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Review

Roles of DDX5 in the tumorigenesis, proliferation, differentiation, metastasis and pathway regulation of human malignancies

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ABSTRACT

The DEAD-box RNA helicase DDX5 is a member of a family of highly conserved proteins involved in gene-expression regulation and ATP-dependent RNA helicase activities. Recently, it has been reported to be aberrantly expressed in many tumors, and is linked to the regulation of many cancer-related pathways. It co-activates many transcription factors, with profound implications for cancer development, and the de-regulation of its functions is ultimately associated with tumor formation and progression. Moreover, it is strongly implicated in the tumorigenesis, invasiveness and metastasis, as well as the proliferation of several cancer types. In this review, we seek to elucidate the role of DDX5 in the development and progression of human malignancies and put forward its prospective applications in future cancer research.

1. Introduction

DDX5 is an important helicase which is implicated in many stages of the gene expression pathway including RNA processing (splicing, transport and translation) [1,2], DNA replication [3,4], ribosome and miRNA biogenesis [5–7], and transcription regulation [8–11]. In human malignancies, many studies have detected the overexpression of DDX5 and confirmed its involvement in tumorigenesis, progression, invasion, proliferation, differentiation and metastasis. Its expression also correlates with the regulation of pathways that are critical in cancer development and progression. Thus, DDX5 is a potentially valuable diagnostic and prognostic marker, and its value as a therapeutic target for many tumors has been sufficiently established. Illuminating its role in different tumors, therefore, will give insight into possible intervention points and better management of human malignancies. This review aims at improving the understanding of the exact role played by DDX5 in different stages of human malignancies and the pathways involved, while highlighting advancements in current research that might illuminate the path to achieving early diagnosis, effective therapeutic options, and prediction of response to treatment of human tumors.

1.1. Background of DEAD/H box helicases

The earliest account of RNA helicases was a report by Ray et al. [12] which described the susceptibility of mRNA to nucleases, following the

Abbreviations: DDX5, DEAD-box protein 5; EMT, epithelial-mesenchymal transition; EPSC, EMT promoting Smad complexes; ERα, estrogen receptor alpha; FOXO, forkhead box; HDAC 1, histone deacetylase 1; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; RORγt, retinoid-related orphan receptor gamma-t; TCF, T cell factor; TGF-β, transforming growth factor-beta; TNFα, tumor necrosis factor alpha; HCV, Hepatitis C virus; HIV1, Human immunodeficiency virus 1; SAGE, Serial analysis of gene expression; mTOR, mammalian target of rapamycin; MyoD, Myogenic differentiation; RNAP II, RNA polymerase II; STAT3, Signal transducer and activator of transcription 3; AR, Androgen Receptor; RUNX 2, Runt-related transcription factor 2; IRES, internal ribosome entry site; TCF-4, transcription factor 4; MAML, mastermind-like; NSCLC, non-small cell lung cancer; PDGF, platelet derived growth factor; MIAT, myocardial infarction associated transcript; SRA, steroid receptor RNA activator; VDR, vitamin D receptor; NICD, notch intracellular domain; RBP-J, recombination signal binding protein for immunoglobulin kappa J region; MDM2, murine double minute 2 homolog; RYBP, RING1 And YY1 Binding Protein; EGF, Epidermal Growth Factor; RTK, Receptor Tyrosine Kinase; TSC, Tuberous Sclerosis; RHEB, Ras homolog enriched in brain; LRP, Lipoprotein receptor-related protein; eIF4a, eukaryotic initiation factor 4a; GSK-3β, Glycogen synthase kinase-3β; NFAT, Nuclear Factor of activated T Cells

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incubation of globin mRNA with translation initiation factor (eIF4A) and ATP. RNA helicases are ubiquitously expressed in almost all organisms and are largely found in differentiated cells [13–16]. The helicases utilize energy from nucleotide triphosphate (NTP) hydrolysis to perform biological functions like ribosome biogenesis, pre-mRNA splicing, transcription and translation [17,18]. The expression pattern, sequence, interacting molecules and subcellular localization of the helicases determine their specificity to the target molecules they bind and regulate [17]. RNA helicases are divided into 6 super-families (SF) with the largest being SF2 comprising of highly conserved proteins with seven domains including the 'DEAD/H' sequence [19]. They are further classified into DEAD, DEAH, and DExH depending on their motifs and specific amino acid sequences [9,20]. The DEAD-box family, characterized by the Asp-Glu-Ala-Asp motif, is the largest of all helicase families with 37 members in humans [21]. Several RNA helicases have been implicated in cancer development due to their altered expression, mutations in tumors, and their regulation of pathways concerned with oncogenesis and progression [22]. Recently, some reviews on DEAD/H-Box helicases and their functions that link them to cancer have been published [23,24]. In this review, we will narrow our focus on DDX5 and its role in human cancers.

1.2. Sequence, structure and functions of DDX5 and other DEAD-box helicases

DEAD-box helicases are eukaryotic RNA helicases that do not form ring structures [21,25]. They have a helicase core that comprises of two conserved recombinase A (RecA)-like domains; an N-terminal RecA-like domain (NTD) and a C-terminal RecA-like domain (CTD) joined together by a short flexible linker [26]. The NTD/DEAD domain is responsible for ATP binding, while the CTD/helicase domain contains the binding site for RNA substrates [27,28]. DEAD-box proteins have 13 characteristic sequence motifs, 9 of which are conserved [19,29]. The NTD harbors motifs Q, I (Walker A), Ia, Ib, II (Walker B), and III whereas the CTD contains motifs IV, V and VI [30]. Motifs I, II and Q form the nucleotide-binding site while motif III links ATP binding, hydrolysis and helical activity [31]. As much as the structures of DEAD-box proteins have similar conserved NTD and CTD folds, the loop conformation within the domain structures and the inter-domain orientations differ from each other [32,33]. Analysis of the crystal structures of the domains of members of the DEAD-box family reveals some differences presented in Table 1 [34]. The domain structure of DDX5 is well described in a review by Cheng et al. [28]. The CTD of DDX5 contains motifs IV, V, and VI common to other DEAD-box members, and additional RGS-RGG (Arg-Gly-Ser-Arg-Gly-Gly) and Ile-Gln (IQ) motifs which form the RNA binding site [1,35]. The NTD has been successfully crystallized and is made up of 305 amino acid residues, 8 β strands, 9 α helicases and is structurally similar to DDX3X [30,36]. It also contains the N terminal region (57–78 residues) which forms the extensive loop and adds an extra α helix to the helicase core. All the other features of DDX5 are similar to the other members of the DEAD-box family.

DDX5 was first reported to be a nuclear antigen that was immunologically cross-reactive to the T-antigen of the Simian Virus 40 [16]. The ATPase and RNA unwinding activities of DDX5 were first reported in protein from human cells and recombinant proteins expressed in *E. coli* [13,16,39]. The molecular weight of DDX5 is 69 kDa with 614 amino acids and it is located on chromosome 17q23. Following transcription, the DDX5 gene yields an mRNA precursor which is spliced to form two 2.3 kb and 4.4 kb mRNA transcripts. While the 2.3 kb transcript codes for full-length DDX5, the 4.4 kb transcript does not code for any viable product [40]. Originally, DDX5 was thought to be an exclusively nuclear protein [16]. However, transient cytoplasmic localization and staining in ovarian, colon and breast cancer cell lines have challenged this paradigm [41]. Eventually, Wang et al. [42] affirmed the conclusion that DDX5 is actually a nucleocytoplasmic shuttling protein. The main mutation of DDX5 (S480A mutation) has been reported by Guo et al. [43] in hepatic stellate cells. Other numerous mutations have recently been observed on the DDX5 gene in different malignancies as reported by Cai et al. [23] Several post-translational modifications of DDX5 are reported including ubiquitination, sumorylation and phosphorylation [7,44,45]. A summary of DDX5 functions and the significant roles in cancer is presented in Table 2.

2. Emerging roles of DDX5 in viral infections associated with cancer

Recent studies have linked approximately 12% of human malignancies to oncoviral infections [70]. Besides interfering with the function of critical cellular proteins, some oncoviruses cause malignancies by maintaining viral latency and producing latently expressed oncoproteins [71]. DEAD-box helicases interact with viruses and help them complete their life cycles by ATP hydrolysis and assembly of big ribonucleoprotein complexes [72]. DDX5 is reported to regulate the replication of several oncogenic viruses like HCV, HIV-1, EBV and HPV [28] as summarized in Table 3. As much as HIV is not by direct mechanism an oncogenic virus, the immunodeficient state caused by the infection is a possible oncogenic mechanism [73]. DDX5 regulates the HIV-1 Rev. factor which induces late-phase replication. Experimental inhibition of the DDX5-Rev interaction significantly reduces HIV-1 replication. Thus, since HIV-1 does not encode its own RNA helicase, host DDX5 is therefore a potential anti-HIV 1 therapeutic agent [28,74]. A recent study has shown that DDX5 controls viral transcription at different phases of the HIV-1 life cycle [75]. Moreover, DDX5 has been largely implicated in the replication of hepatitis C virus (HCV) which in

Table 1
Differences in the domain structure of DEAD-box helicases.

Distinguishing features	Differences	DEAD-Box helicase	Reference
1. Flexible P-loop	Wide-open conformation	DDX19, DDX20, DDX3X	[34]
	Closed conformation	DDX2B, DDX5	[30,34]
	DDX3X P-loop is in complex with AMP		[36]
	DDX5 P-loop is in APO form		[30]
2. ATP co-ordination	Phenylalanine[a]	DDX5	[34]
	Tyrosine[a]	DDX10	
	Tryptophan[a]	DDX47	
	Isoleucine[b]	DDX53	[34]
3.Helicase domain variation	Flexible helicase domain	DDX25, DDX41	[34]
	Phenylalanine stacks with the adenosine ring	DDX19	
4.RNA binding site	Conserved motif Ib forms part of the RNA binding site	DDX5, DDX47, DDX19	[34,37]
5.Auxilliary domains	Insertion of other domains into the amino-terminal helicase domain	DDX24, DDX1	[38]

[a] Describes the Side-chain of the 6th aromatic residue.
[b] Describes the alternative of the aromatic residue.

Table 2
Summary of DDX5 functions.

DDX5 function	Factors associated	Significance and role in cancer	References
miRNA biogenesis (growth suppressive and oncogenic miRNAs)	DROSHA/DGCR8 complex	Deregulation of miRNA biogenesis leads to tumor development	[5–7,46–48]
Splicing (Pre-mRNA/Pre-/rRNA/alternative splicing)	Part of DROSHA complex	Required for pre-mRNA splicing, alternative splicing and exon skipping	[49–55]
Co-activator/Co-regulator of transcription	AR, ER α, β-catenin	Activate transcription of pro- and anti-proliferative genes	[2,8,11,24,41,56–61]
	MyoD, SMAD, Runx2,	Regulates promoter switching	
	Vitamin D receptor,	Co-activates transcription factors associated with tumor development	
	Notch, NFAT5,c-myc, P53	Transcription of genes required for DNA replication	
Mediates DNA damage response:	Co-activation of p53	Influences cell cycle arrest/apoptosis decision	[3,62,63]
Mediate EMT, cell migration and metastasis	Association with SMAD and MYOD, PDGF, NFAT5, Calmodulin	Regulates PDGF-induced EMT	[64–66]
		Regulates cell migration	
	Phosphorylation by c-Abl	Causes increased motility through ATPase activity	
Mediates Oxiplatin induced Apoptosis	P38 MAP Kinase	Induces apoptosis	[67]
Chromatin re-modelling	SNAIL 1	Mediates gene transcription by modulating chromatin remodeling complex	[68]
DNA methylation and de-methylation	–	Plays a role in development and differentiation	[69]

its chronic form causes hepatocellular carcinoma [76]. It regulates HCV replication by interacting with the HCV NS5B protein [77]. Recently, DDX5 has been reported to influence the translation of HCV viral internal ribosome entry site (IRES), which is responsible for the initiation of viral protein synthesis [78]. The expression level of DDX5 in HCC is of significant research interest, since downregulation is only recorded in HBV positive, HBV negative, and non-HCV HCC but not in HCV-positive HCC [48,76]. As much as DDX5 has been implicated in the development of HCC, there is insufficient evidence to link its deregulation to its interaction with HCV and/or HBV.

3. Role of DDX5 in tumorigenesis

DDX5 is over-expressed in several tumors except hepatocellular carcinoma (HCC) in comparison with matched normal tissue (Fig. 1). It has been implicated in several tumors either through aberrant expression or through its role in the regulation of pathways that directly influence oncogenesis, proliferation, invasion, and metastasis. Post-translational modifications like phosphorylation, sumorylation and polyubiquitylation have been cited as reasons for overexpression of DDX5 and are associated with cellular transformation and survival of tumor cells [85]. Table 4 presents a summary of experimental evidence on the expression level of DDX5 in human malignancies and the corresponding cell fate.

The role of DDX5 in tumorigenesis has long been established. There is compelling evidence linking DDX5 and tumorigenesis in different tumors like; breast [86–88], colorectal [89,90], colon [67,91,92], multiple myeloma [93–95], non-small cell lung cancer [96], cutaneous squamous cell carcinoma [97] and head and neck squamous cell carcinoma [98]. The exact mechanisms by which DDX5 causes tumorigenesis differ from one tumor type to the other, and in some tumors, are yet to be fully elucidated.

Its aberrant expression in many malignancies strongly points to an oncoprotein. Research by Wei and Hu, [99] asserts that the DDX5 gene is an oncogene with the capacity to induce tumor formation in nude mice. Knock-out mouse models also confirm that DDX5 is an important transcriptional factor that regulates growth and is essential for tumor development [100]. Its overexpression both in cell lines and in primary tumors, points to an indisputable role in tumorigenesis, cancer progression and drug resistance [101].

In human colon and breast cancer cells, deregulated activation of β-catenin/TCF4 is associated with tumorigenesis and cancer progression through activation of the Wnt/β signaling pathway [45]. Both β-catenin and DDX5 are important transcriptional regulators that are required for cell growth, development, and proliferation as well as organ differentiation and maturation [45,102]. However, their dysregulation is potentially disastrous, and is considered to lead to oncogenesis. Reports of tumorigenesis in breast and non-small cell lung cancer, suggest that the malignancy originates at the cell surface receptor level through aberrant activation of the Wnt/β-catenin signaling pathway [96,103]. Additionally, Prosperi and Goss [104] affirm that over-expression of Wnt/β-catenin pathway activators and its subsequent dysregulation results in breast cancer tumorigenesis in mouse models.

Direct evidence of the role of DDX5 in the tumorigenesis of colon cancer is presented by recent studies reporting that the overexpression of DDX5 positively regulates the AKT signaling pathway. An increase in the expression level of DDX5 causes a corresponding increase in the expression levels of AKT protein and mRNA, which stimulates DDX5, β-

Table 3
Summary of the role of DDX5 in oncoviral infections.

Virus type	Viral binding protein	Outcome/role of DDX5	Associated oncogenic pathways that are regulated by DDX5	Malignancy caused	Ref
HCV	NS5B	Increased viral replication	P53; Wnt/β-catenin	HCC	[77–79]
	CRE	Transcription of viral RNA			
HIV-1	REV	Enhanced viral replication	mTOR; NF-κB	Kaposi's sarcoma	[74,75,80,81]
HBV	SUZ12	Inhibits viral replication	Wnt/β-catenin; P53; NF-κB	HCC	[82]
	PRC2	Inhibit transcription from the HBV chromosome			
EBV	EBNA2	Splicing, Tumorigenesis Transcriptional activation	NF-Kb; mTOR	Burkitt's lymphoma	[83]
HHV8/KSSV	–	–	NF-Kb; mTOR	Kaposi's sarcoma	[71]
HPV	–	Potential biomarker for cervical cancer	P53; mTOR	Cervical cancer	[84]

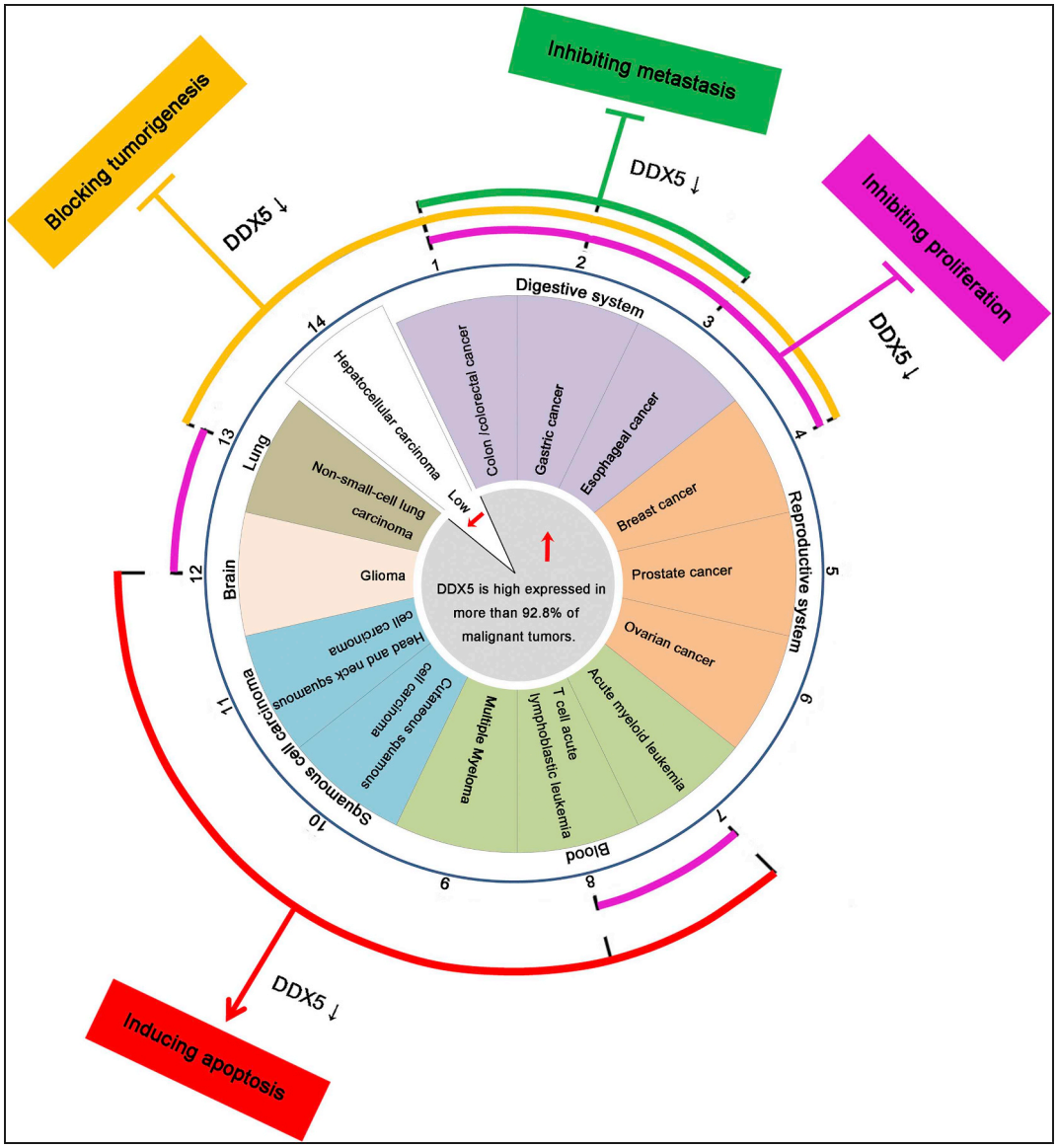

Fig. 1. Expression level of DDX5 in different malignancies.
DDX5 is overexpressed in in 92.8% of the human cancer reported except in hepatocellular carcinoma. Experimental knock-down of DDX5 in cancer cell lines and animal models results in induced apoptosis, blocking of tumorigenesis, EMT and metastasis as well as inhibition of proliferation.

catenin and NF-κB to occupy the AKT promoter, potentiating transcription of AKT genes [24,105]. By mediating an increase in AKT transcription and in turn depleting tumor suppressor FOXO3a (a downstream gene), DDX5 promotes tumorigenesis in colon cancer.

In colorectal cancer, DDX5 is poly-ubiquitylated and expressed both in pre-invasive as well as invasive lesions [44] which strongly suggests that the deregulation of DDX5 happens early in the development of colorectal neoplasms and hence, could play a leading role in tumorigenesis. Similarly, in cervical squamous cell carcinoma, the overexpression of DDX5 has been linked to tumorigenesis and human papilloma virus infection [84].

Elsewhere, the involvement of DDX5 in the regulation of Notch-mediated transcription in T-ALL leukemia cells implicates it in NOTCH 1-mediated T-ALL pathogenesis [101]. DDX5 interacts with the NOTCH transcriptional coactivator MAML, initiating pathogenesis while promoting the growth and survival of T-ALL leukemic cells. Oncogenic NOTCH signaling is deeply correlated with transcriptional regulation of cell growth and metabolism [106]. Moreover, Zhan et al. [95] and Mattioli et al. [94] report an overexpression of DDX5 in multiple myeloma cells as compared to normal bone marrow cells. Serial analysis of gene expression (SAGE) has identified DDX5 as one of the genes implicated in the tumorigenesis of Multiple Myeloma [93] further affirming that DDX5 contributes to tumorigenesis.

Another significant contributor to cancer development and progression is decontrolled miRNA expression. DDX5 plays a substantial role in miRNA biogenesis by being part of the DROSHA micro-processor complex [107,108], and thus, tumor development is attributable to its deregulation. In hepatocellular carcinoma (HCC), decreased miRNA biogenesis is linked to hepatocarcinogenesis: It is attributed to histone modification and the under-expression of DDX5, a component of DROSHA [48]. Besides being associated with increased risk of liver carcinogenesis and tumor recurrence, this deregulation gives an overall verdict of poor prognosis. Put together, these reports assert that the contextual role of DDX5 in tumorigenesis is tied to its functions and the pathways it regulates, however, its involvement in other cancers and the detailed mechanisms are yet to be explored.

Table 4
Experimental evidence of DDX5 expression in human malignancies.

Cancer type	No.	Cancer name	DDX5 level	Experimental regulation (depletion) of DDX5	Outcome	Ref.
Digestive System	1	Colon/Colorectal cancer	↑	HCT-116 (shRNA) Nude mice (shRNA) Colon cancer tissues (Polyps, adenomas and adenocarcinomas)	Blocking tumorigenesis Inhibiting cell proliferation Inhibiting EMT and metastasis	[44,89–92,167]
	2	Gastric cancer	↑	Lentivirus-mediated DDX5 up- or down-regulation models (NCI-N87, KATO III, MKN28, HCT116 cell lines) Nude mice (shRNA)	Inhibiting cell proliferation, migration and invasion	[124,127,143]
	3	Esophageal cancer	↑	EC9706, EC109, TE13, and ECA109 cell lines Nude mice (shRNA)	Inhibiting cell proliferation and metastasis	[116]
Reproductive System	4	Breast cancer	↑	HEK293T, MCF7, MDA-MB231, 4 T1, H1299, HCT116 (SiRNA)	Blocking tumorigenesis Reducing proliferation Sensitizing a subset of BC cells to trastuzumab	[15,47,86,88,103,104,112]
	5	Prostate cancer	↑	LNCaP, COS-7, and HEK293 cell lines Silencing p68 protein expression by RNAi (siRNA)	Inducing proliferation and EMT Reducing androgen receptor and prostate specific antigen proteins	[56,141]
	6	Ovarian cancer	↑	SEREX ARRAY ANALYSIS (Report overexpression of DDX5 mRNA)	Suggested role in tumorigenesis	[166]
Blood	7	AML	↑	Doxycycline-induced shRNA (AML mouse model) MV4–11, MOML 13,THP 1, HL-60, NB4,HEL (shRNA)	Inducing AML cell apoptosis lock progression *in vivo* Inhibit proliferation	[113]
	8	T-ALL	↑	KOPT-K1, HPB-ALL, MOLT4 and Jurkat cells (shRNA) NCr nude mice (*in vivo*)	Reducing proliferation; Inducing apoptosis; Limiting xenograft growth	[52]
	9	Multiple Myeloma	↑	SAGE analysis	Responsible for tumorigenesis	[93–95]
Squamous Cell Carcinoma	10	CSCC	↑	Tissue specimen Expression level of DDX5	Associated with metastasis and proliferation	[97]
	11	HNSCC	↑	UMSCC-10B, UTSCC-19A mRNA levels of DDX5	Inducing proliferation	[14,98]
Brain	12	Glioma	↑	T98G, HT-29 cells (siRNA) H-4, HS-683, U-87, U-251, U-343 cells (shRNA) Nude mice (shRNA)	Inducing apoptosis (DT Phosphorylation) Prevents cell proliferation NF-kB p50 binds DDX5 promoting proliferation	[142]
Lung	13	NSCLC	↑	H520 and A549 cells (siRNA) Nude mice (siRNA)	Blocking tumorigenesis Preventing cell proliferation *in vitro* and growth of NSCLC xenografts *in vivo*	[96]
Liver	15	HCC	↓	NONE	Low expression of DDX5 in HBV and non-HCV HCC Indicates poor prognosis	[48,76]

4. Role of DDX5 in tumor proliferation

Proliferation, a hallmark of disease progression, is marked by an increase in the number of malignant cells and growth of tumor xenografts in experimental mouse models. The specific role played by DDX5 in promoting proliferation largely depends on the upstream or downstream factors and pathways that it regulates [10]. While most of the factors differ from one tumor type to another, some are common and/or activate more than one tumor-related pathway resulting in disease progression. Downregulation of DDX5 in several human cancer cell lines and animal models abrogates proliferation (Table 4) [66,91,96,109,110].

One of the mechanisms by which DDX5 promotes proliferation is through activation of the Wnt/β-catenin signaling pathway [86,103]. For instance, proliferation in NSCLC cells is amplified by the interaction of DDX5 with β-catenin which promotes its nuclear translocation and co-activates the expression of downstream genes c-jun, c-Myc and cyclin D1 that directly increase proliferation [96]. Further, Fu et al. [111] reports that a complex formed by DDX5, β-catenin and HDGF modulates a miR-296-3p-PRKCA-FAK-Ras-c-Myc feedback loop that regulates proliferation, metastasis and resistance to chemotherapy in Lung adenocarcinoma. Additionally, DDX5 is reported to regulate the expression of H-Ras protein and a signal transduction pathway associated with proliferation [54].

According to Mazurek et al. [112], tumor cell proliferation in breast cancer depends largely on amplification of the DDX5 locus, and upregulation of the transcription of genes that express DNA replication proteins. These authors also suggest that DDX5 directly regulates the expression of DNA replication factors by recruiting RNAP II to the E2F-regulated gene promoter, causing progression from G1 to S phase. It is noteworthy that breast cancer cells that are dependent on DDX5 for proliferation have higher expression profiles of DDX5 when compared to those that do not, implying a strong positive correlation.

A previous study asserts that acute myeloid leukemia (AML) is DDX5 dependent and that inhibition of its expression significantly reduces AML proliferation *in vitro*, and progression *in vivo* [113]. Consistent with these findings, Lin et al. [101] also confirmed the dependence of T-ALL cells on DDX5 for proliferation, while its depletion induces apoptosis through stimulation of NOTCH-regulated genes.

Phosphorylation is the most common form of post-translational modification reported in over 90% of human malignancies. Cell proliferation and cancer development are also attributed to phosphorylation of DDX5 at Y593 and Y595 (tyrosine) residues [45]. A subsequent report by Yang et al. [66] provided an analogous result that phosphorylation of DDX5 at Y593 and Y595 residues mediates cell proliferation, EMT and metastasis, as well as blocking TRAIL induced apoptosis and promoting disease progression [110,114,115]. On the other hand, phosphorylation at T564 and T446 (threonine/serine) residues is associated with an increase in apoptosis and mediates the function of anti-cancer drugs like oxaliplatin [67].

A recent report has documented the role of DDX5 in proliferation, metastasis and invasion of esophageal cancer both *in vitro* and *in vivo*, through activation of the Wnt/β-catenin signaling pathway [116]. Altogether, the anomalous expression of DDX5 in many tumor types and its regulatory role both in the wild type and modified forms impart a weighty role in cell proliferation, transformation and viability [10,55,117]. Taken together, these findings illustrate an essential role played by DDX5 in promoting cancer cell proliferation.

5. Role of DDX5 in cancer metastasis

Metastasis is the movement of malignant cells from the primary tumor into circulation, invasion of another (distant) site and eventual proliferation. Tumor cells acquire the capacity to migrate, invade, and metastasize when they undergo epithelial to mesenchymal transition (EMT). This is after they have developed the hallmark properties of invasiveness which are decreased cell-cell adhesion and increased motility [66,118]. Besides normal developmental functions like organogenesis, morphogenesis and homeostasis, EMT is also responsible for tumor initiation, chemotherapy and immunotherapy resistance [64]. Some metastasis suppressor genes have been identified, but the exact mechanisms for their actions have not been entirely understood [119]. Numerous studies have linked DDX5 to EMT and metastasis [50,64,66,120].

DDX5 can induce metastasis by two possible means: TGF- induced EMT and PDGF-induced EMT. TGF-β cytokine is key in promoting EMT by phenotype-switching in tumor-infiltrating immune cells and by crosstalk with other stem cell pathways [121,122]. To initiate transcription programs responsible for TGF-β-induced EMT and myogenesis, over-expression of DDX5 and its subsequent co-regulation of SMAD is necessary [8,50]. PDGF-induced EMT is also dependent on phosphorylation of DDX5 on the Y593 tyrosine residue [123]. Yang et al. [66] report that elevated levels of tyrosine phosphorylation are reported in metastatic cancer tissues samples as compared to samples from primary sites. Tyrosine phosphorylation causes dissociation of β-catenin from the Axin destruction complex and its subsequent translocation to the nucleus, stimulating EMT [66,123]. Knockdown of DDX5 has been confirmed to block EMT and metastasis and thus, inhibitors of pathways (c-Abl-DDX5-β-catenin) that promote EMT are novel targets in the prevention of metastasis.

The interaction of DDX5 and Ca-calmodulin also explicates the role of DDX5 in metastasis. Cell migration and metastasis have successfully been blocked in two experimental animal models by use of a peptide fragment spanning the IQ motif of DDX5 [65]. The fragment blocks the interaction of DDX5 and CaM, inhibiting the transport of CaM to leading edges of migrating cells, hence preventing metastasis. Likewise, the DDX5-CaM interaction is crucial for DDX5 ATPase activity, and the formation of filopodia and lamellipodia in migratory cells [124]. Since cell migration is an imperative facet of metastasis [125], curbing cell migration is a viable strategy for metastasis inhibition [119,126]. Additionally, a study using a mouse model of tumor progression reported that DDX5 regulates alternative splicing of numerous DNA and chromatin binding factors, thus contributing to tumor cell migration and invasion [49]. The depletion of DDX5 inhibited migration and invasion of tumor cells, and the results are in tandem with those of Wang et al. [97] where metastatic tissue expresses a significantly higher level of DDX5 as compared to corresponding normal tissue.

DDX5 interacts with long non-coding RNAs (lncRNAs) to regulate gene expression. Recently, Sha et al. [127] have identified a lncRNA known as myocardial infarction associated transcript (MIAT) which plays a role in oncogenesis and metastasis of gastric cancer. Remarkably, MIAT positively regulates miR-144 and DDX5. Knock-down of MIAT led to a negative feedback loop resulting in the decreased expression of miR-144 and DDX5, and an eventual decrease in cell proliferation, invasion and migration. DDX5 also interacts with LOC284454, an lncRNA that contributes to the modulation of cancer-related pathways and pathology of breast cancer [128]. All these reports confirm the well-established role played by DDX5 in metastasis.

6. Role of DDX5 in cancer cell differentiation

The functional role of DDX5 in regulating RNA processing is responsible for the expression of proteins that contribute to differentiation. Murine DDX5 expression is correlated with the onset of organ differentiation [102] and is supported by the abundant expression of DDX5 in differentiating embryonic tissue [129]. DDX5 is associated with the differentiation of monocytic leukemia cells (U937) to macrophages [130], and its knockdown blocks differentiation of C2C12, a multipotent cell line [8]. A recent study reported that DDX5 plays an active role in proliferation (U-937 cell line) and G1 to S/G2 phase differentiation with an increase in DDX5 expression early in the differentiation process as compared to later in the process [109].

Moreover, it is required in the differentiation of fibroblasts to adipocytes and is involved in the initiation and regulation of adipogenesis [131,132].

DDX5 regulates the transcription of downstream genes that directly influence differentiation. One of the mechanisms by which it regulates differentiation is through co-regulation of the transcription of MyoD and SMAD which mediate TGF β-induced EMT and myogenesis, [8,59,60] resulting in the production of critical secondary differentiation regulators [50]. On the other hand, DDX5 is co-regulated by SRA, an RNA co-regulator responsible for nuclear receptor signaling. The co-regulation causes overexpression of DDX5 [133], and actuates a synergistic relationship with MyoD which induces myogenic differentiation of mouse fibroblasts, linking DDX5 with skeleto-muscular differentiation [8,134]. Osteoblast differentiation and maturation at different stages of the life cycle is dependent on Runx2, [11] a transcription factor that is co-activated by DDX5. Tissue differentiation is also attributed to the modulatory role of DDX5 on the structure of RNA and the subsequent protein expression [17]. Farther, the expression of DDX5 is upregulated by calcitriol. Conversely, Nuclear vitamin D receptor (VDR), which is involved in cell processes like proliferation and differentiation, is naturally activated by calcitriol [135,136]. Thus there exists a positive feedback loop between DDX5 and calcitriol which implicates DDX5 in the differentiation of SiHa cells [2].

The lack of hematopoietic progenitor cell differentiation leads to an increase in leukemic osteoblasts in circulation, causing AML. Zuber et al. [137], reiterates that the pathogenesis of AML is mostly contributed to by mutations that block the expression of genes responsible for differentiation. The differentiation of AML cells is induced by high production of reactive oxygen species and apoptosis [138] thus, depletion of DDX5 promotes apoptosis, inhibits cell proliferation, and prevents differentiation both in AML and T-ALL cells [101,113].

Emerging research has identified a novel role of DDX5 in the regulation of reprogramming of somatic cells into pluripotent stem cells. A unique observation has been put forth on how the interaction of DDX5, miR-125b and RYBP functions to control cell fate. Knockdown of DDX5 is required for reprogramming in the direction of pluripotency [139,140]. This new angle is significant in the exploration of nuclear programming and malignant transformation and could give useful insights into early events leading to oncogenesis.

7. Cancer-related pathways regulated by DDX5

Intracellular and extracellular signaling pathways form the link between cellular genome and the extracellular environment. A cell's phenotype can be influenced by the effects of post-translational modifications and aberrant expression of significant regulatory molecules on its signaling networks. Malignant tumors hijack such signaling pathways and deploy them to maximize proliferation and metastasis. As such, to come up with better management strategies for cancer, it is imperative to clearly understand the genetic aberrations that augment pro-tumor signaling pathways. The pathways are novel diagnostic, prognostic and therapeutic targets.

There is sufficient evidence to prove that altered regulatory pathways contribute to tumorigenesis, proliferation, invasion and metastasis of human malignant cells [22]. The most significant cancer-related pathways regulated by DDX5 are; Wnt/β catenin signaling [103,104], Notch signaling [101], Estrogen signaling [86], Androgen signaling [56,141], NF-KB signaling [142], mTOR signaling [143,144] and NFAT5 signaling [51]. The most deregulated pathways, the specific factors involved, and the regulatory role of DDX5 are illustrated in Figs. 2, 3, 4 and 5.

One of the major pathways associated with cancer and regulated by DDX5 is the Wnt/β catenin pathway. It is largely associated with tumorigenesis, proliferation and EMT in breast, esophageal, colon/colorectal and non-small cell lung cancer (Fig. 2). Accumulation of β-catenin in the nucleus is responsible for tumor development and thus, the interaction of β-catenin with phosphorylated DDX5 leads to its nuclear translocation which causes the co-activation of transcription factors associated with EMT and proliferation [66,110]. The role of DDX5 in the regulation of Wnt/β catenin signaling that leads to tumorigenesis has been largely explored in breast cancer [103,104]. As such, DDX5 is a valuable target for breast cancer chemoprevention.

The NOTCH signaling pathway is based on cell-cell communication and its dysregulation accounts for over 60% of T-ALL cases [101]. It is also reported in several other tumors like breast, colorectal, prostate, central nervous system and lung cancers [145]. Activation by binding of the NOTCH receptor releases the NOTCH intracellular domain (NICD) which translocates to the nucleus forming a complex with RBP-J [146,147]. The NICD/RBP-J complex binds to MAML, DDX5, or SRA which then co-activates the transcription of NOTCH signaling genes [148,149]. DDX5 is implicated in the co-activation of oncogenic NOTCH signaling [106] and production of genes responsible for cell proliferation, differentiation and survival of breast cancer cells, and lymphomas [150,151]. Considering that strict regulation of NOTCH induces tumor growth arrest and promotes apoptosis, it follows that development of NOTCH inhibitors is a potential stride in targeted therapy. Moreover, the use of combination therapy including notch inhibitors, radiotherapy and chemotherapy could substantially improve patient response to chemotherapy [152].

The androgen signaling pathway is also regulated by DDX5. Aberrant androgen signaling is linked with prostate cancer tumorigenesis *via* co-activation of androgen receptor (AR) by tyrosine phosphorylated DDX5 [141]. By regulating β-catenin and RNA polymerase II (RNAP II), DDX5 regulates the expression levels of AR-mediated genes [53,56].

Estrogen signaling pathway is another significant pathway regulated by DDX5. Most human breast tumors are estrogen receptor alpha (ER-α) positive, which makes estrogen signaling a key player in breast cancer research [153]. DDX5 and its homolog DDX17 are co-activators of ER-α [154]. Samaan et al. [53] report that DDX5 controls splicing and transcription of both upstream and downstream estrogen-related genes, and co-activates ER-α dependent gene transcription [136,155]. Aberrant estrogen signaling is responsible for oncogenesis, progression, and metastasis of a majority of human breast cancers [156,157].

Aberrant NF-κB signaling is associated with brain tumors. NF-kB is a p68 binding protein that plays a vital role in neural stem cell proliferation and inflammation in parts of the brain [158,159]. NF-κB activity levels are higher in glioma tissue as compared to normal tissue, and correspond with higher grade astrocyte tumors, and reduced overall survival [142]. The N terminal domain of DDX5 binds the p50 subunit; the most active NF-κB dimer in cancer, inducing its transcription and accumulation in the nucleus, thus promoting the transcription of NF-κB target genes [160] (Fig. 4). In human malignancies, this pathway is concerned with tumor initiation, cell growth and proliferation, cell migration and invasion, angiogenesis, as well as apoptosis and drug resistance which inherently promotes the proliferation of glioma cells and development of glioma tumors [161]. NF-κB also plays a role in the immune activation against cancer and therefore its inhibition may prove counter-productive. Therefore, combination of specific inhibitors with conventional chemotherapeutic drugs could result in better synergy.

There is evidence indicating that nuclear factor of activated T cells 5 (NFAT5) signaling pathway is involved in differentiation, invasive migration, and survival of tumor cells. DDX5 has been implicated in the co-activation of NFAT5, which induces the expression of NFAT5 target genes that are responsible for tumor cell migration and invasion [51]. DDX5 also induces alternative splicing of the NFAT5 mRNA transcript, subsequently causing its down-regulation by nonsense-mediated decay [51], while increasing tumor invasiveness and redox gene expression by controlling alternative splicing of DNA and chromatin binding factors like micro H2A 1 histone (MH2A 1) [49].

Recently, DDX5 has been reported to regulate the mTOR signaling

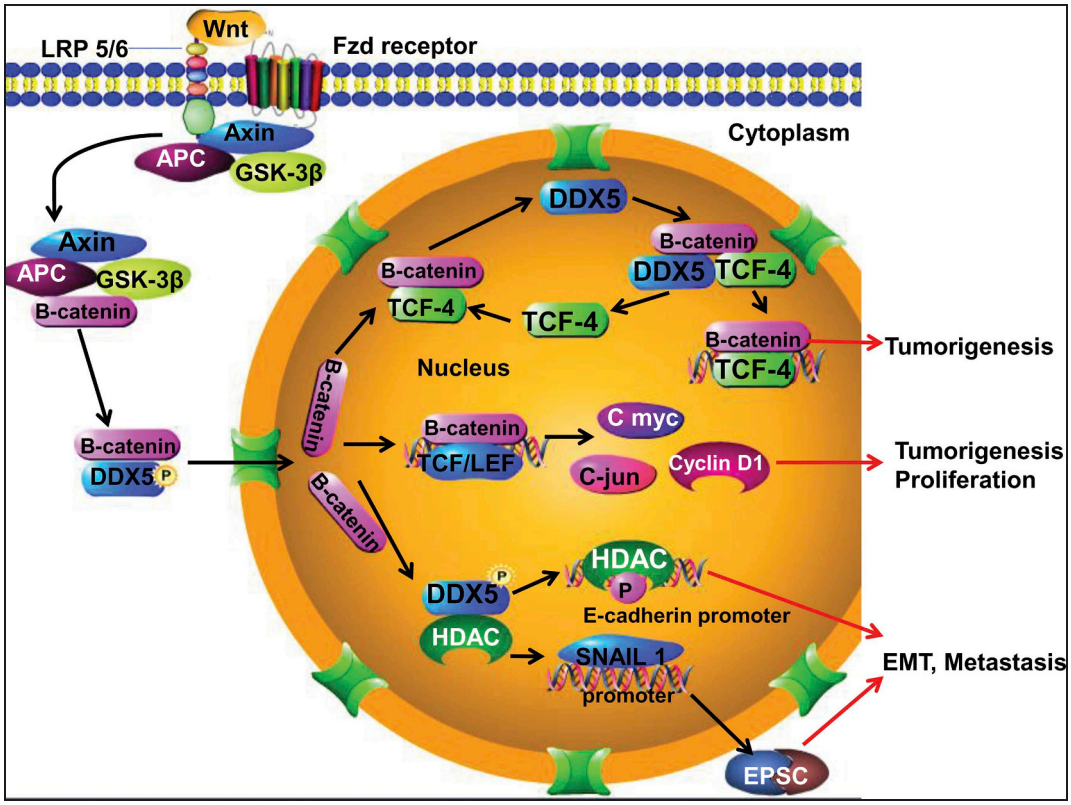

Fig. 2. Wnt/β catenin pathway associated to DDX5.
Activated Wnt binds to frizzled receptors on the cell membrane forming a complex with LRP 5/6 and binds to the Axin, APC and GSK-3β complex which also binds to β-catenin. Phosphorylated DDX5 dissociates β-catenin from the complex causing its nuclear accumulation. (1) Increase in DDX5 gene expression increases the gene expression of TCF4 forming a positive feedback loop enhancing tumorigenesis of breast cancer. (2) β-catenin binds TCF/LEF transcription factors and promotes transcription of c-myc, c-jun, and cyclin D1 which cause tumorigenesis and proliferation. (3) Phosphorylated DDX5 dissociates HDAC from the snail I promoter leading to accumulation of EMT Promoting SMAD Complexes and recruits HDAC to the E-cadherin promoter leading to EMT.

pathway that is responsible for cell proliferation, metastasis, colony formation and growth of xenografts as confirmed by *in vitro* and *in vivo* experiments in gastric cancer [143]. Activation of the mTOR pathway leads to proliferation and is an indicator of poor prognosis in gastric, ovarian, breast, colon, and liver cancers [162–164]. Interestingly, depletion of DDX5 causes activation of an mTOR/MDM2 cell survival mechanism that inhibits apoptosis by blocking the action of pro-apoptotic factor, p53 [144]. Inhibition of the mTOR pathway by targeting down-regulation of DDX5 has proven to be of therapeutic value in prostate cancer [165]. These findings affirm that DDX5 is a noteworthy regulator of the mTOR pathway which is a promising therapeutic target for many human malignancies.

8. Perspectives on potential role of DDX5 in diagnosis, prognosis, and targeted therapy

A considerable amount of research has been conducted on the potential use of DDX5 in diagnosis. In ovarian cancer, DDX5 is identified as a biomarker for serous ovarian cancer [166]. Besides, Hammoudi et al. [167] report that it is a potentially novel biomarker of colorectal cancer. Since DNA replication, one of the major functions of DDX5, is a hallmark of cancer, understanding the regulation of DNA replication can give insights into cancer development which can be explored in diagnostics and therapy. Recently, Qing et al. [84] have identified DDX5 as one of the potential diagnostic biomarkers of cervical squamous cell carcinoma. Similarly, DDX5 has been identified as a reference gene for esophageal squamous cell carcinoma [168], further firming up its great potential in the diagnosis of human malignancies.

The correlation between DDX5 expression and survival (prognosis) has been explored in several malignancies. Experimental evidence affirms that high expression levels of DDX5 correlate with advanced clinical stage and decreased survival rate in NSCLC [96], colorectal cancer [89,169] and cutaneous squamous cell carcinoma [97]. Conversely, decreased expression of DDX5 depicts poor prognosis in some subsets of hepatocellular carcinoma [48,82]. Similarly, in breast tumors increased DDX5 expression correlates with the expression of Ki67, a nuclear marker for tumor cell proliferation which indicates poor prognosis and high invasiveness [47]. For glioma patients, overexpression of DDX5 is associated with decreased overall survival and increased resistance to treatment with temozolomide (RT-TMZ) and radiotherapy [142,170]. A recent report by Zheng et al. [164] depicts regulation of proteins in the mTOR signaling pathway, one of the oncogenic pathways regulated by DDX5, as a novel prognostic target in gastric cancer. DDX5 can therefore be used to determine choice of therapy and act as a prognosis indicator in several human malignancies.

The consideration of DDX5 as a novel therapeutic target in human malignancies is due to its modulatory role in oncogenesis, proliferation and metastasis. Experimental depletion of DDX5 has been shown to sensitize breast cancer cells to proliferation inhibition by trastuzumab [112]. In AML, DDX5 knockdown induces apoptosis but the effect is countered by the overexpression of B-cell lymphoma 2 (BCL2). Consequently, when DDX5 depletion is coupled with the use of BCL2 family inhibitor, apoptosis is induced in AML cells [113]. Similarly, in lung carcinoma, the depletion of DDX5 increases the apoptotic activity of camptothecin [171]. A Tumor suppressor drug targeting DDX5, Zinc finger protein (ZNF331) is reported by Yu et al. [124]. ZNF 331 acts by suppressing growth and invasiveness of gastric cancer cells by repressing many genes including DDX5 which are responsible for proliferation and metastasis. Moreover, recent *in vitro* and *in vivo* studies affirm that depletion of DDX5 inhibits proliferation and colony formation in gastric

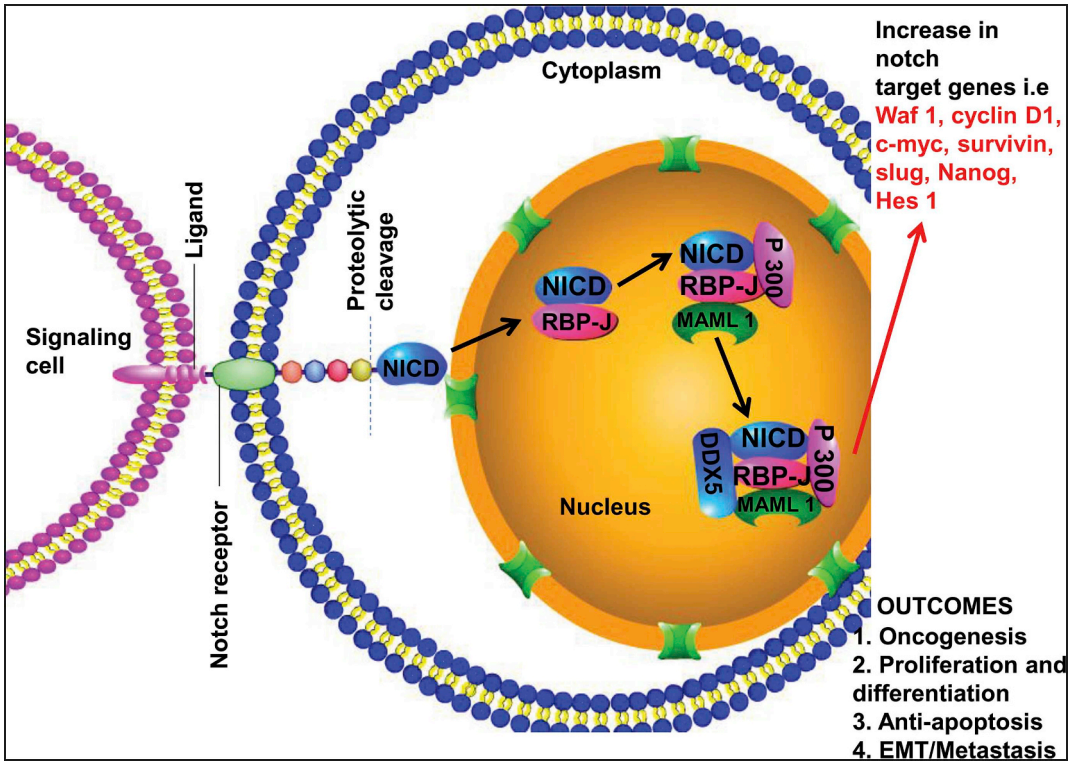

Fig. 3. NOTCH signaling associated to DDX5.
The notch receptor binds a ligand and releases NICD through proteolytic cleavage. The NICD then translocates to the nucleus and binds RBP-J, then forms a complex with acetyltransferase p300 and MAML 1. DDX5 binds to MAML 1 and activates the transcription of notch-related genes which promote oncogenesis, proliferation, EMT/metastasis and reduced apoptosis.

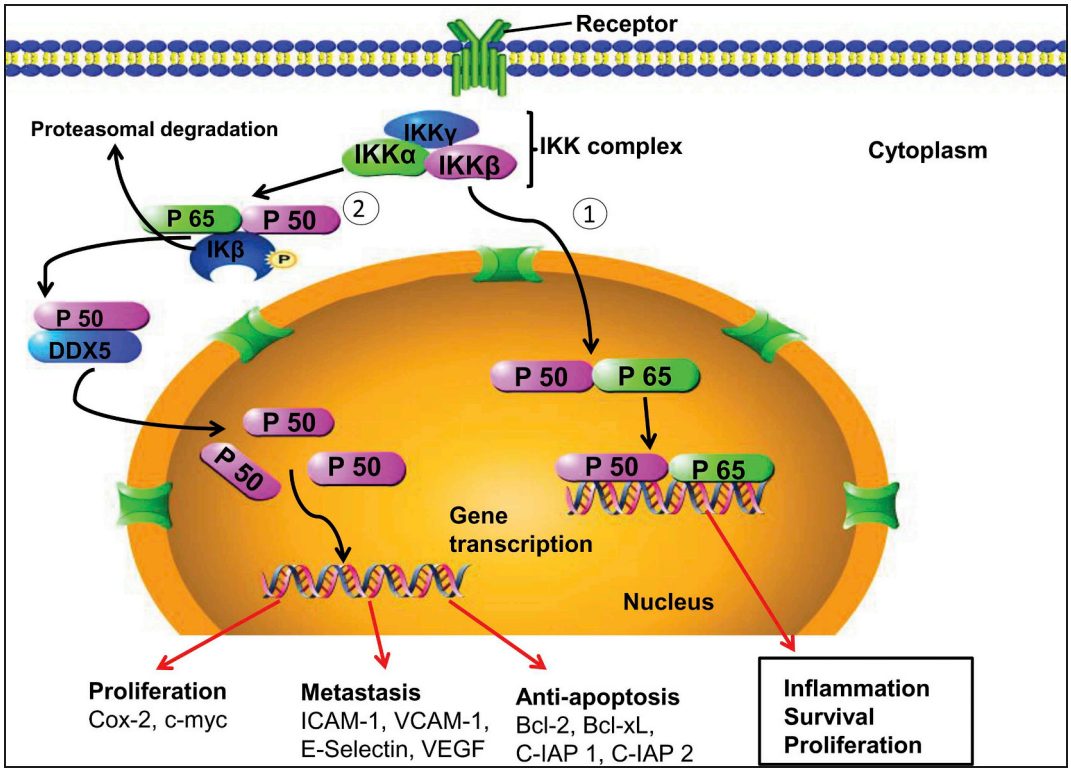

Fig. 4. NF-κB signaling associated to DDX5.
Receptor activation by Toll-like receptor ligands, antigens or cytokines *i.e.* TNF causes activation of the IKK complex which in turn phosphorylates Ikβ then activates the P50 subunit of NF-κB. The phosphorylated Ikβ then undergoes proteasomal degradation (1) while the active transcription subunits (P50 and P65/Rel A) translocate to the nucleus and induce the transcription of target genes responsible for inflammation, survival and proliferation. (2) DDX5 binds the NF-κB P50 subunit in the cytoplasm and causes its nuclear accumulation and transcription of target genes which promote growth and proliferation, metastasis, and apoptosis inhibition.

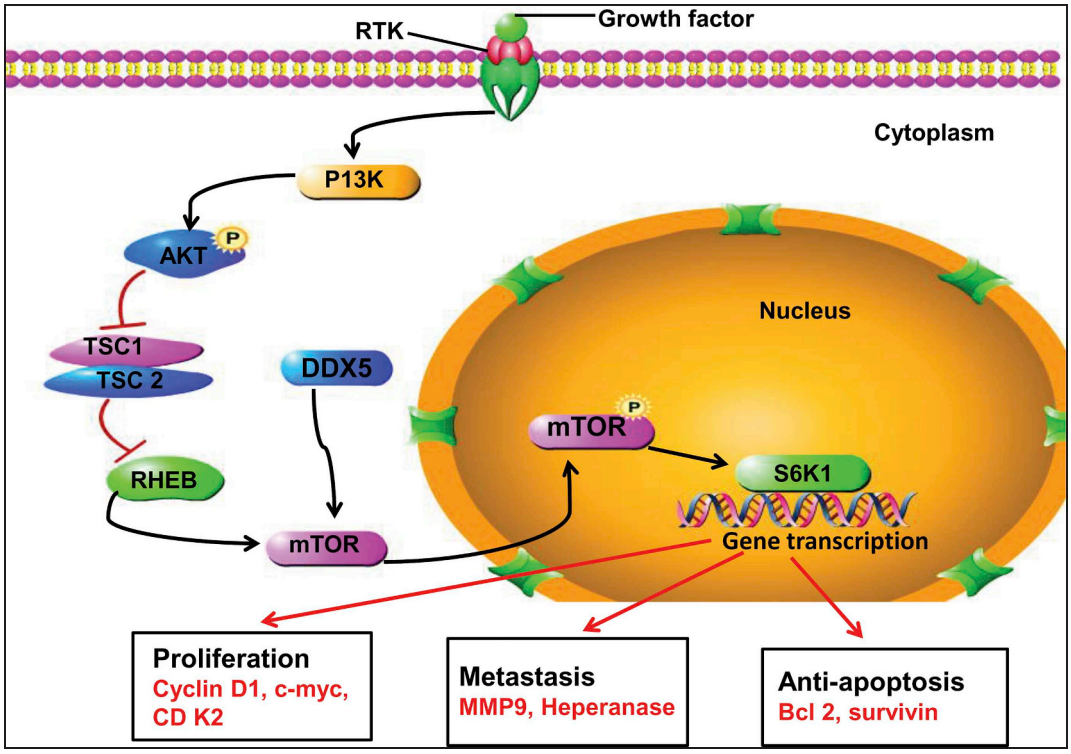

Fig. 5. mTOR signaling associated to DDX5.
Growth factor (EGF) binds to RTK on the cell surface and that causes activation of P13K. P13K then activates AKT which inhibits TSC 1 and TSC 2 molecules, which in a normal cell block RHEB. By blocking TSC 1 and TSC 2, RHEB is left free and thus activates mTOR. In many malignant tumors, DDX5 phosphorylates mTOR which in turn activates S6 K1 which directs the synthesis of proteins responsible for proliferation, metastasis, angiogenesis and anti-apoptotic activity.

cancer cells as well as the growth of xenografts in mice [143]. Dysregulated expression of DDX5 has been shown to confer resistance to existing anticancer drugs [170].

Modulation of post-translational modification of DDX5 has also been proven to be invaluable in improving the response of tumors to anticancer drugs, and pharmacological drug development. It is also vital in curbing the anti-apoptotic features conferred to tumor cells by the overexpression of DDX5 and the mutation of the DDX5 gene [110]. Since phosphorylation of DDX5 at the tyrosine residue is related to cancer development and cell proliferation, anticancer agents like piceatannol, etoposide, and taxol, combined with treatment of cells with anti-apoptotic agents like TNF-α reduces tyrosyl phosphorylation hence offer better treatment outcome [45]. Tyrosyl phosphorylation of DDX5 is of significant prognostic and diagnostic value [115,172]. Therefore, strict regulation of post-translational modifications of DDX5 can improve the potency of anticancer drugs. Targeting rational design of specific and potent inhibitors against phospho-p68 is of great promise in developing anticancer agents.

Targeting DDX5 in the context of the roles it plays in pathway regulation has also proven successful in chemotherapeutic drug research. Cencic and Pettelier [173] confirm that the activity of DEAD-Box helicases can be selectively targeted by small molecule inhibitors in therapeutic research. DDX5 has been confirmed to be the cellular target of RX-5902, a small molecule inhibitor that exhibits strong growth inhibition in several human cancer cell lines [174], with great success in clinical trials in many solid tumors [175–178]. The mechanism of action of RX-5902 is blocking of the β-catenin pathway and its downstream genes like c-Myc, c-Jun and cyclin-D1 by inhibiting the interaction of Y593 phosphorylated DDX5 and β-catenin [174,176]. This affirms the great potential of focusing drug development on DDX5 and the oncogenic pathways it regulates. Besides, since RX-5902 targets phosphorylated DDX5, recent advances in proteomic technologies can be beneficial in studying post-translational modifications and protein interactions. This will improve the understanding of the molecular dynamics of DDX5 leading to the development of small molecule inhibitors which are indispensable in pharmacological drug discovery.

Recent advances in high throughput sequencing methods like whole exome and whole genome sequencing have enhanced the precision of studying gene mutations. The DDX5 gene has numerous mutations across malignancies like stomach, colorectal, lung and melanoma with a high-frequency hot-spot mutation at the X147 splice (refer to a recent review by Cai et al. [23]. An in-depth analysis of the genome of cancer tumors using next-generation sequencing is an invaluable tool that can be applied in the development of targeted therapy and identification of genes associated with drug resistance [179].

The DDX5 locus is usually amplified in many cancers. Considering the significance of DDX5 in the oncogenesis, disease progression and drug resistance in tumor cells, development of DDX5 inhibitors holds great potential in targeted therapy. It can also be applied in improving drug sensitivity of tumors that overexpress DDX5. Also, DDX5 and its related pathways hold great potential for prognostic and diagnostic value in human malignancies.

9. Conclusion

This review highlights remarkable progress in our understanding of RNA helicase DDX5 and the multifaceted role it plays in the regulation of gene expression in different cancer-related pathways, as well as its central role in determining cell fate. Considering the frequency of amplification of the DDX5 locus in several tumors, it qualifies to be a promising candidate for cutting edge research in diagnosis, prognosis, and targeted therapy. Despite the remarkable knowledge on the roles played by DDX5 in cancer development and progression, the most notable area of unmet need is the potential use of DDX5 in diagnosis. DDX5 holds great promise in molecular diagnostics and therapy. The available knowledge of its role in prognosis is limited to just a few

cancer types and can therefore be further explored. This review affirms that DDX5 plays an indisputable role in human malignancies. In view of its role in anticancer drug resistance and its potential role in targeted therapy of many tumors, DDX5 is a novel target for cancer treatment. Further research targeting prevention of dysregulation in the expression of DDX5 and its down-stream genes could limit oncogenesis and disease progression. Therefore, more focus should be placed on elucidating the pathway regulation mechanisms of DDX5 and the potential for modulation of post-translational modifications in the development of small molecule inhibitors.

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Competing interests statement

The authors declare no competing interests.

Author contributions

RN and WJ were responsible for the first draft, which was critically reviewed, further developed and approved by all authors. RN and WJ prepared the pictures. YL and XX performed the literature search, collected and extracted the data. RN performed the quality assessment of included published papers. ZFM edited and revised the manuscript. All authors contributed to data interpretation, critically reviewed all manuscript versions and approved the final version.

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