gene expression and tissue microarrays, DDX1 RNA overexpression and increased cytoplasmic DDX1 protein have been shown to be correlated with early recurrence, proposing that DDX1 might be an independent prognostic marker for early recurrence in breast cancer [86]. Nonetheless, there have been several contradicting studies regarding the role of DDX1 in tumor development. For instance, in one investigation, high DDX1 expression in neuroblastoma has been demonstrated to be correlated with better survival [87]; whereas, another report found that DDX1 expression was correlated with improved local relapse-free , distant metastasis-free and overall survival in patients diagnosed with early-stage node-negative breast cancer [88], proposing a potential tumor suppressor role for DDX1. Nevertheless, a former study found no evidence of any impact of DDX1 amplification on prognosis of patients with MYCN-amplified neuroblastomas [89], whilst other studies proposed that the prognostic effect of DDX1 amplification/overexpression on MYCN is diverse among various subgroups [90, 91], giving a potential clarification for the conflicting findings acquired from the different reports. Consistent with a possible tumor suppressor role, DDX1 has been shown to repress ovarian tumor progression, with low DDX1 levels have been demonstrated to be correlated with poor clinical outcome in patients with serous ovarian cancer [92]. Even though the majority of studies show an oncogenic role for DDX1 in tumor development, a significant part of the evidence is occasional instead of mechanistic. Hence, its exact role might rely both upon the cancer type (or even subtype), therapeutic regimens, as well as context: i.e., the expression of other factors that might affect both DDX1 role and, independently, the therapy selected for the particular cancer (Table 3).

DDX2

There are three paralogs of eukaryotic initiation factor 4A (eIF4A), eIF4A1 (DDX2A), eIF4A2 (DDX2B), and eIF4A3. In spite of the fact that eIF4A1 and eIF4A2 share nearly 90% homology, they are functionally distinguished, with contradicting roles in cancers. The primary indication that DDX2A might be involved in cancer development came from an in vitro investigation, which showed consistent overexpression of DDX2A mRNA in human melanoma cells [93]. Undoubtedly, anti-sense-mediated down-regulation of DDX2A in melanoma cell lines brought about suppression of proliferation, proposing that DDX2A may play a role in melanoma carcinogenesis [94]. Deregulation of DDX2A is not limited to melanoma; it has additionally been shown to be up-regulated in hepatocellular carcinoma (HCC) [95]. Also, as the malignant phenotype is hugely the result of deregulated gene expression, transformed cells rely upon an altered translational milieu wherein pro-oncogenic mRNAs are translationally up-regulated. Such mRNAs have been

Table 3 Dual role of DEAD-box helicases as oncogenes or oncosuppressors in various cancer types

DEAD-box helicase	Cancer type	Role(s)	Possible pathways and mechanisms	References
DDX1	Neuroblastoma	Oncogene/TSG	Oncogene: overexpressed and co-amplified with MYCN gene TSG: DDX1 overexpression is associated with better survival	[81–84] [87]
	Retinoblastoma	Oncogene	Overexpressed and co-amplified with MYCN gene	[80, 83]
	Testicular carcinoma	Oncogene	Required for testicular tumorigenesis, partially through the transcriptional activation of stem cell-associated genes	[85]
	Breast cancer	Oncogene/TSG	Oncogene: DDX1 overexpression is associated with early recurrence TSG: DDX1 overexpression is associated with improved local relapse-free-, distant metastasis-free- and overall survival	[86] [88]
	Ovarian cancer	TSG	Inhibits ovarian tumor progression; low DDX1 expression is associated with poor clinical outcome	[92]
DDX2	Melanoma	Oncogene	DDX2A overexpression	[93, 94]
	Hepatocellular carcinoma	Oncogene	DDX2A up-regulation	[95]
	Breast cancer	Oncogene	Preferential DDX2A-mediated translation of genes involved in pro-oncogenic signaling	[97]
	Endometrial cancer	Oncogene	DDX2A overexpression	[98]
	Cervical cancer	Oncogene	DDX2A is overexpression	[99]
DDX3	Hepatocellular carcinoma	Oncogene/TSG	Oncogene: acts as a cellular transforming gene in hepatocarcinogenesis TSG: down-regulates cyclinD1 and up-regulates p21 impeding cell cycle progression TSG: activates the expression of tumor-suppressive miRNAs	[106] [130] [134]
	Colorectal cancer	Oncogene/TSG	Oncogene: increases KRAS transcription via the β-catenin/ZEB1 signaling pathway Oncogene: Wnt/β-catenin pathway Oncogene: activates β-catenin/TCF signaling via the CK1ε/Dvl2 axis Oncogene: increases cell aggressiveness via the KRAS/HIF-1α/YAP1/SIX2 cascade TSG: DDX3 down-regulation causes Snail up-regulation with decreased E-cadherin expression and reduced cell aggregation	[109] [107] [108] [129] [132]
	Lung cancer	Oncogene/TSG	Oncogene: Wnt/β-catenin axis TSG: p53/p21 pathway TSG: MDM2/Slug/E-cadherin pathway	[112] [131] [133]
	Breast cancer	Oncogene	Promotes oncogenesis through HIF-1α/DDX3/E-cadherin signaling pathway	[38, 110, 127, 128]
	Ewing sarcoma	Oncogene	DDX3 knockdown resulted in decreased survival and tumorigenicity of Ewing sarcoma cells	[115]
	Gallbladder carcinoma	Oncogene	Positive DDX3 expression is associated with poor prognosis	[113]

Table 3 (continued)

DEAD-box helicase	Cancer type	Role(s)	Possible pathways and mechanisms	References
	Pancreatic ductal adenocarcinoma	Oncogene	Positive DDX3 expression is associated with poor clinical outcome	[114]
	Medulloblastoma	Oncogene	Mutant DDX3 in combination with mutant β-catenin strengthen transactivation of a TCF promoter and enhance cell viability	[116]
	Chronic lymphocytic leukemia	Oncogene	Patients with mutated DDX3 exhibited a poor prognosis and a shorter survival	[117, 118]
	Natural killer (NK)/T-cell lymphoma	Oncogene	DDX3 mutants exhibited loss of suppressive effects on cell cycle progression and transcriptional activation of NF-κB and MAPK pathways	[119]
DDX5	Colorectal cancer	Oncogene	DDX5 is overexpressed and poly-ubiquitylated	[137]
	Gastric cancer	Oncogene	DDX5 induces gastric cancer cell proliferation via mTOR signaling pathway	[138]
	Esophageal cancer	Oncogene	Knockdown of DDX5 suppresses esophageal cancer cells proliferation and invasion through inhibiting the Wnt/β-catenin signaling pathway	[139]
	Breast cancer	Oncogene	DDX5 regulates a subset of microRNAs including miR-21 and miR-182; knockdown of DDX5 results in reorganization of actin cytoskeleton and reduction of cellular proliferation DDX5 is regulated by β-catenin/TCF4 to maintain a positive-feedback loop in control of breast cancer progression DDX5 stimulates the expression of the oncogenic protein kinase Polo-like kinase-1 (PLK1)	[70] [140] [141]
	Ovarian cancer	Oncogene	DDX5 is overexpressed	[142]
	Prostate cancer	Oncogene	DDX5 acts as androgen receptor transcriptional co-activator; DDX5 is overexpressed in prostate cancer DDX5 supports β-catenin and RNA polymerase II during androgen receptor-mediated gene transcription	[43] [143]
	Non-small-cell lung cancer	Oncogene	DDX5 induces proliferation and tumorigenesis of non-small-cell lung cancer cells by activating β-catenin signaling pathway	[144]
	Head and neck squamous cell carcinoma	Oncogene	DDX5 is overexpressed; DDX5 is involved in the malignant transformation or progression of HNSCC	[145]
	Cutaneous squamous cell carcinoma	Oncogene	DDX5 is overexpressed; DDX5 is involved in the development and progression of CSCC	[146]
	Glioma	Oncogene	DDX5 induces glioma tumor growth through binding with NF-κB p50, regulating NF-κB p50 nucleus accumulation and transcription activity	[45]
	Multiple myeloma	Oncogene	DDX5 is overexpressed; DDX5 is involved in myeloma tumorigenesis	[147]

Table 3 (continued)

DEAD-box helicase	Cancer type	Role(s)	Possible pathways and mechanisms	References
	T-cell acute lymphoblastic leukemia	Oncogene	DDX5 induces efficient Notch-mediated transcription in leukemic cells	[148]
	Acute myeloid leukemia	Oncogene	Inhibition of DDX5 expression slows AML cell proliferation in vitro and AML progression in vivo; Inhibition of DDX5 expression induces apoptosis of AML cells via induction of reactive oxygen species	[149]
	Hepatocellular carcinoma	TSG	DDX5 is down-regulated; low DDX5 expression is associated with poor prognosis	[150]
DDX5/DDX17	Colon cancer	Oncogene	DDX5 and DDX17 are overexpressed; DDX5 and DDX17 contribute to colon cancer by directly up-regulating β-catenin-regulated genes and indirectly by down-regulating the growth suppressor p21(WAF1/CIP1)	[166]
	Breast cancer	Oncogene	DDX5 and DDX17 are overexpressed DDX5 and DDX17 act as transcriptional co-activators of ERα DDX5 and DDX17 act as transcriptional co-regulators of ER	[55, 167] [167] [168]
	Prostate cancer	Oncogene	DDX5 and DDX17 act as transcriptional co-regulators of AR	[168]
DDX6	Neuroblastoma, glioblastoma, rhabdomyosarcoma and lung cancer	Oncogene	DDX6 is overexpressed	[171]
	Colorectal cancer	Oncogene	DDX6 is overexpressed; DDX6 facilitates c-Myc translation, thereby increasing the synthesis of c-Myc protein	[172, 173]
	Hepatocellular carcinoma	Oncogene	DDX6 is overexpressed	[174]
	Nodal marginal zone lymphoma	Oncogene	A t(11;14) involving IGH and DDX6 provides an evidence for a contribution of DDX6 to lymphomagenesis by deregulation of BCL6	[181]
DDX10	Breast cancer	Oncogene	RNAi-mediated suppression of DDX10 leads to inhibition of breast cancer cell growth	[183]
	Myeloid malignancies	Oncogene	NUP98-DDX10 fusion interferes with the normal functions of NUP98 in the synthesis and/or transport of proteins involved in myelopoiesis	[184]
DDX20	Breast cancer	Oncogene	DDX20 expression is up-regulated and correlated with patient survival; DDX20 plays a critical role in driving metastasis in breast cancer cells through DDX20–NF-κB–MMP9 axis	[189, 190]
	Prostate cancer	Oncogene	DDX20 is overexpressed and high DDX20 expression induces the proliferation and metastatic potential of prostate cancer cells through the NF-κB pathway	[191]
	Hepatocellular carcinoma	TSG	DDX20 expression is down-regulated; DDX20 inhibits NF-κB activity by regulating the function of the NF-κB-suppressing miRNA-140 in order to inhibit liver cancer progression	[192–194]

Table 3 (continued)

DEAD-box helicase	Cancer type	Role(s)	Possible pathways and mechanisms	References
DDX21	Breast cancer	Oncogene	DDX21 promotes tumorigenesis by inducing activator protein 1 (AP-1) transcriptional activity and rRNA processing	[195]
DDX41	Myeloid neoplasms	TSG	DDX41 mutations cause altered pre-mRNA splicing and RNA processing	[196–200]
DDX43	Breast cancer	Oncogene	DDX43 is overexpressed; DDX43 expression is associated with aggressive clinico-pathological features and poor prognosis	[202]
	Acute myeloid leukemia	TSG	DDX43 promoter hypomethylation correlates with DDX43 expression, and predicts favorable clinical outcome	[203]
DDX53	Gastric cancer	Oncogene	DDX53 is overexpressed; DDX53 promoter hypomethylation is associated with DDX53 overexpression, and contributes to carcinogenesis	[205]

demonstrated to have longer and more structured 5′-UTRs requiring high levels of eIF4A helicase activity for effective translation [96]. Strikingly, deregulation of mRNA unwinding has been shown to contribute to the malignant phenotype in breast cancer through preferential DDX2A-mediated translation of a group of genes implicated in pro-oncogenic signaling, with DDX2A has been recognized as an independent predictor of poor outcome in breast cancer [97]. Moreover, DDX2A overexpression has additionally been demonstrated in endometrial and cervical cancers [98, 99]. Dissimilar to DDX2A, DDX2B has been shown to have tumor suppressor-like roles with elevated expression linked to improved survival outcome, potentially through DDX2B-dependent anti-proliferative impacts via miRNA-mediated gene regulation [100] (Table 3).

DDX3

Lately, DDX3 is getting growing interest because of its fundamental roles in cancer progression. As a 'dual-edged sword' gene, DDX3 either induces cancer progression or functions as a tumor suppressor [101, 102]. Indeed, DDX3 has been demonstrated to have double functions and can be an oncogene or a tumor suppressor in various cancer types, enhancing or inhibiting cancer progression [103] (Table 3). The exact function of DDX3 in cancer might be tumor and/or context dependent and is also likely to be reliant on the availability of other factors that regulate transcription [104, 105].

DDX3 as an oncogene

The primary proposition that DDX3 can function as an oncogene originated from an investigation of HCC, which revealed overexpression of DDX3 mRNA in a panel of HCC tissues, and indicated that ectopic expression of DDX3 invigorated anchorage-independent growth of HCC cells, a sign of cell transformation [106]. These observations have been upheld by findings from a previous report demonstrating that overexpression of DDX3 inhibited E-cadherin expression and stimulated an epithelial-mesenchymal-like transformation, increased motility and invasive properties in breast cancer cell lines [38]. In colorectal tumors, high cytoplasmic DDX3 expression has been shown to be associated with nuclear β-catenin expression, a marker of activated Wnt signaling. Indeed, DDX3 knockdown in colorectal cancer cell lines brought about decreased proliferation and led to a G1 arrest, confirming a possible oncogenic function of DDX3 in colorectal cancer [107]. In addition, DDX3 has been appeared to induce tumor invasion in colorectal cancer by β-catenin/T-cell factor (TCF) activation through the casein kinase 1ε/dishevelled segment polarity protein 2 (CK1ε/Dvl2) axis [108]. Moreover, DDX3 has been shown to enhance KRAS-mediated tumor growth and invasion in colon cancer cells by elevating KRAS transcription through the β-catenin/zinc finger E-box-binding homeobox 1 (ZEB1) axis [109]. More recently, DDX3 expression has been demonstrated to be up-regulated in distant breast cancer metastases, and to associate with worse survival [110]. Likewise, nuclear DDX3 expression has been shown to be associated with worse overall survival in both colorectal

and breast cancer [111]. Also, DDX3 has been found to be overexpressed in lung cancer, and DDX3 up-regulation has been demonstrated to be correlated with poor survival in lung cancer patients [112]. Additionally, positive DDX3 expression has been demonstrated to be correlated with bad prognosis in gallbladder cancer [113] and pancreatic ductal adenocarcinoma [114]. In the majority of sarcomas, increased DDX3 expression is common and silencing DDX3 expression has been demonstrated to decrease survival and carcinogenesis of Ewing sarcoma cells. Furthermore, DDX3 suppression changed the Ewing sarcoma cellular proteome, particularly proteins implicated in DNA replication, mRNA translation and proteasome function [115]. Notably, the mutant DDX3 has been affirmed to possess oncogenic roles in medulloblastoma [116], chronic lymphocytic leukemia (CLL) [117, 118] and natural killer (NK)/T-cell lymphoma [119]. In medulloblastomas, frequent somatic mutations have been detected in DDX3, with the mutant DDX3, in conjunction with mutant, but not wild-type, β-catenin, has been demonstrated to potentiate transactivation of TCF promoter and enhance cell viability [116]. DDX3 mutants have additionally been identified in CLL, with patients harboring the mutations exhibited a bad prognosis and a lower survival [117]. In a later report, frequent truncated DDX3 mutations have additionally been detected in CLL, with DDX3 mutants have been considerably identified in relapsed cases [118]. In NK/T-cell lymphoma patients, somatic DDX3 mutations have been identified, with DDX3 mutants showed diminished RNA-unwinding activity, loss of suppressive impacts on cell cycle progression in NK cells and transcriptional activation of NF-κB and mitogen-activated protein kinase (MAPK) pathways. Interestingly, patients with DDX3 mutations exhibited a bad prognosis [119]. DDX3 has additionally been detected as a myeloid/lymphoid or mixed-lineage leukemia translocated to 10 (MLLT10) fusion partner in pediatric T-cell acute lymphoblastic leukemia (T-ALL) [120].

DDX3-mediated signaling pathways to promote cancer progression DDX3 has been found to induce translation initiation of cyclin E1, consequently facilitating G1/S transition and promoting cell growth [121]. Other reports have proposed that DDX3 possesses an anti-apoptotic role. It has been shown to be critical in preventing tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis by associating with the TRAIL receptor 2 (TRAILR2, also known as death receptor 5 [DR5]) and preventing apoptotic signaling [122]; this observation has been upheld by findings revealing that DDX3 siRNA knockdown increased TRAILR2-mediated apoptosis [123]. Indeed, DDX3 has been demonstrated to partake in multiple pathways, whose dysregulation is frequently linked to malignant transformation.

Wnt/β-catenin pathway The DDX3/Wnt/β-catenin signaling pathway has been shown to play a crucial function in tumor invasion. DDX3 straightforwardly binds to CK1ε to invigorate its kinase activity, and further enhance phosphorylation of the scaffold protein Dvl, hence, facilitating β-catenin translocation into the nucleus in a Wnt-dependent way, showing a function of DDX3 as a regulator of Wnt-β-catenin network [124]. In addition, DDX3 has been demonstrated to increase protein levels of both Rac1 and β-catenin, thereby induces Wnt signaling to modulate cell adhesion, motility and metastasis, showing a function of the DDX3–Rac1–β-catenin regulatory axis in modulating the expression of Wnt/β-catenin target genes [125] (Fig. 3a).

DDX3/Snail/E-cadherin pathway The transcription factor Snail has been demonstrated to interact with diverse corepressors and epigenetic remodeling complexes to inhibit particular target genes, such as the E-cadherin gene. An integrated and complex signaling network, including the receptor tyrosine kinases (RTKs), TGF-β, Notch, Wnt, tumor necrosis factor alpha (TNFα), and BMPs pathways, activates Snail, thereby enhancing epithelial–mesenchymal transition (EMT); Snail inhibits expression of cellular adhesion proteins, resulting in increased cell migration and metastasis of numerous types of tumors. The EMT process, alongside E-cadherin down-regulation and Snail up-regulation, quickens the invasion and metastasis of tumor cells [126]. DDX3 has been shown to be required for Snail expression. Indeed, DDX3 has been shown to help tumor progression by boosting elevated levels of Snail [37] (Fig. 3b).

HIF-1α/DDX3/E-cadherin pathway DDX3 has been distinguished as a direct downstream target of hypoxia-inducible factor-1 alpha (HIF-1α, a transcriptional factor inducible by hypoxia) in breast cancer cell lines, and DDX3 has been demonstrated to stimulate tumorigenesis in breast cancers via HIF-1α/DDX3/E-cadherin pathway. Under hypoxic conditions, HIF-1α binds to the HIF-1α responsive elements located in the DDX3 promoter region to promote the transcriptional activation of DDX3. Therefore, up-regulation of DDX3 inhibits E-cadherin expression, accordingly prompting the EMT process to facilitate breast cancer invasion [127, 128] (Fig. 3b).

KRAS/HIF-1α/YAP1/SIX2 cascade In KRAS wild-type colorectal malignancy, DDX3 has been demonstrated to increase cell aggressiveness by means of a KRAS/reactive oxygen species (ROS)/HIF-1α cascade feedback loop. ROS creation by DDX3-mediated KRAS expression induces yes-associated protein 1 (YAP1) transcription via increasing HIF-1α bound to YAP1 promoter. Ultimately, the YAP1/SIX2 axis leads to the DDX3-induced cell invasiveness [129] (Fig. 3b).

Collectively, the above findings uphold the idea that DDX3 can promote cell proliferation via cell cycle regulation, repressing apoptosis, and inducing cell transformation

and migration. These are all in agreement with DDX3 possessing a tumor-promoting or oncogenic function in the cell.

DDX3 as a tumor suppressor

There is additionally evidence that, at least in certain contexts, DDX3 possesses a tumor suppressor role. As opposed to the primary study of DDX3 overexpression in HCC [106], a subsequent report revealed a decrease of DDX3 expression in HCC from HBV-positive but not HCV-positive patients, proposing that this discrepancy in HCC might be related to the virus predisposing to cancer, HBV- versus HCV-related HCC, the former possess the more conspicuous connections with down-regulation [130]. In addition, the latter study additionally demonstrated that siRNA knockdown of DDX3 in a non-transformed mouse fibroblast cell line, NIH-3T3, led to enhanced cell proliferation and premature entry into S-phase, concomitant with down-regulation of p21waf1/cip1 and up-regulation of cyclin D1; these results obviously differ from those showing that DDX3 can induce G1/S transition and cell growth [121]. Moreover, constitutive DDX3 siRNA knockdown in NIH-3T3 cells brought about an increase in Ras-induced anchorage-independent growth and resistance to apoptosis [130]; these findings again contrast with those from prior studies [106, 123]. In another report, DDX3 has been shown to suppress cell growth in a scope of cancer cells, in a p21waf1/cip1-dependent way via transcriptional activation of the p21waf1/cip1, a cyclin-dependent kinase inhibitor, promoter. Indeed, DDX3 has been demonstrated to interact and collaborate with Sp1 to up-regulate the promoter activity of p21waf1/cip1 in a way independent of p53 status [36]. Similarly, in a separate study, DDX3 has been demonstrated to synergistically invigorate p53-dependent transcription of p21waf1/cip1; furthermore, in early-stage human papillomavirus (HPV)-associated lung cancer, HPV E6 protein has been shown to inhibit DDX3 expression in a p53-dependent way, consequently lessening p21waf1/cip1 levels. Indeed, DDX3 has been shown to be positively correlated with p21waf1/cip1 expression, and diminished expression of p21waf1/cip1 by the alteration of the p53-DDX3 pathway has been shown to play a fundamental role in early-stage HPV-associated lung carcinogenesis, and to associate with inferior relapse-free survival of lung cancer patients [131]. Both these investigations uphold a tumor suppressor function for DDX3, via activation of p21waf1/cip1 expression (Fig. 4). These findings conflict with those from a previous report [38], which demonstrated that DDX3 has no influence on p21waf1/cip1 expression in breast cancer cells, and high DDX3 levels have been shown to be correlated with low p21waf1/cip1 levels in aggressive breast cancers. In contrast to the previous study of DDX3 up-regulation in colorectal cancers [107], a later report showed that DDX3 down-regulation caused up-regulation of Snail and diminished E-cadherin expression, with ensuing decreased cell aggregation, proposing that diminished DDX3 expression induces Snail/E-cadherin pathway-mediated cancer metastasis. Consistently, low DDX3 expression in colorectal cancer patients has been found to be associated with unfavorable clinical outcome [132]. It has been shown that DDX3 plays a tumor suppressor function in non-small cell lung cancer (NSCLC) cells via the mouse double minute 2 homolog (MDM2)/Slug/E-cadherin pathway. Indeed, loss of DDX3 by p53 inactivation resulted in increased MDM2/Slug/E-cadherin pathway signaling, inducing tumor malignancy and adverse treatment outcome in NSCLC [133] (Fig. 4). Interestingly, in HCC, DDX3 has been demonstrated to block the creation of cancer stem cells via epigenetically regulating a subclass of tumor-suppressive miRNAs expressions. Undoubtedly, DDX3 has been proposed to interact with transcription factors on promoter regions of tumor-suppressive miR-200b, miR-200c, miR-122 and miR-145, which likely activates the expression of these miRNAs, hence, inhibiting cancer stem cell properties and carcinogenesis in HCC, reinforcing the tumor suppressor function of DDX3 [134] (Fig. 4). To further confuse the image, DDX3 has been shown to prevent cell growth in the human HCC cells via suppressing cap-dependent translation by binding and repressing the translation initiation factor eIF4E [39]. This contrasts with the observations from a previous report [121] and is in agreement with the findings that DDX3 can both invigorate and repress translation in a context-dependent way.

It stays obscure, nonetheless, whether the malignant connections with DDX3 are straightforwardly linked to its helicase activity or probably some alternative pathway and even whether the alteration in DDX3 levels are an active or secondary process. Additionally, it is not obvious why changes in DDX3 levels yield such contradicting tumor-suppressing and proliferation- or tumor-promoting influences in various cell lines, in spite of the fact that the impact may rely upon the expression of other cellular factors in the various systems and/or the model systems/genes under investigation. In this regard, changes in nucleo-cytoplasmic shuttling and subsequently the cellular localization of DDX3 might be critical since it could possess deep influences on its role, based upon context. The explanations for the disparities regarding DDX3 localization in the different studies stay ambiguous [30], albeit one investigation demonstrated a change of DDX3 subcellular localization from the nucleus to the cytoplasm in a high percentage of cutaneous squamous cell carcinoma [36]. This may probably clarify the contrasting studies indicating an elevation in DDX3 expression in some cases, and a reduction in others, being linked to cancer development and/or progression.
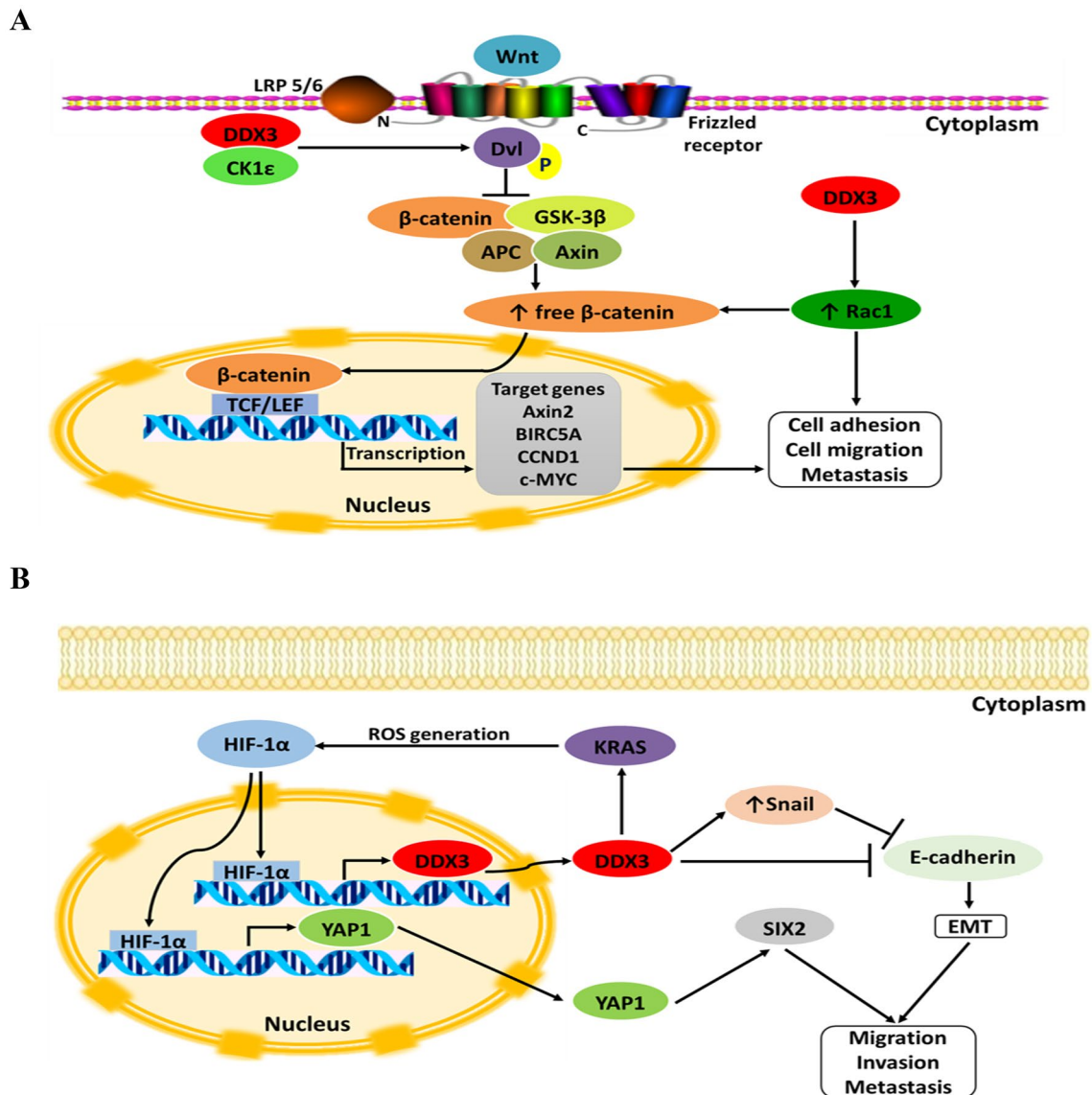
Fig. 3 DDX3 acts as an oncogene **a** through the Wnt/β-catenin pathway and **b** by promoting the EMT process. **a** Activated Wnt binds to frizzled receptors on the cell membrane forming a complex with LRP 5/6 and binds to the Axin, APC and GSK-3β complex which also binds to β-catenin. DDX3 interacts with CK1ε to form a complex, which phosphorylates Dvl. In turn, phosphorylated Dvl inhibits the generation of a destruction complex that includes axin, GSK3β, APC and β-catenin, thereby increasing free β-catenin, which translocates from the cytoplasm to the nucleus. Nuclear β-catenin could interact with two major transcription factors, TCF and LEF, regulating multiple gene transcription, such as AXIN2, BIRC5A, CCND1 and c-Myc. In addition, DDX3 elevates Rac1 expression, thereby increasing β-catenin stability and its signaling. Rac1 and/or β-catenin can regulate cell adhesion, migration and metastasis. APC, adenomatous polyposis coli; AXIN2, axis inhibition protein 2; BIRC5A, birc5a baculoviral IAP repeat containing 5a; CCND1, cyclin D1; CK1ε, casein kinase 1ε; Dvl, disheveled; GSK3β, glycogen synthase kinase 3 beta; LEF, lymphocyte enhancer factor; LRP 5/6, low density lipoprotein receptor-related protein 5/6; TCF, T-cell factor. **b** DDX3 increases Snail expression, which decreases E-cadherin levels, thereby inducing the EMT process. In breast cancer cells, HIF-1α binds to the HIF-1α responsive element located in the DDX3 promoter region to induce the transcriptional activation of DDX3. Subsequently, up-regulation of DDX3 represses E-cadherin expression, thereby inducing the EMT process to facilitate cell invasion. In KRAS wild-type colorectal cancer, DDX3 increases cell aggressiveness via a DDX3/KRAS/ROS/HIF-1α/DDX3 cascade feedback loop. ROS generation by DDX3-mediated KRAS expression promotes YAP1 transcription through increasing HIF-1α bound to YAP1 promoter. Finally, the YAP1/SIX2 axis results in the DDX3-mediated tumor aggressiveness. EMT, epithelial-mesenchymal transition; HIF-1α, hypoxia-inducible factor-1 alpha; ROS, reactive oxygen species; YAP1, yes-associated protein 1
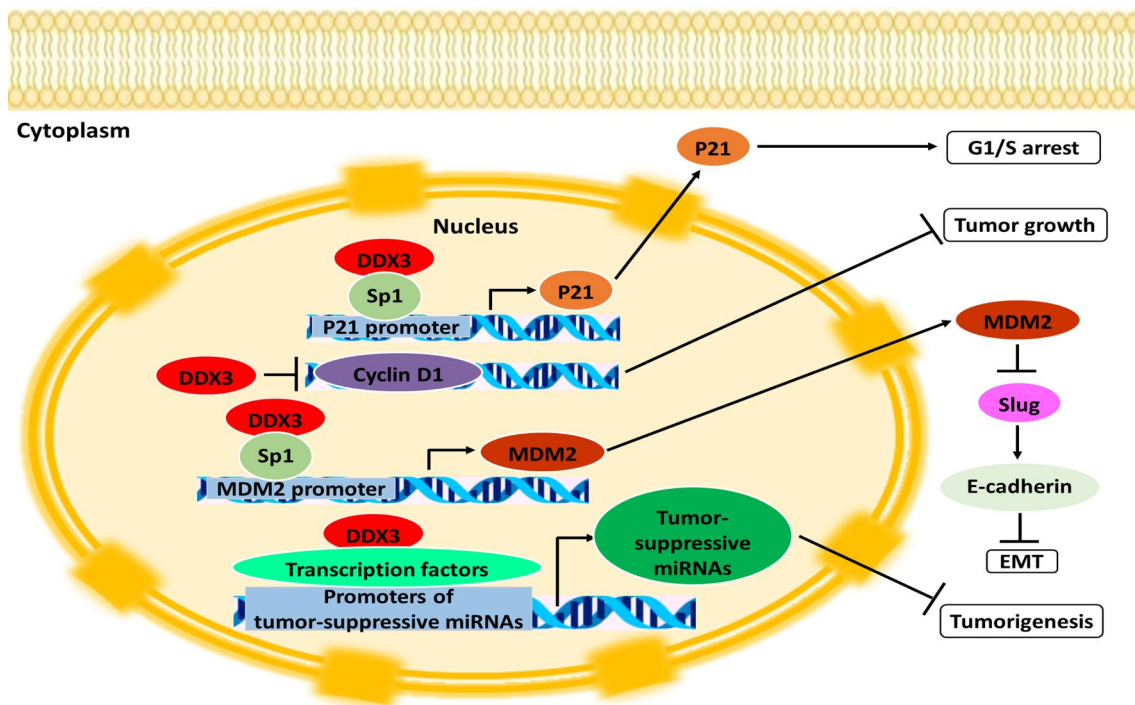
Fig. 4 DDX3-mediated signaling pathways to suppress tumor growth. DDX3 interacts with the transcription factor Sp1 to increase the promoter activity of p21, thus leading to S-phase arrest. DDX3 also down-regulates cyclin D1 to inhibit tumor growth in hepatitis virus-associated hepatocellular carcinoma. In addition, DDX3 increases MDM2 transcription by inducing binding of the transcription factor SP1 to the MDM2 promoter, thereby activating MDM2, which in turn inhibits the expression of the transcription factor Slug. MDM2 activation promotes E-cadherin expression, which in turn inhibits tumor malignancy via mediating proteasomal degradation of Slug in lung cancer cells. Moreover, DDX3 interacts with transcription factors on promoter regions of tumor-suppressive miR-200b, miR-200c, miR-122 and miR-145, thereby activating their expression, thus suppressing tumorigenesis in HCC. MDM2, mouse double minute 2 homolog

DDX5 and its paralog, DDX17

DDX5 has been involved in diverse cancers either via aberrant expression or through its role in the regulation of pathways that straightforwardly affect tumorigenesis, proliferation, invasion, and metastasis. The mechanisms by which DDX5 causes oncogenesis vary from one cancer type to the other. It has additionally been shown that the particular role played by DDX5 in inducing cancer proliferation could rely upon the upstream or downstream factors and pathways it interacts with. While the vast majority of the factors vary from one cancer type to another, some are common to more than one cancer or activate more than one cancer-related pathway leading to disease progression [135]. In the first report characterizing the discovery of DDX5, its expression has been demonstrated to be developmentally regulated and associated with organ differentiation/maturation [136]. The primary investigation of aberrant DDX5 expression in cancer originated from a report which indicated that DDX5 was overexpressed and unusually modified (by polyubiquitination) in colorectal cancer, proposing a cancer-associated post-translational modification [137]. This was followed by various studies revealing DDX5 overexpression in a scope of tumors, including gastric [138], esophageal [139], breast [70, 140, 141], ovarian [142], prostate, [43, 143], NSCLC [144], head and neck squamous cell carcinoma [145], cutaneous squamous cell carcinoma [146], glioma [45] and multiple myeloma [147], as well as several leukemias, including T-ALL [148] and acute myeloid leukemia (AML) [149], proposing that DDX5 is oncogenic in specific tumors. Indeed, experimental knockdown of DDX5 in different cancer cell lines and animal models has been demonstrated to impede carcinogenesis, repress cell proliferation, EMT and metastasis, while promoting apoptosis [135]. Conversely, DDX5 expression has been shown to be remarkably diminished in primary HCC, particularly in non-viral HCC subtypes, compared to the non-cancerous liver. Furthermore, decreased DDX5 expression in HCC has been found to be correlated with bad prognosis [150] (Table 3).

DDX5-modulated oncogenic signaling pathways

There is growing evidence indicating that DDX5 plays a crucial role in carcinogenesis, and tumor progression via regulation of oncogenic pathways. Indeed, it has been shown that DDX5 might contribute to tumor development

by modulating several signaling pathways. The most important tumor-related pathways regulated by DDX5 are Wnt/β catenin signaling, Notch signaling, NF-κB signaling, mammalian target of rapamycin (mTOR) signaling and AKT/forkhead box O3 (FOXO3a) signaling [135].

Wnt/β-catenin pathway Wnt/β-catenin signaling has been demonstrated to play a vital role in breast cancer progression via DDX5 up-regulation. Indeed, β-catenin can straightforwardly stimulate transcription of DDX5 promoter or indirectly via regulation of c-Myc in breast cancer cells. Furthermore, both β-catenin and transcription factor 4 (TCF4) have been shown to occupy the endogenous DDX5 promoter, which is further promoted by Wnt signaling [140].

DDX5 promotes EMT via two essential pathways both connected to the nuclear translocation of β-catenin via Wnt/β-catenin signaling. First, tyrosine phosphorylation of DDX5 at Y593 has been demonstrated to mediate platelet-derived growth factor (PDGF)-induced EMT by dissociating β-catenin from the axin destruction complex and its subsequent translocation to the nucleus and eventual activation of T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors associated with EMT, which initiates invasion and metastasis [46, 151]. Second, phosphorylation of DDX5 at Y593 has been demonstrated to mediate PDGF-induced cell proliferation by activating the transcription of cyclin D1 and c-Myc genes [47]. Furthermore, phosphorylated DDX5 has been shown to activate transcription of the Snail1 gene by inducing HDAC1 dissociation from the Snail1 promoter, thereby down-regulating E-cadherin, resulting in EMT [49] (Fig. 5a).

Notably, DDX5 has been demonstrated to induce proliferation and tumorigenesis of NSCLC cells by activating β-catenin signaling pathway. Indeed, DDX5 has been shown to straightforwardly interact with β-catenin, induced its nuclear translocation, and co-activated the expression of cyclin D1 and c-Myc [144].

It has been shown that post-translational modifications of DDX5 hugely control its regulation of pathways, as well as its transcription regulation role [152]. DDX5 phosphorylation, specifically on tyrosine residue(s), has been indicated to be associated with cellular transformation and tumor development. On the other hand, phosphorylation of DDX5 at threonine residues has been demonstrated to be associated with cancer cell apoptosis under the treatments with apoptosis agents, such as TNF-α and TRAIL [153]. Also, DDX5 phosphorylation at threonine residues (T446 and/or T564) by MAPK has been found to contribute to colon cancer cells apoptosis induced by oxaliplatin [154]. Besides, a dual phosphorylation on Y593 and Y595 of DDX5 has been reported to confer resistance to apoptosis in glioblastoma cells treated with TRAIL [155].

NOTCH pathway Activation of the NOTCH signaling pathway by binding of a NOTCH ligand to the NOTCH receptor liberates the NOTCH intracellular domain (NICD), which translocates to the nucleus forming a complex with the recombination signal-binding protein for immunoglobulin kappa J region (RBPJ) [156, 157]. The NICD/RBPJ complex binds to either mastermind-like 1 (MAML1), DDX5, or the long non-coding RNA steroid receptor RNA activator (SRA), which then co-activates the transcription of NOTCH signaling target genes [158]. Indeed, DDX5 has been demonstrated to interact with MAML1, and is associated with the NOTCH1 transcription activation complex in human T-ALL cells, uncovering an important role of DDX5 in inducing effective Notch-mediated transcription in leukemic cells, and proposing that DDX5 may be vital for NOTCH1-mediated T-ALL pathogenesis [148] (Fig. 5b).

NF-κB pathway The N terminal of DDX5 has been demonstrated to binds the NF-κB p50 subunit in the cytoplasm, promoting its amassing in the nucleus, and activating the transcription of NF-κB target genes, thereby inducing cancer inception, cell growth and proliferation, cell migration and invasion, angiogenesis, while repressing apoptosis [159] (Fig. 5C).

mTOR pathway DDX5 has been found to invigorate mTOR/ribosomal protein S6 kinase B1 (RPS6KB1) activation, leading to enhanced cell growth, proliferation and metastasis (Fig. 5D). Indeed, DDX5 has been shown to induce gastric cancer cell proliferation via mTOR signaling pathway [138]. Furthermore, DDX5 depletion has been demonstrated to reduce cell growth, and to activate the mTOR/MDM2 cell survival mechanism, leading to suppression of the pro-apoptotic factor p53, which eventually brought about repression of the pro-apoptotic activity [160].

AKT/FOXO3a pathway In colon oncogenesis, a novel mechanism of carcinogenesis has been ascribed to DDX5 by up-regulation of AKT and ensuing nuclear exclusion and degradation of the tumor suppressor FOXO3a, the downstream target of AKT. Indeed, DDX5 has been demonstrated to occupy AKT promoter with β-catenin as well as NF-κB, and to collaborate with these in potentiating AKT transcription, proposing that DDX5 lessens FOXO3a level in an AKT-dependent way [161] (Fig. 5e).

Another considerable involvement of DDX5 in carcinogenesis, particularly gastric cancer, has been evidenced by the observations from two prior studies [162, 163]. One study identified DDX5 as a target of miR-141, indicating that DDX5 expression is negatively regulated by miR-141. In addition, the long non-coding RNA myocardial infarction-associated transcript (MIAT) has been shown to directly

bind to miR-141 and to serve as miR-141 sponge in gastric cancer cells. Since miR-141 could inhibit proliferation and metastasis of gastric cancer, MIAT exerted oncogenic influence on gastric cancer by negatively regulating miR-141 expression. Consistent with these results, in gastric cancer tissues, MIAT has been found to be up-regulated; whereas, miR-141 has been shown to be down-regulated. More importantly, by acting as miR-141 sponge, MIAT appeared to positively regulate DDX5 expression. These findings suggested that MIAT promotes gastric cancer growth and metastasis through regulation of miR-141/DDX5 pathway [162]. A more recent study identified DDX5 as a direct target of miR-5590-3p, whose expression has been found to be down-regulated in gastric cancer tissues. Indeed, miR-5590-3p has been demonstrated to translationally repress DDX5 by targeting specific sequences in the 3′ UTR of DDX5. Importantly, miR-5590-3p has been shown to inhibit cell proliferation and tumor growth in gastric cancer by targeting DDX5/AKT/mTOR pathway [163].

The DDX5 and DDX17 genes share a noteworthy level of homology [164]. DDX5 and its homolog DDX17 role in numerous cellular processes; nonetheless, despite the fact that they seem to share some functional overlap in some contexts, many studies have indicated that they additionally possess particular non-repetitive roles. There have been multiple investigations reporting that the expression of DDX5 and DDX17 is dysregulated in a scope of tumors. Also, both DDX5 and DDX17 have been functionally embroiled in cancer development: numerous studies have proposed oncogenic or pro-proliferation roles for these proteins, while some have suggested possible tumor suppressor roles, proposing that the role of DDX5 and DDX17 in tumor development and progression is intricate and is probably context dependent [42] (Table 3).

Along with their capability to invigorate cell proliferation and inhibit apoptosis, the reported overexpression of DDX5/DDX17 in numerous human malignancies robustly proposed that DDX5/DDX17 induce carcinogenesis and may even represent proto-oncoproteins [165]. In a former study, DDX5/DDX17 has been found to contribute to colon carcinogenesis by straightforwardly up-regulating proto-oncogenes (β-catenin-regulated genes: c-Myc, cyclin D1, c-jun and fra-1) and indirectly by down-regulating the growth suppressor p21waf1/cip1, proposing that DDX5/DDX17 overexpression may be a possible marker of colon cancer [166]. In a later investigation of ERα-positive breast cancers, DDX5 and DDX17 have been demonstrated to function as transcriptional co-activators for a wide scope of transcription factors, including ERα. DDX17 expression has been shown to be correlated with superior relapse-free and overall survival, and to be inversely correlated with human epidermal growth factor receptor 2 (Her2) expression, conversely, DDX5 exhibited no correlation with relapse-free, or overall

survival; however, it has been associated with an increased expression of Her2, amplified in breast cancer 1 (AIB1) and higher tumor grade, affirming a pivotal role for both DDX5 and DDX17 in ERα co-activation, and giving evidence in support of distinguished but crucial roles for both DDX5 and DDX17 in regulating ERα activity in breast cancer [167].

Obviously, post-translational modification of DDX5 and DDX17 has great influences on DDX5/DDX17 role and this might be vital to their function in cancer. For instance, both DDX5 and DDX17 contain one consensus sumoylation site, and both have been shown to be overexpressed in breast cancers, in which the SUMO pathway is up-regulated. These observations proposed that sumoylation of DDX5 and DDX17 increases during breast carcinogenesis and probably contributes to their overexpression, and that sumoylation exerts pleiotropic impacts on DDX5/DDX17 [55]. Moreover, in another investigation, acetylation has been demonstrated to increase the stability of DDX5 and DDX17, and to invigorate their capability to coactivate the ER, thereby possibly contributing to its aberrant activation in breast cancers [56]. Collectively, these results propose that post-translation modification of DDX5 and DDX17 might play critical roles in tumor development/progression and that DDX5/DDX17 possess pro-proliferation/-transformation roles that can be modulated by post-translational modification.

Notably, DDX5 and DDX17 have been shown to contribute to cancer-cell invasiveness by regulating alternative splicing of numerous DNA- and chromatin-binding factors [65].

ER and AR play key roles in breast and prostate tumors, respectively, where they regulate the transcription of huge varieties of genes. The activities of ER and AR are controlled by huge networks of protein kinases and transcriptional co-regulators, including DDX5 and its profoundly related paralog DDX17. Indeed, DDX5 and DDX17 have been recognized as prime regulators of the estrogen- and androgen-signaling pathways by controlling transcription and splicing both upstream and downstream of the receptors. First, DDX5 and DDX17 are needed downstream of ER and AR for the transcriptional and splicing regulation of countless steroid hormone target genes. Second, DDX5 and DDX17 function upstream of ER and AR by controlling the expression, at the splicing level, of multiple key regulators of ER and AR activities [168].

DDX5 and DDX17 have additionally been demonstrated to possess a double function in the control of the pro-migratory NFAT5 transcription factor. First, DDX5 and DDX17 function as transcriptional co-activators of NFAT5 and are required for activating NFAT5 target genes implicated in tumor cell migration. Second, at the splicing level, DDX5 and DDX17 increase the inclusion of NFAT5 exon 5. As exon 5 contains a premature translation termination codon, its inclusion results in the regulation of NFAT5 mRNAs

by the nonsense-mediated mRNA decay pathway and to a reduction in NFAT5 protein level. This double regulation, where DDX5 and DDX17 promote the transcriptional activity of NFAT5 albeit diminishing its protein expression level, proposes an important role for DDX5 and DDX17 in cancer cell migration via the accurate regulation of NFAT5 pathway [58].
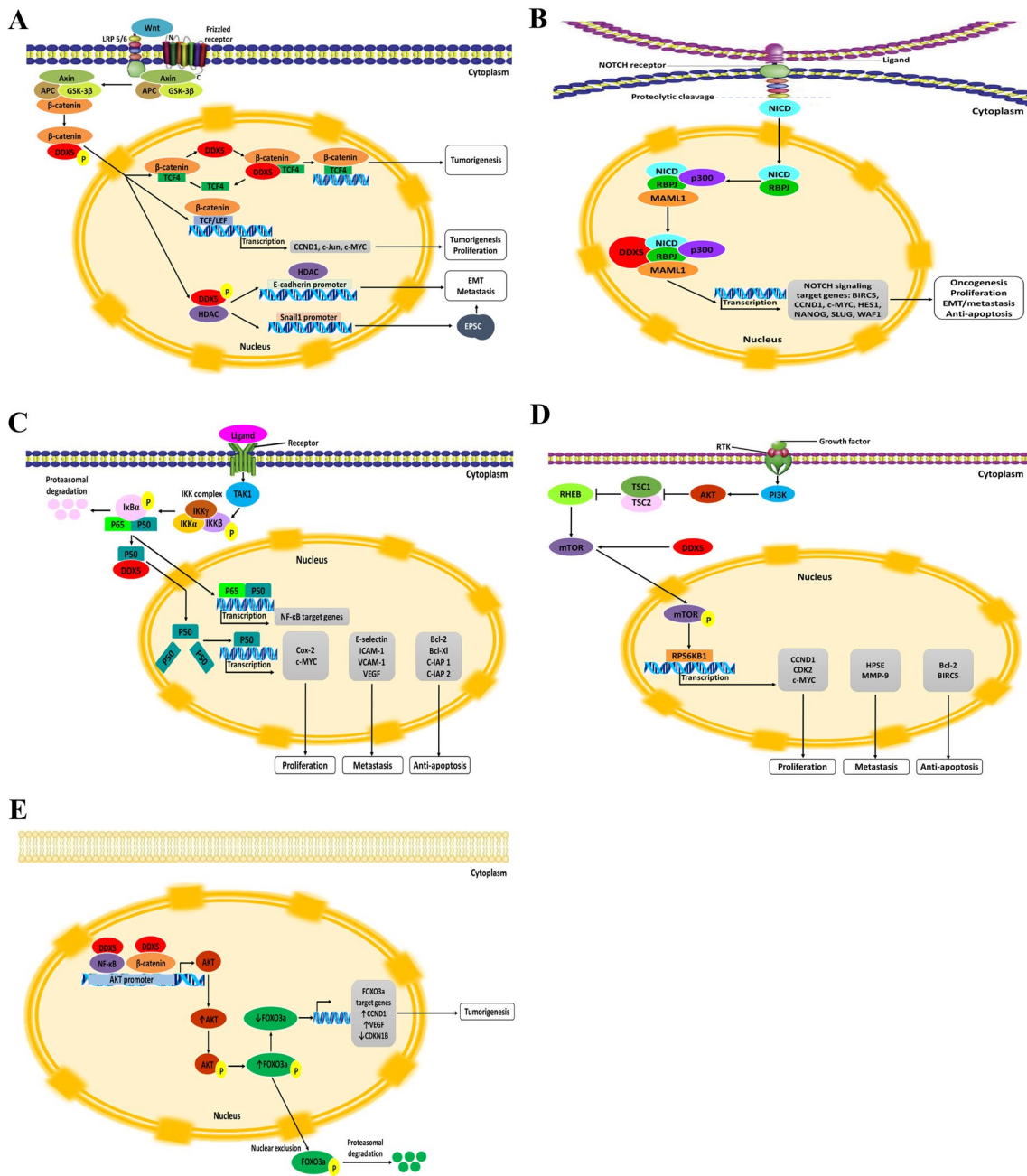
DDX6

DDX6 has been recognized as a putative RNA helicase involved in t(11;14)(q23;q32) present in a cell line derived from a diffuse large B-cell lymphoma. The breakpoint in the DDX6 gene happened in the 5′ non-coding region bringing about its fusion to the immunoglobulin heavy chain (IgH) gene. Despite the fact that DDX6 mRNA and protein sizes were not changed because of the translocation, the expression of DDX6 has been shown to be increased compared to normal lymphocytes, proposing that might be implicated in cancer development [169, 170].

DDX6 as an oncogene

Previous findings propose that DDX6 plays a critical, evolutionarily conserved, positive role in cell cycle progression and proliferation, probably via regulating translation of particular mRNAs that play key roles in cell cycle progression. This would be in agreement with the notion that DDX6 can function as an oncogene and is upheld by the numerous studies indicating that it is overexpressed in a broad scope of tumors [171–174] (Table 3). Earlier studies showed that the DDX6 protein is overexpressed in neuroblastoma, glioblastoma, rhabdomyosarcoma and lung cancer cell lines as compared with normal tissue [171], in colorectal tumors [172, 173] and in cases of HCV-related chronic hepatitis and HCC [174]. In a subsequent study, in cancer cells, DDX6 has been shown to post-transcriptionally down-regulate mature miR-143/145, their expression has been demonstrated to be down-regulated in several human cancer cells, suggesting that they act as tumor suppressors. DDX6 exerts its effect on miR-143 and -145 not only by down-regulating their host gene, the non-coding RNA

Fig. 5 Association of DDX5 with the Wnt/β catenin pathway (**a**), the NOTCH signaling (**b**), the NF-κB signaling (**c**), the mTOR signaling (**d**) and AKT/FOXO3a pathway (**e**). **a** Activated Wnt binds to frizzled receptors on the cell membrane forming a complex with LRP 5/6 and binds to the Axin, APC and GSK-3β complex which also binds to β-catenin. Phosphorylated DDX5 dissociates β-catenin from the complex causing its nuclear accumulation. DDX5 is regulated by β-catenin/TCF4 to maintain a positive-feedback loop in controlling tumorigenesis. In addition, β-catenin binds TCF/LEF transcription factors and promotes transcription of CCND1, c-Jun and c-Myc, thereby resulting in tumorigenesis and proliferation. Moreover, phosphorylated DDX5 dissociates HDAC from the snail1 promoter, resulting in accumulation of EPSC, and recruits HDAC to the E-cadherin promoter leading to EMT. APC, adenomatous polyposis coli; CCND1, cyclin D1; EPSC, EMT promoting SMAD complexes; GSK-3β, glycogen synthase kinase 3 beta; HDAC, histone deacetylase; LEF, lymphocyte enhancer factor; LRP 5/6, low density lipoprotein receptor-related protein 5/6; TCF, T-cell factor; TCF4, transcription factor 4. **b** The notch receptor binds a ligand and releases NICD through proteolytic cleavage. The NICD then translocates to the nucleus and binds RBPJ, then forms a complex with the histone acetyltransferase p300 and the transcriptional coactivator MAML1. DDX5 binds to MAML1, thereby activating the transcription of notch-related genes, which in turn, promote oncogenesis, proliferation, EMT/metastasis and reduce apoptosis. MAML1, mastermind-like 1; NICD, notch intracellular domain; RBPJ, recombination signal-binding protein for immunoglobulin kappa J region. **c** Receptor activation by Toll-like receptor ligands, antigens or cytokines, i.e., tumor necrosis factor leads to the activation of the transforming growth factor beta-activated kinase-1(TAK1) kinase, which in turn phosphorylates and activates the IKKs (IKK complex). Activated IKKs eventually phosphorylate the IκBα inhibitory subunit of NF-κB. IκBα is then polyubiquitinated, leading to its degradation by the proteasome, and to nuclear translocation of free NF-κB dimers, ultimately ending in activation of NF-κB target genes. DDX5 binds the NF-κB P50 subunit in the cytoplasm and causes its nuclear accumulation, thereby activating the transcription of target genes, which in turn promotes proliferation, metastasis, and apoptosis inhibition. ► Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra-large; C-IAP 1, cellular inhibitor of apoptosis protein 1; C-IAP 2, cellular inhibitor of apoptosis protein 2; Cox-2, cyclooxygenase-2; ICAM-1, intercellular adhesion molecule 1; IKK, inhibitory kappa-B kinase; IKKα, inhibitor of nuclear factor kappa-B kinase subunit alpha; IKKβ, inhibitor of nuclear factor kappa-B kinase subunit beta; IKKγ, inhibitor of nuclear factor kappa-B kinase subunit gamma; IκB, inhibitor of nuclear factor kappa-B; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor. **d** Growth factor (epidermal growth factor) binds to RTK on the cell surface, causing the activation of PI3K, which in turn activates the protein kinase AKT, which inhibits the tumor suppressor TSC1 and TSC2 proteins, which normally block the small GTPase RHEB. By blocking TSC1 and TSC2, RHEB is left free and, thus, activates mTOR. DDX5 promotes mTOR/RPS6KB1 activation, which directs the synthesis of proteins responsible for proliferation, metastasis, angiogenesis and anti-apoptotic activity. Bcl-2, B-cell lymphoma 2; CCND1, cyclin D1; CDK2, cyclin-dependent kinase 2; HPSE, heparanase; MMP-9, matrix metallopeptidase 9; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; RHEB, Ras homolog enriched in brain; RPS6KB1, ribosomal protein S6 kinase B1; RTK, receptor tyrosine kinase; TSC1, tuberous sclerosis complex 1; TSC2, tuberous sclerosis complex 2. **e** DDX5 triggers the initial event, it cooperates with β-catenin as well as NF-κB in significantly up-regulating the protein kinase AKT transcription. Increased AKT activity leads to the phosphorylation of the tumor suppressor FOXO3a and results in its nuclear exclusion, eventually leading to its proteasomal degradation. The resultant decrease of FOXO3a is manifested upon its target genes, like down-regulation of CDKN1B. Also, the repressive effect imposed on CCND1 and VEGF by FOXO3a is released, resulting in their up-regulation. These sequences of events cumulatively contribute to the process of oncogenesis. CCND1, cyclin D1; CDKN1B, cyclin-dependent kinase inhibitor 1B; FOXO3a, forkhead box O3; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; VEGF, vascular endothelial growth factor

143/145 (NCR143/145), which encodes both miR-143 and -145, but also by promoting NCR143/145 degradation in the P-bodies [175]. Mechanistically, DDX6 has been shown to contribute to cell proliferation and oncogenesis in the development of colorectal cancers at the translational level [172], by increasing the synthesis of c-Myc protein [173]. Similarly, DDX6 has been demonstrated to act as an oncogene in gastric cancer cells through promotion of c-Myc expression by association with the mRNA of c-Myc [176]. Indeed, in vitro investigations demonstrated nonspecific unwinding activity of DDX6 towards c-Myc mRNAs, proposing that DDX6 may play a role at the translation level by modulating mRNA structure to facilitate c-Myc translation [177]. In colon cancer cells, DDX6 has been identified as a direct target of miR-124, which has been shown to play a tumor suppressor role against various cancers, including colorectal cancer, suggesting that DDX6 expression is partly regulated by miR-124. Moreover, miR-124 has been found to target polypyrimidine tract-binding protein 1 (PTB1) and to modulate energy metabolism in colon cancer cells through the regulation of pyruvate kinase muscle (PKM) isoforms. More importantly, DDX6 has been demonstrated to affect the Warburg effect through the DDX6/c-Myc/PTB1 positive-feedback circuit regulated partly by miR-124

[178]. In gastric cancer cells, DDX6 has been demonstrated to serve as an RNA-binding protein for human epidermal growth factor receptor 2 (HER2) and fibroblast growth factor receptor 2 (FGFR2) mRNAs, thereby acting as an upstream molecule that positively regulates the expression of HER2 and FGFR2 at the post-transcriptional level [179]. Interestingly, in a more recent study, a synthetic miR-143 has been shown to indirectly down-regulate the expression of HER2, an upstream molecule of KRAS, through silencing of DDX6, which enhanced HER2 protein expression at the translational step in HER2-positive gastric cancer cells. These findings suggest a novel therapeutic strategy against HER2-positive gastric cancer involving perturbation of KRAS networks including the DDX6 mediated by the tumor suppressor miR-143 [180]. A chromosomal translocation t(11;14)(q23;q32) involving the IgH gene and DDX6 has been detected in nodal marginal zone lymphoma. DDX6 has been suggested to contribute to lymphomagenesis by dysregulating the expression of B-cell lymphoma 6 (BCL6) [181]. All these observations affirmed an embroilment of DDX6 in tumor development.

Growth inhibitory/tumor suppressor role of DDX6

There has been one study that overexpression of DDX6 brings about a prevention of cell growth and a decrease in anchorage-independent growth, a sign of malignant transformation [182] (Table 3). While these findings propose that DDX6 in these contexts have a negative role on cell proliferation, the inconsistency could be because of the fact that the vast majority of the investigations indicating a positive impact of DDX6 on cell proliferation utilized siRNA depletion of endogenous DDX6 whereas those demonstrating a negative influence on proliferation depended on ectopic overexpression. Probably, possessing the correct physiological quantity of DDX6 in cells is crucial and the exact role of DDX6 will rely upon the levels of the protein in the cell as well as the availability of interacting partners.

DDX10

DDX10 has been recognized as one of the new genes that has undergone aberrant genomic rearrangements in hormone receptor-negative breast tumors, where RNAi-mediated inhibition of DDX10 resulted in suppression of breast tumor cell growth. Additionally, down-regulation of DDX10 in breast tumor cells results in an increased frequency of apoptotic nuclear morphology [183].

DDX10 has been shown to be involved in a frequent chromosomal aberration associated with de novo and therapy-related myeloid malignancies, the inv(11)(p15q22), which leads to the in-frame fusion of DDX10 to the N-terminus of the nucleoporin 98 (NUP98) [184], a gene encoding a member of the nucleoporin complex, which is involved in the active transport of proteins and RNA between the nucleus and cytoplasm [185]. It has been proposed that the NUP98–DDX10 fusion interferes with the normal functions of NUP98 in the synthesis and/or transport of proteins involved in myelopoiesis. Also, the NUP98–DDX10 fusion leads to the loss of the ATPase function of DDX10 [184]. Furthermore, NUP98–DDX10 has been shown to significantly increase proliferation and self-renewal of primary human CD34$^+$ cells, and deactivates their erythroid and myeloid differentiation, demonstrating that it possesses a role in leukemogenesis [186]. In a chronic myeloid leukemia (CML) patient undergoing treatment with imatinib, the inv(11)(p15q22) with NUP98/DDX10 fusion gene has been detected as a clonal evolution, augmenting the likelihood that the NUP98/DDX10 fusion may be implicated in imatinib resistance as well as in acute transformation of CML [187] (Table 3).

DDX20

DDX20 has been shown to be embroiled in anomalous cell signal transduction pathway activity, which is a key factor in tumor pathogenesis [188].

DDX20 levels have been demonstrated to be up-regulated in metastatic human breast tumors and they associate with patient survival. Remarkably, depletion of DDX20 in an invasive breast tumor cell line has been found to hinder cell migration and invasion. Conversely, forced overexpression of DDX20 increased the invasive potential of a normal human breast epithelial cell line. Also, mice injected with DDX20-transfected breast cancer cells had a higher occurrence of lung and liver metastases compared with controls. DDX20 has been demonstrated to function as an important co-factor of TGF-β-activated kinase-1 (TAK1)-mediated activation of the IκB kinase 2 (IKK2), which, in turn, is a key for activating the oncogenic transcription factor NF-κB. Elevated NF-κB activation, in turn, brought about boosted metastasis and the acquisition of chemotherapy resistance by means of elevated expression of matrix metalloproteinase 9 (MMP9), an NF-κB target which degrades the extracellular matrix, a main step in metastasis. Increased expression of active NF-κB and MMP9, mirrors the expression of DDX20, thereby setting up a function for the DDX20–NF-κB–MMP9 axis in breast cancer metastasis. Noteworthy, the helicase activity of DDX20 is not needed for its function in driving metastasis in breast cancer cells [189]. These results confirmed that DDX20 is not only a prognostic biomarker for breast cancer oncogenesis and progression, but also a novel predictive marker for cancer metastasis [190]. Interestingly, DDX20 levels have additionally been demonstrated to be up-regulated in tissue samples derived from prostate cancer patients, with DDX20 high expression has been found to promote the proliferation

and metastatic capability of prostate cancer cells via the NF-κB pathway [191], an observation that reinforces the function of DDX20 in metastasis. The function of DDX20 in tumorigenesis, nevertheless, has been demonstrated to vary among various tumor types. Hence, in contrast with its role as a tumor promoter in breast and prostate cancer, DDX20 functions as a tumor suppressor in HCC. In this respect, DDX20 has been recognized as a liver tumor suppressor candidate in an oncogenomics-based in vivo RNAi screen [192]. Also, diminished expression of DDX20 has recurrently been seen in human HCC. DDX20 has been shown to normally repress NF-κB activity, an important intracellular signaling pathway firmly connected with hepatocarcinogenesis, by regulating the function of the NF-κB-inhibiting miRNA-140 to suppress liver cancer progression [193, 194] (Table 3).

DDX21

Elevated DDX21 expression has been detected in breast cancer tissues and cell lines, where it has been demonstrated to enhance activator protein 1 (AP-1) transcriptional activity and rRNA processing, and consequently, induce carcinogenesis by two independent mechanisms [195] (Table 3).

DDX41

Frequent mutations in DDX41 have been detected in familial and acquired cases of myelodysplastic syndrome (MDS) and AML. These DDX41 germline and acquired somatic mutations resulted in changed pre-mRNA splicing and RNA processing, revealing the possible tumor-suppressive role of DDX41 in myeloid neoplasms [196, 197]. In a subsequent study, five new mutations including missense mutations within critical functional domains and splicing mutations anticipated to bring about truncated proteins, have been detected in families with MDS or AML and lymphoid malignancies [198]. In later investigations, new germline DDX41 mutations and heterozygous variations have been identified in families with MDS/AML [199, 200] (Table 3).

DDX43

DDX43 has been shown to be up-regulated in various cancers of several histological types [201]. DDX43 expression has been demonstrated to be up-regulated in breast cancer, and its expression has been found to be remarkably correlated with aggressive clinico-pathological characteristics and bad prognosis in breast cancer patients [202]. In AML, DDX43 promoter has been demonstrated to be recurrently hypomethylated, and DDX43 hypomethylation has been recognized as a favorable prognostic marker [203] (Table 3).

DDX53

DDX53 has been demonstrated to be up-regulated in several tumor tissues and tumor cell lines [204]. It has been shown that the methylation status of the CpG sites of DDX53 determines its expression, proposing a firm connection between the methylation status of the DDX53 promoter and the expression of DDX53. Indeed, hypomethylation of the DDX53 promoter has been shown associated with DDX53 overexpression. The presence of hypomethylated DDX53 promoter in pre-cancerous conditions such as chronic gastritis proposed that overexpression of DDX53 may contribute to tumorigenesis [205] (Table 3).

DEAD-box helicases as anticancer drugs

The embroilment of DEAD-box helicases in numerous tumors has prompted the discovery of small molecules targeting this family of proteins for the development of anticancer medications. Various therapeutic strategies targeting DEAD-box helicases have demonstrated to have antineoplastic abilities such as inhibitors against nucleoside-triphosphatase (NTPase) activity, small molecules influencing RNA binding and helicase activity, and compounds that disrupt specific protein–protein interactions [79] (Table 4).
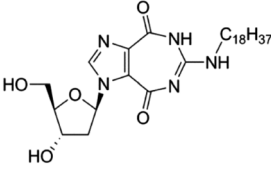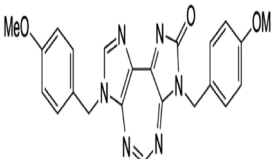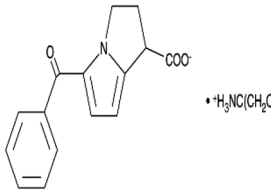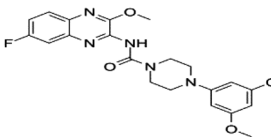
DDX3

The embroilment of DDX3 in numerous malignancies makes it a worthy target for the development of DDX3-specific therapeutics for efficient cancer therapy. Lately, new small molecule inhibitors targeting DDX3 are created as potential target chemical medications for cancer treatment [101, 102, 206]. While targeting DDX3 has shown promise in treating tumors, the conflicting double functions of DDX3 as an oncogene and tumor suppressor, observed in some tumors, should be considered when treating tumors with DDX3 inhibitors [103].

Ring-expanded nucleosides (RENs) are a class of purine nucleosides analogs containing imidazodiazepine or imidazotriazepine ring system of natural/synthetic origin. Most of the natural RENs are synergistic antitumor and/or antiviral agents which potentiate the influences of other antitumor or antiviral agents via repression of key enzymes. Nonetheless, they have not been confirmed as efficacious clinically as expected due to the tremendously high toxicity associated with their utilization. A significant number of the synthetic RENs, on the other hand, have biological activities of their own, specifically against a broad range of tumors and viruses with little toxicity to the host cells, and consequently hold enormous promise as chemotherapeutic agents. The promising preliminary in vitro findings regarding the influences

Table 4 DEAD-box helicase inhibitors with anticancer activity

Drug	Chemical structure	Target DEAD-box helicase	Mode of action	Reference(s)
NZ51		DDX3	The 5:7-fused imidazodiazepine ring of NZ51 was incorporated into the ATP-binding pocket of DDX3 Inhibits the ATP-dependent helicase activity of DDX3 Inhibits motility and viability of breast cancer cells by targeting DDX3	[208]
RK-33		DDX3	Fits into the ATP-binding cleft of DDX3 and impedes its helicase activity Causes a global delay in cell cycle progression Exhibits antineoplastic activity against several cancers	[105] [209] [107, 112, 115, 210–212]
Ketorolac salt		DDX3	Inhibits the DDX3 ATPase activity through direct interaction with the P-loop region of DDX3 Inhibits the growth of OSCC cells through down-regulation of DDX3 expression	[213]
RX-5902		DDX5	Binds to Y593 phospho-DDX5, inhibiting its β-catenin-dependent ATPase activity	[214]

of RENs on human tumors, specifically prostate and breast cancer cells, uphold their further pursuit in animal and clinical investigations [207]. Among the RENs, NZ51 (an analog containing a 5:7-fused imidazodiazepine ring system with a C18 alkyl chain tail) has been distinguished as a possible DDX3 inhibitor by revoking the ATP-dependent unwinding activity of DDX3. It has been shown that NZ51 treatment diminished cell viability and cellular motility of breast cancer cell lines with IC_{50} values in the low micromolar range. Regrettably, NZ51 treatment had no impact on primary tumor growth rates in a mouse model system, although in vivo investigations showed that DDX3 knockdown by short hairpin RNA brought about diminished tumor volume and metastasis [208].

The small molecule inhibitor RK-33 (3,7-Bis(4-methoxybenzyl)-3,7-dihydro-1,3,4,6,7,9-hexaaza-2H-cyclopenta[e]azulene-2-one, also known as 3,7-Dihydro-3,7-bis[(4-methoxyphenyl)methyl]-2H-diimidazo[4,5-d:4′,5′-f][1,3]diazepin-2-one) has been designed to fit into the ATP-binding cleft of DDX3 and hereby disrupt its helicase activity. Consequently, RK-33 has been suggested as a potential candidate for cancer therapy [105]. DDX6 role in mRNA decapping has been demonstrated to give a mechanism by which it can regulate translation of mRNAs via RNA degradation [209]. RK-33 has been shown to exhibit anti-proliferative activity against various tumors. Suppression of DDX3 by RK-33 has been demonstrated to induce tumor regression in numerous mouse models of lung cancer. Mechanistically, loss of DDX3 function by RK-33 destroyed Wnt signaling via perturbation of the DDX3–β-catenin axis [112]. Treatment of colorectal cancer cell lines and patient-derived 3D cultures with RK-33 has been demonstrated to suppress growth, and to stimulate cell death. Indeed, suppression of DDX3 with RK-33 led to repression of Wnt signaling and might accordingly be a promising treatment strategy for a subset of colorectal cancers [107]. Treatment with RK-33 has additionally been shown to be cytotoxic to Ewing sarcoma cells [115]. Also, RK-33 has been found to radiosensitize prostate cancer cells by blocking DDX3, showing that obstructing DDX3 by RK-33 in combination with radiation therapy is a feasible choice for treating locally advanced prostate cancer [210]. Additionally, DDX3 suppression with RK-33 has been demonstrated to cause radiosensitization in breast cancer cell lines via blocking of mitochondrial translation [211]. Recently, RK-33 has been shown to radiosensitize medulloblastoma cells by hindering DDX3 activity via down-regulation of Wnt/β-catenin signaling,

proposing that RK-33 may be utilized as a frontline treatment strategy for DDX3-expressing medulloblastomas in combination with radiation [212].

Another DDX3 inhibitor that demonstrated to have interesting anticancer activity is the Ketorolac salt (($\pm$)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, tris (hydroxymethyl) amino methane salt). This bioactive compound can block the DDX3 ATPase activity via direct interaction within the P-loop region (Gly 227, Gly 229 and Thr 231) of DDX3 by forming stable hydrogen bonds. Ketorolac salt has been shown to successfully repress the growth of H357, a human oral squamous cell carcinoma (OSCC) cell line, in a dose-dependent way where it down-regulated DDX3 expression and up-regulated the expression levels of E-cadherin [213].

DDX5

DDX5 has additionally been distinguished as a possible candidate for anticancer drugs. Targeting DDX5 in the context of the functions it plays in tumor development and pathway regulation has been effectively investigated both in vivo and in vitro [135]. The accumulated information on the functions played by DDX5 in tumor progression has promoted the recent development of a new, DDX5-specific anticancer molecule RX-5902. DDX5 has been affirmed to be a cellular target of RX-5902, 4-(3,5-dimethoxyphenyl)-N-(7-fluoro-3-methoxy-quinoxalin-2-yl)piperazine-1-carboxamide, a drug that displays robust growth suppression in numerous human tumor cell lines. RX-5902 has been demonstrated to bind straightforwardly and specifically to Y593 phospho-DDX5, blocking the β-catenin-dependent ATPase activity of DDX5. Treatment of tumor cells with RX-5902 led to the down-regulation of the expression of specific genes, which are known to be regulated by the β-catenin pathway, such as c-Myc, cyclin D1 and p-c-Jun. The blocking of Y593 phospho-DDX5-β-catenin interaction by direct binding of RX-5902 to Y593 phospho-DDX5 has been shown to contribute to the anti-cancer activity of this compound [214].

Concluding remarks and future perspectives

Most DEAD-box proteins have currently been assigned roles in one or more biological processes, including ribosome biogenesis, pre-mRNA splicing, mRNA export, translation and RNA decay. Nonetheless, understanding the molecular basis for how DEAD-box proteins function in these biological processes has proven challenging. In spite of the amazing advancement made in our understanding of the structures, functions and biological roles of DEAD-box helicases, numerous significant inquiries stay unresolved. We totally lack data about where precisely these proteins bind to their RNA or RNP targets. To innovate physical models for how DEAD-box helicases function, it is critical to characterize where a given protein binds its RNA target, whether and how the RNA structure is altered, and in which way ATP is used for this reaction. Also, it is crucial to clarify how biochemical functions of the DEAD-box proteins are modified by other factors, which constantly surround the helicase in huge multicomponent complexes. The various biochemical characteristics of DEAD-box RNA helicases would permit them to integrate various processes in RNA metabolism: for instance they could couple transcription, RNA processing and RNA export by means of arranged and controlled interactions with various protein partners. Such multi-functionality would, nonetheless, be profoundly context dependent and would rely upon the availability of interacting partners. There are numerous central questions that required to be addressed with respect to the exact mechanism(s) of action of DEAD-box proteins. For instance, it has been affirmed that many of these proteins function as transcriptional coregulators, modulating transcriptional initiation via their interactions with components of the transcription machinery at responsive promoters, in spite of the fact that there is no evidence that they straightforwardly bind chromatin. Nonetheless, it is indistinct what determines whether they function as co-activators or corepressors. Moreover, the mechanisms by which they may couple transcriptional initiation to post-transcriptional processes stay to be clarified: it is unknown whether these proteins bind the nascent RNAs and then function as 'adaptor' molecules to recruit splicing or export factors to facilitate these processes. In this regard, it would additionally be intriguing to test the significance of helicase activity in these events since it seems to be required for some but not all the identified roles. Likewise, the exact functions of DEAD-box proteins in other processes, e.g., regulation of translation or miRNA biogenesis, are not completely understood and a significant proportion of the evidence depends on their association with the respective protein complexes and the impacts of overexpression or siRNA knockdown investigations.

Numerous DEAD-box proteins are aberrantly expressed in cancer tissues as compared with matched normal tissue and in some cases, they additionally seem to be differentially post-translationally modified, supporting the notion that changes in protein levels or modification can affect their role in cell proliferation and/or transformation. Nonetheless, the exact function of DEAD-box proteins will obviously rely upon their interacting partners, the expression and/or role of which might additionally be independently changed during tumor development. In this regard, alterations in post-translational modification of DEAD-box proteins will additionally affect their interactions with partners and their influence on various cellular processes, adding further intricacy. Consequently, 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 reliance would obviously have deep implications for the consideration of DEAD-box proteins as potential markers or therapeutic targets in cancer. Accordingly, before deciding to therapeutically target a particular DEAD-box protein, it will be critical to consider the type, or indeed subtype, of malignancy and the expression of other interacting partners, since the treatment could have contradicting impacts in various contexts. Another issue to be taken into consideration, is the fact that, not all the roles of DEAD-box proteins rely upon their catalytic activities. Many, actually, are mediated by direct protein–protein interactions. Others rely upon the ATPase, but not on the helicase activity. Hence, by cautiously choosing chemical compounds able to target a particular function, either a catalytic activity or a protein–protein interaction, it is additionally possible to imagine of accomplishing the desired selectivity against the diseased cells, leaving the normal ones unaffected. Undoubtedly, at this point we cannot rule out the risk of long-term toxicity issues following continuous inhibition of a DEAD-box protein. This needs to be more cautiously investigated in preclinical models. For a DEAD-box protein to become a feasible therapeutic target in cancer, we need to develop an improved comprehension of its numerous functions to target them selectively and with negligible perturbation to cell homoeostasis.

Declarations

Conflict of interest Mohamed A. M. Ali has no conflicts of interest directly relevant to the content of this article.

References

1. Fairman-Williams ME, Guenther UP, Jankowsky E (2010) SF1 and SF2 helicases: family matters. Curr Opin Struct Biol 20(3):313–324
2. Linder P, Lasko PF, Ashburner M et al (1989) Birth of the D-E-A-D box. Nature 337(6203):121–122. Erratum in: (1989) Nature 340(6230):246
3. Linder P, Fuller-Pace FV (2013) Looking back on the birth of DEAD-box RNA helicases. Biochim Biophys Acta 1829(8):750–755
4. Russell R, Jarmoskaite I, Lambowitz AM (2013) Toward a molecular understanding of RNA remodeling by DEAD-box proteins. RNA Biol 10(1):44–55
5. Rocak S, Linder P (2004) DEAD-box proteins: the driving forces behind RNA metabolism. Nat Rev Mol Cell Biol 5(3):232–241
6. Caruthers JM, McKay DB (2002) Helicase structure and mechanism. Curr Opin Struct Biol 12(1):123–133
7. Putnam AA, Jankowsky E (2013) DEAD-box helicases as integrators of RNA, nucleotide and protein binding. Biochim Biophys Acta 1829(8):884–893
8. Fuller-Pace FV (2006) DExD/H box RNA helicases: multifunctional proteins with important roles in transcriptional regulation. Nucleic Acids Res 34(15):4206–4215
9. Abdelhaleem M (2004) Do human RNA helicases have a role in cancer? Biochim Biophys Acta 1704(1):37–46
10. Fuller-Pace FV (2013) DEAD box RNA helicase functions in cancer. RNA Biol 10(1):121–132
11. Robert F, Pelletier J (2013) Perturbations of RNA helicases in cancer. Wiley Interdiscip Rev RNA 4(4):333–349
12. Steimer L, Klostermeier D (2012) RNA helicases in infection and disease. RNA Biol 9(6):751–771
13. Jankowsky E (2011) RNA helicases at work: binding and rearranging. Trends Biochem Sci 36(1):19–29
14. Cordin O, Banroques J, Tanner NK et al (2006) The DEAD-box protein family of RNA helicases. Gene 367:17–37
15. Singleton MR, Dillingham MS, Wigley DB (2007) Structure and mechanism of helicases and nucleic acid translocases. Annu Rev Biochem 76:23–50
16. Andersen CB, Ballut L, Johansen JS et al (2006) Structure of the exon junction core complex with a trapped DEAD-box ATPase bound to RNA. Science 313(5795):1968–1972
17. Hilbert M, Karow AR, Klostermeier D (2009) The mechanism of ATP-dependent RNA unwinding by DEAD box proteins. Biol Chem 390(12):1237–1250
18. Mallam AL, Sidote DJ, Lambowitz AM (2014) Molecular insights into RNA and DNA helicase evolution from the determinants of specificity for a DEAD-box RNA helicase. eLife 3:e04630
19. Tanner NK (2003) The newly identified Q motif of DEAD box helicases is involved in adenine recognition. Cell Cycle 2(1):18–19
20. Samatanga B, Klostermeier D (2014) DEAD-box RNA helicase domains exhibit a continuum between complete functional independence and high thermodynamic coupling in nucleotide and RNA duplex recognition. Nucleic Acids Res 42(16):10644–10654
21. Hardin JW, Hu YX, McKay DB (2010) Structure of the RNA binding domain of a DEAD-box helicase bound to its ribosomal RNA target reveals a novel mode of recognition by an RNA recognition motif. J Mol Biol 402(2):412–427
22. Schütz P, Karlberg T, van den Berg S et al (2010) Comparative structural analysis of human DEAD-box RNA helicases. PLoS ONE 5(9):e12791
23. Jarmoskaite I, Russell R (2014) RNA helicase proteins as chaperones and remodelers. Annu Rev Biochem 83:697–725
24. Bourgeois CF, Mortreux F, Auboeuf D (2016) The multiple functions of RNA helicases as drivers and regulators of gene expression. Nat Rev Mol Cell Biol 17(7):426–438
25. Bléoo S, Sun X, Hendzel MJ et al (2001) Association of human DEAD box protein DDX1 with a cleavage stimulation factor involved in 3'-end processing of pre-MRNA. Mol Biol Cell 12(10):3046–3059
26. Chen HC, Lin WC, Tsay YG et al (2002) An RNA helicase, DDX1, interacting with poly(A) RNA and heterogeneous nuclear ribonucleoprotein K. J Biol Chem 277(43):40403–40409
27. Kanai Y, Dohmae N, Hirokawa N (2004) Kinesin transports RNA: isolation and characterization of an RNA-transporting granule. Neuron 43(4):513–525
28. Li L, Monckton EA, Godbout R (2008) A role for DEAD box 1 at DNA double-strand breaks. Mol Cell Biol 28(20):6413–6425

29. Ishaq M, Ma L, Wu X et al (2009) The DEAD-box RNA helicase DDX1 interacts with RelA and enhances nuclear factor kappaB-mediated transcription. J Cell Biochem 106(2):296–305

30. Schröder M (2010) Human DEAD-box protein 3 has multiple functions in gene regulation and cell cycle control and is a prime target for viral manipulation. Biochem Pharmacol 79(3):297–306

31. Zhou Z, Licklider LJ, Gygi SP et al (2002) Comprehensive proteomic analysis of the human spliceosome. Nature 419(6903):182–185

32. Merz C, Urlaub H, Will CL et al (2007) Protein composition of human mRNPs spliced in vitro and differential requirements for mRNP protein recruitment. RNA 13(1):116–128

33. Lai MC, Lee YH, Tarn WY (2008) The DEAD-box RNA helicase DDX3 associates with export messenger ribonucleoproteins as well as tip-associated protein and participates in translational control. Mol Biol Cell 19(9):3847–3858

34. Choi YJ, Lee SG (2012) The DEAD-box RNA helicase DDX3 interacts with DDX5, co-localizes with it in the cytoplasm during the G2/M phase of the cycle, and affects its shuttling during mRNP export. J Cell Biochem 113(3):985–996

35. Oshiumi H, Sakai K, Matsumoto M et al (2010) DEAD/H BOX 3 (DDX3) helicase binds the RIG-I adaptor IPS-1 to up-regulate IFN-beta-inducing potential. Eur J Immunol 40(4):940–948

36. Chao CH, Chen CM, Cheng PL et al (2006) DDX3, a DEAD box RNA helicase with tumor growth-suppressive property and transcriptional regulation activity of the p21waf1/cip1 promoter, is a candidate tumor suppressor. Cancer Res 66(13):6579–6588

37. Sun M, Song L, Zhou T et al (2011) The role of DDX3 in regulating Snail. Biochim Biophys Acta 1813(3):438–447

38. Botlagunta M, Vesuna F, Mironchik Y et al (2008) Oncogenic role of DDX3 in breast cancer biogenesis. Oncogene 27(28):3912–3922

39. Shih JW, Tsai TY, Chao CH et al (2008) Candidate tumor suppressor DDX3 RNA helicase specifically represses cap-dependent translation by acting as an eIF4E inhibitory protein. Oncogene 27(5):700–714

40. Soto-Rifo R, Rubilar PS, Limousin T et al (2012) DEAD-box protein DDX3 associates with eIF4F to promote translation of selected mRNAs. EMBO J 31(18):3745–3756

41. Fuller-Pace FV (2013) The DEAD box proteins DDX5 (p68) and DDX17 (p72): multi-tasking transcriptional regulators. Biochim Biophys Acta 1829(8):756–763

42. Fuller-Pace FV, Moore HC (2011) RNA helicases p68 and p72: multifunctional proteins with important implications for cancer development. Future Oncol 7(2):239–251

43. Clark EL, Coulson A, Dalgliesh C et al (2008) The RNA helicase p68 is a novel androgen receptor coactivator involved in splicing and is overexpressed in prostate cancer. Cancer Res 68(19):7938–7946

44. Jensen ED, Niu L, Caretti G et al (2008) p68 (Ddx5) interacts with Runx2 and regulates osteoblast differentiation. J Cell Biochem 103(5):1438–1451

45. Wang R, Jiao Z, Li R et al (2012) p68 RNA helicase promotes glioma cell proliferation in vitro and in vivo via direct regulation of NF-κB transcription factor p50. Neuro Oncol 14(9):1116–1124

46. Yang L, Lin C, Liu ZR (2006) P68 RNA helicase mediates PDGF-induced epithelial mesenchymal transition by displacing Axin from beta-catenin. Cell 127(1):139–155

47. Yang L, Lin C, Zhao S et al (2007) Phosphorylation of p68 RNA helicase plays a role in platelet-derived growth factor-induced cell proliferation by up-regulating cyclin D1 and c-Myc expression. J Biol Chem 282(23):16811–16819

48. Mazurek A, Luo W, Krasnitz A et al (2012) DDX5 regulates DNA replication and is required for cell proliferation in a subset of breast cancer cells. Cancer Discov 2(9):812–825

49. Carter CL, Lin C, Liu CY et al (2010) Phosphorylated p68 RNA helicase activates Snail1 transcription by promoting HDAC1 dissociation from the Snail1 promoter. Oncogene 29(39):5427–5436

50. Caretti G, Schiltz RL, Dilworth FJ et al (2006) The RNA helicases p68/p72 and the noncoding RNA SRA are coregulators of MyoD and skeletal muscle differentiation. Dev Cell 11(4):547–560

51. Bates GJ, Nicol SM, Wilson BJ et al (2005) The DEAD box protein p68: a novel transcriptional coactivator of the p53 tumour suppressor. EMBO J 24(3):543–553

52. Nicol SM, Bray SE, Black HD et al (2013) The RNA helicase p68 (DDX5) is selectively required for the induction of p53-dependent p21 expression and cell-cycle arrest after DNA damage. Oncogene 32(29):3461–3469

53. Wagner M, Rid R, Maier CJ et al (2012) DDX5 is a multifunctional co-activator of steroid hormone receptors. Mol Cell Endocrinol 361(1–2):80–91

54. Jacobs AM, Nicol SM, Hislop RG et al (2007) SUMO modification of the DEAD box protein p68 modulates its transcriptional activity and promotes its interaction with HDAC1. Oncogene 26(40):5866–5876

55. Mooney SM, Grande JP, Salisbury JL et al (2010) Sumoylation of p68 and p72 RNA helicases affects protein stability and transactivation potential. Biochemistry 49(1):1–10

56. Mooney SM, Goel A, D'Assoro AB et al (2010) Pleiotropic effects of p300-mediated acetylation on p68 and p72 RNA helicase. J Biol Chem 285(40):30443–30452

57. Wilson BJ, Bates GJ, Nicol SM et al (2004) The p68 and p72 DEAD box RNA helicases interact with HDAC1 and repress transcription in a promoter-specific manner. BMC Mol Biol 5:11

58. Germann S, Gratadou L, Zonta E et al (2012) Dual role of the ddx5/ddx17 RNA helicases in the control of the pro-migratory NFAT5 transcription factor. Oncogene 31(42):4536–4549

59. Yao H, Brick K, Evrard Y et al (2010) Mediation of CTCF transcriptional insulation by DEAD-box RNA-binding protein p68 and steroid receptor RNA activator SRA. Genes Dev 24(22):2543–2555

60. Dutertre M, Gratadou L, Dardenne E et al (2010) Estrogen regulation and physiopathologic significance of alternative promoters in breast cancer. Cancer Res 70(9):3760–3770

61. Liu ZR (2002) p68 RNA helicase is an essential human splicing factor that acts at the U1 snRNA-5′ splice site duplex. Mol Cell Biol 22(15):5443–5450

62. Lee CG (2002) RH70, a bidirectional RNA helicase, co-purifies with U1snRNP. J Biol Chem 277(42):39679–39683

63. Hönig A, Auboeuf D, Parker MM et al (2002) Regulation of alternative splicing by the ATP-dependent DEAD-box RNA helicase p72. Mol Cell Biol 22(16):5698–5707

64. Camats M, Guil S, Kokolo M et al (2008) P68 RNA helicase (DDX5) alters activity of *cis-* and *trans*-acting factors of the alternative splicing of H-Ras. PLoS ONE 3(8):e2926

65. Dardenne E, Pierredon S, Driouch K et al (2012) Splicing switch of an epigenetic regulator by RNA helicases promotes tumor-cell invasiveness. Nat Struct Mol Biol 19(11):1139–1146

66. Salzman DW, Shubert-Coleman J, Furneaux H (2007) P68 RNA helicase unwinds the human let-7 microRNA precursor duplex and is required for let-7-directed silencing of gene expression. J Biol Chem 282(45):32773–32779

67. Croce CM (2009) Causes and consequences of microRNA dysregulation in cancer. Nat Rev Genet 10(10):704–714

68. Suzuki HI, Yamagata K, Sugimoto K et al (2009) Modulation of microRNA processing by p53. Nature 460(7254):529–533

69. Davis BN, Hilyard AC, Lagna G et al (2008) SMAD proteins control DROSHA-mediated microRNA maturation. Nature 454(7200):56–61

70. Wang D, Huang J, Hu Z (2012) RNA helicase DDX5 regulates microRNA expression and contributes to cytoskeletal reorganization in basal breast cancer cells. Mol Cell Proteom M111.011932:1–12

71. Minshall N, Kress M, Weil D et al (2009) Role of p54 RNA helicase activity and its C-terminal domain in translational repression, P-body localization and assembly. Mol Biol Cell 20(9):2464–2472

72. Chu CY, Rana TM (2006) Translation repression in human cells by microRNA-induced gene silencing requires RCK/p54. Version 2. PLoS Biol 4(7):e210

73. Coller J, Parker R (2005) General translational repression by activators of mRNA decapping. Cell 122(6):875–886

74. Ernoult-Lange M, Baconnais S, Harper M et al (2012) Multiple binding of repressed mRNAs by the P-body protein Rck/p54. RNA 18(9):1702–1715

75. Akao Y, Matsumoto K, Ohguchi K et al (2006) Human DEAD-box/RNA unwindase rck/p54 contributes to maintenance of cell growth by affecting cell cycle in cultured cells. Int J Oncol 29(1):41–48

76. Lin F, Wang R, Shen JJ et al (2008) Knockdown of RCK/p54 expression by RNAi inhibits proliferation of human colorectal cancer cells in vitro and in vivo. Cancer Biol Ther 7(10):1669–1676

77. Westermarck J, Weiss C, Saffrich R et al (2002) The DEXD/H-box RNA helicase RHII/Gu is a co-factor for c-Jun-activated transcription. EMBO J 21(3):451–460

78. Henning D, So RB, Jin R et al (2003) Silencing of RNA helicase II/Gualpha inhibits mammalian ribosomal RNA production. J Biol Chem 278(52):52307–52314

79. Cai W, Xiong Chen Z, Rane G et al (2017) Wanted DEAD/H or alive: helicases winding up in cancers. J Natl Cancer Inst 109(6):1–15

80. Godbout R, Squire J (1993) Amplification of a DEAD box protein gene in retinoblastoma cell lines. Proc Natl Acad Sci USA 90(16):7578–7582

81. Manohar CF, Salwen HR, Brodeur GM et al (1995) Co-amplification and concomitant high levels of expression of a DEAD box gene with MYCN in human neuroblastoma. Genes Chromosomes Cancer 14(3):196–203

82. Squire JA, Thorner PS, Weitzman S et al (1995) Co-amplification of MYCN and a DEAD box gene (DDX1) in primary neuroblastoma. Oncogene 10(7):1417–1422

83. Godbout R, Packer M, Bie W (1998) Overexpression of a DEAD box protein (DDX1) in neuroblastoma and retinoblastoma cell lines. J Biol Chem 273(33):21161–21168

84. George RE, Kenyon RM, McGuckin AG et al (1996) Investigation of co-amplification of the candidate genes ornithine decarboxylase, ribonucleotide reductase, syndecan-1 and a DEAD box gene, DDX1, with N-myc in neuroblastoma. United Kingdom Children's Cancer Study Group. Oncogene 12(7):1583–1587

85. Tanaka K, Okamoto S, Ishikawa Y et al (2009) DDX1 is required for testicular tumorigenesis, partially through the transcriptional activation of 12p stem cell genes. Oncogene 28(21):2142–2151

86. Germain DR, Graham K, Glubrecht DD et al (2011) DEAD box 1: a novel and independent prognostic marker for early recurrence in breast cancer. Breast Cancer Res Treat 127(1):53–63

87. Weber A, Imisch P, Bergmann E et al (2004) Coamplification of DDX1 correlates with an improved survival probability in children with MYCN-amplified human neuroblastoma. J Clin Oncol 22(13):2681–2690

88. Taunk NK, Goyal S, Wu H et al (2012) DEAD box 1 (DDX1) expression predicts for local control and overall survival in early stage, node-negative breast cancer. Cancer 118(4):888–898

89. De Preter K, Speleman F, Combaret V et al (2005) No evidence for correlation of DDX1 gene amplification with improved survival probability in patients with MYCN-amplified neuroblastomas. J Clin Oncol 23(13):3167–3168 ((**author reply 3168–3170**))

90. Kaneko S, Ohira M, Nakamura Y et al (2007) Relationship of DDX1 and NAG gene amplification/overexpression to the prognosis of patients with MYCN-amplified neuroblastoma. J Cancer Res Clin Oncol 133(3):185–192

91. de Souza DR, Sanabani SS, de Souza AC et al (2011) Prognostic impact of MYCN, DDX1, TrkA, and TrkC gene transcripts expression in neuroblastoma. Pediatr Blood Cancer 56(5):749–756

92. Han C, Liu Y, Wan G et al (2014) The RNA-binding protein DDX1 promotes primary microRNA maturation and inhibits ovarian tumor progression. Cell Rep 8(5):1447–1460

93. Eberle J, Krasagakis K, Orfanos CE (1997) Translation initiation factor eIF-4A1 mRNA is consistently overexpressed in human melanoma cells in vitro. Int J Cancer 71(3):396–401

94. Eberle J, Fecker LF, Bittner JU et al (2002) Decreased proliferation of human melanoma cell lines caused by anti-sense RNA against translation factor eIF-4A1. Br J Cancer 86(12):1957–1962

95. Shuda M, Kondoh N, Tanaka K et al (2000) Enhanced expression of translation factor mRNAs in hepatocellular carcinoma. Anticancer Res 20(4):2489–2494

96. Raza F, Waldron JA, Quesne JL (2015) Translational dysregulation in cancer: eIF4A isoforms and sequence determinants of eIF4A dependence. Biochem Soc Trans 43(6):1227–1233

97. Modelska A, Turro E, Russell R et al (2015) The malignant phenotype in breast cancer is driven by eIF4A1-mediated changes in the translational landscape. Cell Death Dis 6(1):e1603

98. Lomnytska MI, Becker S, Gemoll T et al (2012) Impact of genomic stability on protein expression in endometrioid endometrial cancer. Br J Cancer 106(7):1297–1305

99. Liang S, Zhou Y, Chen Y et al (2014) Decreased expression of EIF4A1 after preoperative brachytherapy predicts better tumor-specific survival in cervical cancer. Int J Gynecol Cancer 24(5):908–915

100. Meijer HA, Kong YW, Lu WT et al (2013) Translational repression and eIF4A2 activity are critical for microRNA-mediated gene regulation. Science 340(6128):82–85

101. He Y, Zhang D, Yang Y et al (2018) A double-edged function of DDX3, as an oncogene or tumor suppressor, in cancer progression (review). Oncol Rep 39(3):883–892

102. Riva V, Maga G (2019) From the magic bullet to the magic target: exploiting the diverse roles of DDX3X in viral infections and tumorigenesis. Future Med Chem 11(11):1357–1381

103. Zhao L, Mao Y, Zhou J et al (2016) Multifunctional DDX3: dual roles in various cancer development and its related signaling pathways. Am J Cancer Res 6(2):387–402

104. Ariumi Y (2014) Multiple functions of DDX3 RNA helicase in gene regulation, tumorigenesis, and viral infection. Front Genet 5:423

105. Bol GM, Xie M, Raman V (2015) DDX3, a potential target for cancer treatment. Mol Cancer 14:188

106. Huang JS, Chao CC, Su TL et al (2004) Diverse cellular transformation capability of overexpressed genes in human hepatocellular carcinoma. Biochem Biophys Res Commun 315(4):950–958

107. Heerma van Voss MR, Vesuna F, Trumpi K et al (2015) Identification of the DEAD box RNA helicase DDX3 as a therapeutic target in colorectal cancer. Oncotarget 6(29):28312–28326

108. He TY, Wu DW, Lin PL et al (2016) DDX3 promotes tumor invasion in colorectal cancer via the CK1ε/Dvl2 axis. Sci Rep 6:21483

109. Wu DW, Lin PL, Cheng YW et al (2016) DDX3 enhances oncogenic KRAS-induced tumor invasion in colorectal cancer via the β-catenin/ZEB1 axis. Oncotarget 7(16):22687–22699

110. Heerma van Voss MR, Schrijver WA, Ter Hoeve ND et al (2017) The prognostic effect of DDX3 upregulation in distant breast cancer metastases. Clin Exp Metastasis 34(1):85–92

111. Heerma van Voss MR, Vesuna F, Bol GM et al (2017) Nuclear DDX3 expression predicts poor outcome in colorectal and breast cancer. Onco Targets Ther 10:3501–3513

112. Bol GM, Vesuna F, Xie M et al (2015) Targeting DDX3 with a small molecule inhibitor for lung cancer therapy. EMBO Mol Med 7(5):648–669

113. Miao X, Yang ZL, Xiong L et al (2013) Nectin-2 and DDX3 are biomarkers for metastasis and poor prognosis of squamous cell/adenosquamous carcinomas and adenocarcinoma of gallbladder. Int J Clin Exp Pathol 6(2):179–190

114. Liang S, Yang Z, Li D et al (2015) The clinical and pathological significance of nectin-2 and DDX3 expression in pancreatic ductal adenocarcinomas. Dis Markers 2015:379568

115. Wilky BA, Kim C, McCarty G et al (2016) RNA helicase DDX3: a novel therapeutic target in Ewing sarcoma. Oncogene 35(20):2574–2583

116. Pugh TJ, Weeraratne SD, Archer TC et al (2012) Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. Nature 488(7409):106–110

117. Wang L, Lawrence MS, Wan Y et al (2011) SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. N Engl J Med 365(26):2497–2506

118. Ojha J, Secreto CR, Rabe KG et al (2015) Identification of recurrent truncated DDX3X mutations in chronic lymphocytic leukaemia. Br J Haematol 169(3):445–448

119. Jiang L, Gu ZH, Yan ZX et al (2015) Exome sequencing identifies somatic mutations of DDX3X in natural killer/T-cell lymphoma. Nat Genet 47(9):1061–1066

120. Brandimarte L, Pierini V, Di Giacomo D et al (2013) New MLLT10 gene recombinations in pediatric T-acute lymphoblastic leukemia. Blood 121(25):5064–5067

121. Lai MC, Chang WC, Shieh SY et al (2010) DDX3 regulates cell growth through translational control of cyclin E1. Mol Cell Biol 30(22):5444–5453

122. Li Y, Wang H, Wang Z et al (2006) Inducible resistance of tumor cells to tumor necrosis factor-related apoptosis-inducing ligand receptor 2-mediated apoptosis by generation of a blockade at the death domain function. Cancer Res 66(17):8520–8528

123. Sun M, Song L, Li Y et al (2008) Identification of an antiapoptotic protein complex at death receptors. Cell Death Differ 15(12):1887–1900

124. Cruciat CM, Dolde C, de Groot RE et al (2013) RNA helicase DDX3 is a regulatory subunit of casein kinase 1 in Wnt-β-catenin signaling. Science 339(6126):1436–1441

125. Chen HH, Yu HI, Cho WC et al (2015) DDX3 modulates cell adhesion and motility and cancer cell metastasis via Rac1-mediated signaling pathway. Oncogene 34(21):2790–2800

126. Wang Y, Shi J, Chai K et al (2013) The role of snail in EMT and tumorigenesis. Curr Cancer Drug Targets 13(9):963–972

127. Botlagunta M, Krishnamachary B, Vesuna F et al (2011) Expression of DDX3 is directly modulated by hypoxia inducible factor-1 alpha in breast epithelial cells. PLoS ONE 6(3):e17563

128. Bol GM, Raman V, van der Groep P et al (2013) Expression of the RNA helicase DDX3 and the hypoxia response in breast cancer. PLoS ONE 8(5):e63548

129. Wu DW, Lin PL, Wang L et al (2017) The YAP1/SIX2 axis is required for DDX3-mediated tumor aggressiveness and cetuximab resistance in KRAS-wild-type colorectal cancer. Theranostics 7(5):1114–1132

130. Chang PC, Chi CW, Chau GY et al (2006) DDX3, a DEAD box RNA helicase, is deregulated in hepatitis virus-associated hepatocellular carcinoma and is involved in cell growth control. Oncogene 25(14):1991–2003

131. Wu DW, Liu WS, Wang J et al (2011) Reduced p21(WAF1/CIP1) via alteration of p53-DDX3 pathway is associated with poor relapse-free survival in early-stage human papillomavirus-associated lung cancer. Clin Cancer Res 17(7):1895–1905. Erratum in: (2015) Clin Cancer Res 21(4):935

132. Su CY, Lin TC, Lin YF et al (2015) DDX3 as a strongest prognosis marker and its downregulation promotes metastasis in colorectal cancer. Oncotarget 6(21):18602–18612

133. Wu DW, Lee MC, Wang J et al (2014) DDX3 loss by p53 inactivation promotes tumor malignancy via the MDM2/Slug/E-cadherin pathway and poor patient outcome in non-small-cell lung cancer. Oncogene 33(12):1515–1526

134. Li HK, Mai RT, Huang HD et al (2016) DDX3 represses stemness by epigenetically modulating tumor-suppressive miRNAs in hepatocellular carcinoma. Sci Rep 6:28637

135. Nyamao RM, Wu J, Yu L et al (2019) Roles of DDX5 in the tumorigenesis, proliferation, differentiation, metastasis and pathway regulation of human malignancies. Biochim Biophys Acta Rev Cancer 1871(1):85–98

136. Stevenson RJ, Hamilton SJ, MacCallum DE et al (1998) Expression of the 'dead box' RNA helicase p68 is developmentally and growth regulated and correlates with organ differentiation/maturation in the fetus. J Pathol 184(4):351–359

137. Causevic M, Hislop RG, Kernohan NM et al (2001) Overexpression and poly-ubiquitylation of the DEAD-box RNA helicase p68 in colorectal tumours. Oncogene 20(53):7734–7743

138. Du C, Li DQ, Li N et al (2017) DDX5 promotes gastric cancer cell proliferation in vitro and in vivo through mTOR signaling pathway. Sci Rep 7:42876

139. Ma Z, Feng J, Guo Y et al (2017) Knockdown of DDX5 inhibits the proliferation and tumorigenesis in esophageal cancer. Oncol Res 25(6):887–895

140. Guturi KK, Sarkar M, Bhowmik A et al (2014) DEAD-box protein p68 is regulated by β-catenin/transcription factor 4 to maintain a positive feedback loop in control of breast cancer progression. Breast Cancer Res 16(6):496

141. Iyer RS, Nicol SM, Quinlan PR et al (2014) The RNA helicase/transcriptional co-regulator, p68 (DDX5), stimulates expression of oncogenic protein kinase, Polo-like kinase-1 (PLK1), and is associated with elevated PLK1 levels in human breast cancers. Cell Cycle 13(9):1413–1423

142. Stone B, Schummer M, Paley PJ et al (2003) Serologic analysis of ovarian tumor antigens reveals a bias toward antigens encoded on 17q. Int J Cancer 104(1):73–84

143. Clark EL, Hadjimichael C, Temperley R et al (2013) p68/DdX5 supports β-catenin & RNAP II during androgen receptor mediated transcription in prostate cancer. PLoS ONE 8(1):e54150

144. Wang Z, Luo Z, Zhou L et al (2015) DDX5 promotes proliferation and tumorigenesis of non-small-cell lung cancer cells by activating β-catenin signaling pathway. Cancer Sci 106(10):1303–1312

145. Beier UH, Maune S, Meyer JE et al (2006) Overexpression of p68 mRNA in head and neck squamous cell carcinoma cells. Anticancer Res 26(3A):1941–1946

146. Wang SJ, Zhang C, You Y et al (2012) Overexpression of RNA helicase p68 protein in cutaneous squamous cell carcinoma. Clin Exp Dermatol 37(8):882–888

147. Felix RS, Colleoni GW, Caballero OL et al (2009) SAGE analysis highlights the importance of p53csv, ddx5, mapkapk2 and ranbp2 to multiple myeloma tumorigenesis. Cancer Lett 278(1):41–48

148. Lin S, Tian L, Shen H et al (2013) DDX5 is a positive regulator of oncogenic NOTCH1 signaling in T cell acute lymphoblastic leukemia. Oncogene 32(40):4845–4853

149. Mazurek A, Park Y, Miething C et al (2014) Acquired dependence of acute myeloid leukemia on the DEAD-box RNA helicase DDX5. Cell Rep 7(6):1887–1899

150. Kitagawa N, Ojima H, Shirakihara T et al (2013) Downregulation of the microRNA biogenesis components and its association with poor prognosis in hepatocellular carcinoma. Cancer Sci 104(5):543–551

151. He X (2006) Unwinding a path to nuclear beta-catenin. Cell 127(1):40–42

152. Dai TY, Cao L, Yang ZC et al (2014) P68 RNA helicase as a molecular target for cancer therapy. J Exp Clin Cancer Res 33(1):64

153. Yang L, Lin C, Liu ZR (2005) Phosphorylations of DEAD box p68 RNA helicase are associated with cancer development and cell proliferation. Mol Cancer Res 3(6):355–363

154. Dey H, Liu ZR (2012) Phosphorylation of p68 RNA helicase by p38 MAP kinase contributes to colon cancer cells apoptosis induced by oxaliplatin. BMC Cell Biol 13:27

155. Yang L, Lin C, Sun SY et al (2007) A double tyrosine phosphorylation of P68 RNA helicase confers resistance to TRAIL-induced apoptosis. Oncogene 26(41):6082–6092

156. Bray SJ (2016) Notch signalling in context. Nat Rev Mol Cell Biol 17(11):722–735

157. Kopan R, Ilagan MX (2009) The canonical Notch signaling pathway: unfolding the activation mechanism. Cell 137(2):216–233

158. Jung C, Mittler G, Oswald F et al (2013) RNA helicase Ddx5 and the noncoding RNA SRA act as coactivators in the Notch signaling pathway. Biochim Biophys Acta 1833(5):1180–1189

159. Hoesel B, Schmid JA (2013) The complexity of NF-κB signaling in inflammation and cancer. Mol Cancer 12:86

160. Kokolo M, Bach-Elias M (2017) Downregulation of p68 RNA helicase (DDX5) activates a survival pathway involving mTOR and MDM2 signals. Folia Biol (Praha) 63(2):52–59

161. Sarkar M, Khare V, Guturi KK et al (2015) The DEAD box protein p68: a crucial regulator of AKT/FOXO3a signaling axis in oncogenesis. Oncogene 34(47):5843–5856

162. Sha M, Lin M, Wang J et al (2018) Long non-coding RNA MIAT promotes gastric cancer growth and metastasis through regulation of miR-141/DDX5 pathway. J Exp Clin Cancer Res 37(1):58

163. Wu N, Han Y, Liu H et al (2018) miR-5590-3p inhibited tumor growth in gastric cancer by targeting DDX5/AKT/m-TOR pathway. Biochem Biophys Res Commun 503(3):1491–1497

164. Lamm GM, Nicol SM, Fuller-Pace FV et al (1996) p72: a human nuclear DEAD box protein highly related to p68. Nucleic Acids Res 24(19):3739–3747

165. Janknecht R (2010) Multi-talented DEAD-box proteins and potential tumor promoters: p68 RNA helicase (DDX5) and its paralog, p72 RNA helicase (DDX17). Am J Transl Res 2(3):223–234

166. Shin S, Rossow KL, Grande JP et al (2007) Involvement of RNA helicases p68 and p72 in colon cancer. Cancer Res 67(16):7572–7578

167. Wortham NC, Ahamed E, Nicol SM et al (2009) The DEAD-box protein p72 regulates ERalpha-/oestrogen-dependent transcription and cell growth, and is associated with improved survival in ERalpha-positive breast cancer. Oncogene 28(46):4053–4064

168. Samaan S, Tranchevent LC, Dardenne E et al (2014) The Ddx5 and Ddx17 RNA helicases are cornerstones in the complex regulatory array of steroid hormone-signaling pathways. Nucleic Acids Res 42(4):2197–2207

169. Lu D, Yunis JJ (1992) Cloning, expression and localization of an RNA helicase gene from a human lymphoid cell line with chromosomal breakpoint 11q23.3. Nucleic Acids Res 20(8):1967–1972

170. Akao Y, Seto M, Yamamoto K et al (1992) The RCK gene associated with t(11;14) translocation is distinct from the MLL/ALL-1 gene with t(4;11) and t(11;19) translocations. Cancer Res 52(21):6083–6087

171. Akao Y, Marukawa O, Morikawa H et al (1995) The rck/p54 candidate proto-oncogene product is a 54-kilodalton D-E-A-D box protein differentially expressed in human and mouse tissues. Cancer Res 55(15):3444–3449

172. Nakagawa Y, Morikawa H, Hirata I et al (1999) Overexpression of rck/p54, a DEAD box protein, in human colorectal tumours. Br J Cancer 80(5–6):914–917

173. Hashimoto K, Nakagawa Y, Morikawa H et al (2001) Co-over-expression of DEAD box protein rck/p54 and c-myc protein in human colorectal adenomas and the relevance of their expression in cultured cell lines. Carcinogenesis 22(12):1965–1970

174. Miyaji K, Nakagawa Y, Matsumoto K et al (2003) Overexpression of a DEAD box/RNA helicase protein, rck/p54, in human hepatocytes from patients with hepatitis C virus-related chronic hepatitis and its implication in hepatocellular carcinogenesis. J Viral Hepat 10(4):241–248

175. Iio A, Takagi T, Miki K et al (2013) DDX6 post-transcriptionally down-regulates miR-143/145 expression through host gene NCR143/145 in cancer cells. Biochim Biophys Acta 1829(10):1102–1110

176. Taniguchi K, Iwatsuki A, Sugito N et al (2018) Oncogene RNA helicase DDX6 promotes the process of c-Myc expression in gastric cancer cells. Mol Carcinog 57(5):579–589

177. Akao Y, Yoshida H, Matsumoto K et al (2003) A tumour-associated DEAD-box protein, rck/p54 exhibits RNA unwinding activity toward c-myc RNAs in vitro. Genes Cells 8(8):671–676

178. Taniguchi K, Sugito N, Kumazaki M et al (2015) Positive feedback of DDX6/c-Myc/PTB1 regulated by miR-124 contributes to maintenance of the Warburg effect in colon cancer cells. Biochim Biophys Acta 1852(9):1971–1980

179. Tajirika T, Tokumaru Y, Taniguchi K et al (2018) DEAD-box protein RNA-helicase DDX6 regulates the expression of HER2 and FGFR2 at the post-transcriptional step in gastric cancer cells. Int J Mol Sci 19(7):2005

180. Tokumaru Y, Tajirika T, Sugito N et al (2019) Synthetic miR-143 inhibits growth of HER2-positive gastric cancer cells by suppressing KRAS networks including DDX6 RNA helicase. Int J Mol Sci 20(7):1697

181. Stary S, Vinatzer U, Müllauer L et al (2013) t(11;14)(q23;q32) involving IGH and DDX6 in nodal marginal zone lymphoma. Genes Chromosomes Cancer 52(1):33–43

182. Akao Y, Mizoguchi H, Ohishi N et al (1998) Growth inhibition by overexpression of human DEAD box protein rck/p54 in cells of a guinea pig cell line. FEBS Lett 429(3):279–83. Erratum in: (1998) FEBS Lett 437(1–2):163

183. Jiao X, Hooper SD, Djureinovic T et al (2013) Gene rearrangements in hormone receptor negative breast cancers revealed by mate pair sequencing. BMC Genom 14:165

184. Arai Y, Hosoda F, Kobayashi H et al (1997) The inv(11)(p15q22) chromosome translocation of de novo and therapy-related myeloid malignancies results in fusion of the nucleoporin gene, NUP98, with the putative RNA helicase gene, DDX10. Blood 89(11):3936–3944

185. Griffis ER, Xu S, Powers MA (2003) Nup98 localizes to both nuclear and cytoplasmic sides of the nuclear pore and binds

to two distinct nucleoporin subcomplexes. Mol Biol Cell 14(2):600–610

186. Yassin ER, Abdul-Nabi AM, Takeda A et al (2010) Effects of the NUP98-DDX10 oncogene on primary human CD34+ cells: role of a conserved helicase motif. Leukemia 24(5):1001–1011

187. Yamamoto M, Kakihana K, Kurosu T et al (2005) Clonal evolution with inv(11)(p15q22) and NUP98/DDX10 fusion gene in imatinib-resistant chronic myelogenous leukemia. Cancer Genet Cytogenet 157(2):104–108

188. Curmi F, Cauchi RJ (2018) The multiple lives of DEAD-box RNA helicase DP103/DDX20/Gemin3. Biochem Soc Trans 46(2):329–341

189. Shin EM, Hay HS, Lee MH et al (2014) DEAD-box helicase DP103 defines metastatic potential of human breast cancers. J Clin Investig 124(9):3807–3824

190. Shin EM, Osato M, Kumar AP et al (2015) RNA helicase DP103 and TAK1: a new connection in cancer. Mol Cell Oncol 2(3):e985911

191. Chen W, Zhou P, Li X (2016) High expression of DDX20 enhances the proliferation and metastatic potential of prostate cancer cells through the NF-κB pathway. Int J Mol Med 37(6):1551–1557

192. Zender L, Xue W, Zuber J et al (2008) An oncogenomics-based in vivo RNAi screen identifies tumor suppressors in liver cancer. Cell 135(5):852–864

193. Takata A, Otsuka M, Yoshikawa T et al (2013) MicroRNA-140 acts as a liver tumor suppressor by controlling NF-κB activity by directly targeting DNA methyltransferase 1 (Dnmt1) expression. Hepatology 57(1):162–170

194. Takata A, Otsuka M, Yoshikawa T et al (2012) A miRNA machinery component DDX20 controls NF-κB via microRNA-140 function. Biochem Biophys Res Commun 420(3):564–569

195. Zhang Y, Baysac KC, Yee LF et al (2014) Elevated DDX21 regulates c-Jun activity and rRNA processing in human breast cancers. Breast Cancer Res 16(5):449

196. Antony-Debré I, Steidl U (2015) Functionally relevant RNA helicase mutations in familial and sporadic myeloid malignancies. Cancer Cell 27(5):609–611

197. Polprasert C, Schulze I, Sekeres MA et al (2015) Inherited and somatic defects in DDX41 in myeloid neoplasms. Cancer Cell 27(5):658–670

198. Lewinsohn M, Brown AL, Weinel LM et al (2016) Novel germ line DDX41 mutations define families with a lower age of MDS/AML onset and lymphoid malignancies. Blood 127(8):1017–1023

199. Cardoso SR, Ryan G, Walne AJ et al (2016) Germline heterozygous DDX41 variants in a subset of familial myelodysplasia and acute myeloid leukemia. Version 2. Leukemia 30(10):2083–2086

200. Li R, Sobreira N, Witmer PD et al (2016) Two novel germline DDX41 mutations in a family with inherited myelodysplasia/acute myeloid leukemia. Haematologica 101(6):e228–e231

201. Martelange V, De Smet C, De Plaen E et al (2000) Identification on a human sarcoma of two new genes with tumor-specific expression. Cancer Res 60(14):3848–3855

202. Abdel-Fatah TM, McArdle SE, Johnson C et al (2014) HAGE (DDX43) is a biomarker for poor prognosis and a predictor of chemotherapy response in breast cancer. Br J Cancer 110(10):2450–2461

203. Lin J, Chen Q, Yang J et al (2014) DDX43 promoter is frequently hypomethylated and may predict a favorable outcome in acute myeloid leukemia. Leuk Res 38(5):601–607

204. Cho B, Lim Y, Lee DY et al (2002) Identification and characterization of a novel cancer/testis antigen gene CAGE. Biochem Biophys Res Commun 292(3):715–726

205. Cho B, Lee H, Jeong S et al (2003) Promoter hypomethylation of a novel cancer/testis antigen gene CAGE is correlated with its aberrant expression and is seen in premalignant stage of gastric carcinoma. Biochem Biophys Res Commun 307(1):52–63

206. Kukhanova MK, Karpenko IL, Ivanov AV (2020) DEAD-box RNA helicase DDX3: functional properties and development of DDX3 inhibitors as antiviral and anticancer drugs. Molecules 25(4):1015

207. Hosmane RS (2002) Ring-expanded ("Fat") nucleosides as broad-spectrum anticancer and antiviral agents. Curr Top Med Chem 2(10):1093–1109

208. Xie M, Vesuna F, Botlagunta M et al (2015) NZ51, a ring-expanded nucleoside analog, inhibits motility and viability of breast cancer cells by targeting the RNA helicase DDX3. Oncotarget 6(30):29901–29913

209. Heerma van Voss MR, Kammers K, Vesuna F et al (2018) Global effects of DDX3 inhibition on cell cycle regulation identified by a combined phosphoproteomics and single cell tracking approach. Transl Oncol 11(3):755–763

210. Xie M, Vesuna F, Tantravedi S et al (2016) RK-33 radiosensitizes prostate cancer cells by blocking the RNA helicase DDX3. Cancer Res. 76(21):6340–6350

211. Heerma van Voss MR, Vesuna F, Bol GM et al (2018) Targeting mitochondrial translation by inhibiting DDX3: a novel radiosensitization strategy for cancer treatment. Oncogene 37(1):63–74

212. Tantravedi S, Vesuna F, Winnard PT Jr et al (2019) Targeting DDX3 in medulloblastoma using the small molecule inhibitor RK-33. Transl Oncol 12(1):96–105

213. Samal SK, Routray S, Veeramachaneni GK et al (2015) Ketorolac salt is a newly discovered DDX3 inhibitor to treat oral cancer. Sci Rep 5:9982

214. Kost GC, Yang MY, Li L et al (2015) A novel anti-cancer agent, 1-(3,5-dimethoxyphenyl)-4-[(6-fluoro-2-methoxyquinoxalin-3-yl)aminocarbonyl] piperazine (RX-5902), interferes with β-catenin function through Y593 phospho-p68 RNA helicase. J Cell Biochem 116(8):1595–1601