RNA Helicases

Subjects: Biology
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RNA helicases constitute a large family of proteins with functions in all aspects of RNA metabolism, including unwinding or annealing of RNA molecules to regulate pre-mRNA, rRNA and miRNA processing, clamping protein complexes on RNA, or remodeling ribonucleoprotein complexes, to regulate gene expression. RNA helicases also regulate the activity of specific proteins through direct interaction. Abnormal expression of RNA helicases has been associated with different diseases, including cancer, neurological disorders, aging, and autosomal dominant polycystic kidney disease (ADPKD) via regulation of a diverse range of cellular processes such as cell proliferation, cell cycle arrest, and apoptosis.

Keywords: DEAD-box RNA helicases ; cell cycle ; treatment ; DDX5 ; DDX3

1. Introduction

RNA helicases are ubiquitous, highly conserved enzymes that involve in nearly all aspects of RNA metabolism. RNA helicases use ATP to bind or remodel RNA, RNA secondary structure or ribonucleoprotein (RNP) complexes that are associated with RNA transcription, degradation, translation initiation, mRNA splicing, and ribosome biogenesis [1][2][3]. RNA helicases are grouped into various superfamilies dependent on the contents of conserved motifs. Most of RNA helicases relate to the superfamily 2 (SF2) of helicases comprising eleven subfamilies, five of which are termed the DExH/D helicases (DEAD-box, RIG-I-like DExH, SKI2-like DExH, viral DExH, and DEAH/RHA) with a conserved motif (Asp-Glu-Ala-Asp/His) [4]. Members of the DEAD-box (DDX) and DExH box families share a similar three-dimensional core structure containing a minimum of 12 conserved amino acid motifs, comprised of two tandemly repeated RecA-like domains [1][3]. The RecA domain 1 includes the ATP binding motifs (Q motif, I motif, and II motif), the ATP hydrolysis motif III, and the RNA-binding motifs (Ia motif and Ib motif) (**Figure 1**). The RecA domain 2 consists of the RNA-binding motifs (IV and V) and motif VI, which may regulate ATPase and unwinding activities [3][5]. Previous studies indicate that motifs Ia and Ib are structurally similar to motifs IV and V, respectively, which should have similar functions [6]. The *N*- and/or *C*-terminal extensions of most of the RNA helicases are able to interact with specific RNA or protein cofactors. This family of DEAD-box RNA helicases is able to unwind and restructure RNA molecules in an ATPase-dependent manner (Figure 2) [7][8].

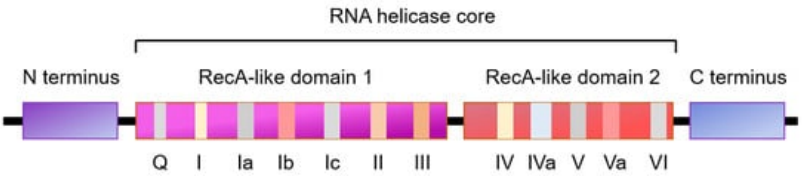


Figure 1. The sequence motifs of DEAD-box RNA helicases family are conserved. The DEAD-box RNA helicases family is characterized by a minimum of 12 conserved domains to form the DEAD-box helicase core, which consists of two RecA-related domains. Domain I and II contains 7 and 5 sequence motifs, respectively. The motifs of Q, I, II, and VI function as ATP binding and hydrolysis, and the motifs of Ia, Ib, Ic, IV, IVa, and V function as RNA binding. The motifs III and Va function as coordination between RNA and ATP binding. Domain II includes the DEAD motif (asp-Glu-ala-asp). The DEAD-box RNA helicases usually contain N and C terminal extensions, which determine their interaction with specific RNA and/or protein.

2. The Role of RNA Helicases in Regulation of Cell Cycle Progression

2.1. RNA Helicases Regulate G1-S Phase Transition

DDX3/Ded1 is one of the most widely studied DEAD-box RNA helicases. DDX3 regulates RNA metabolism, including transcription, pre-mRNA splicing, RNA export, and translation, which plays a critical role in many biological processes [9]. DDX3 also promotes phase separation when it interacts with ATP [10]. DDX3 also regulates cell apoptosis via the p53

signaling pathway during embryonic development in animal models [11]. Dysregulation of DDX3 plays a critical role in various diseases, including inflammation, viral infection, neurological disorders, and cancer [10][12]. The role of DDX3 in oncogenesis is related to the regulation of cell growth, cell cycle, and cell survival. Increased DDX3 expression promotes cancer cell growth in medulloblastoma, colorectal, breast, prostate, and lung cancer [9][13][14][15], whereas depletion of DDX3 induces cell cycle arrest in the G1 phase in cancer cells of those cancers (Table 1) [9][16][17][18][19]. Knockdown of DDX3 also inhibits cell cycle progression by blocking entry into the S phase. Mechanically, DDX3 facilitates translation initiation of the cell cycle regulator cyclin E1 mRNA via its 5′ UTR [20]. In addition, DDX3 inhibits the expression of Krüppel-like factor 4 (Klf4) by altering its mRNA splicing, resulting in an upregulation of the expression of CCNA2 and CDK2 [16]. In sum, DDX3 promotes G1/S transition by promoting cyclin E1 translation, suppressing KLF4 expression, and promoting CDK2 expression (**Figure 2**).

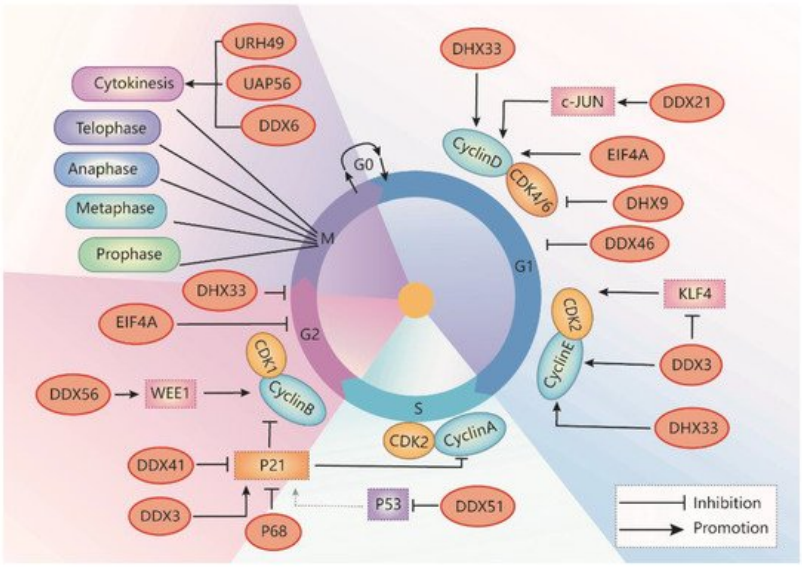


Figure 2. Schematic representation of the RNA helicases which are involved in the regulation of the cell cycle. RNA helicases are involved in G1/S transition: DDX3 positively regulates cyclin E1 translation but negatively regulates KLF4 expression to increase CDK2 expression. DHX33 initiates the transcription of E2F1, cyclin E2, cyclin D1, MMP9, MCMs, CDC6, and CDC20. DHX9 decreases the transcription of CDK6, leading to CIZ1 nuclear translocation. DDX21 activates c-Jun transcription, resulted in the increase of the synthesis of cyclin D1 mRNA. eIF4A regulates G1/S transition through regulation of the translation of cyclin D1, cyclin D2, and CDK6. RNA helicases are involved in S phase progression: DDX51 promotes S phase progression, possibly through negative regulation of cell-cycle-related proteins, p53-p21. RNA helicases are involved in G2-M phase transition: DDX56 promotes G2/M transition via the increase of intron retention and tumor suppressor WEE1 expression. RNA helicases are involved in mitotic phase progression: Knockdown of UAP56 or URH49 leads to mitosis defect. DDX6/CGH-1 functions to regulate microtubule cytoskeleton and chromosome separation. RNA helicases regulate the expression of CDK inhibitor p21: DDX41 and p68 inhibit p21 transcription and translation, respectively.

Table 1. RNA Helicases in each Cell Cycle Stage and their Intracellular Localization.

Cell Cycle Stage	RNA Helicases	Intracellular Location	Expression
G1-S phase transition	Ded1/DDX3	Nuclear speckles and cytoplasm	Upregulation in medulloblastoma, colorectal, breast, prostate, and lung cancer
	DHX33	Nucleus and nucleoli	Upregulation in lung cancers, hepatocellular carcinoma, lymphoma, colon cancer, and glioblastoma
	DHX9	Nucleus	Upregulation in cervical cancer, breast cancer, prostate cancer, colorectal cancer, hepatocellular carcinoma, and Ewing sarcoma
	DDX21	Nucleus and cytoplasm	Dysregulation in colon cancer, lymphomas, neuroblastoma, and breast cancers
	eIF4A	Nucleus and cytoplasm	Dysregulation in pancreatic cancer, breast cancer, prostate cancer
	DDX46	Focal nuclear	Upregulated in colorectal carcinoma, esophageal squamous cell carcinoma, gastric cancer, and osteosarcoma cells
S phase progression	DDX51	Predominantly in nuclear	Dysregulation in NSCLC
G2-M phase transition	DDX56	Nucleolus	Upregulation of DDX56 in various cancer, including osteosarcoma, colorectal cancer, and relates to a poor prognosis
	DHX33	Nucleus and nucleoli	See above
Mitosis	UAP56	Nucleus and cytoplasm	Not clear
	URH49	Nucleus and cytoplasm	Not clear
Cytokinesis	UAP56	Nucleus and cytoplasm	Not clear
	URH49	Nucleus and cytoplasm	Not clear
	DDX6	Nucleus and cytoplasm	colorectal cancer and hepatocellular carcinoma
Regulate the expression of p21(WAF1/CIP1)	DDX41	Nucleus and cytoplasm	DDX41 mutant leads to anemia and acute myeloid leukemia. DDX41 increased in cervical cancer.
	DDX5	Mostly in nucleus, cytoplasmic levels of DDX5 increased in the G2/M phase	p68 increased in a range of cancers except for hepatocellular carcinoma
	DDX3	Predominantly in nuclear speckles and at low levels in cytoplasm	See above

2.2. RNA Helicases Regulate S Phase Progression

During the S phase of the cell cycle, genetic materials, such as DNA, are synthesized for the duplication of the chromatin and reproduction of the whole genome, which is a pre-requisition for cell division. Once cells enter the S phase, cyclin E/CDK2 complex needs to be silenced to eliminate the DNA re-replication [21]. Dissociation of CDK2 from cyclin E/CDK2 complex results in its association with the newly synthesized cyclin A to form CDK2/cyclin A complex, which can phosphorylate proteins that are necessary for completion of the S phase. Alternatively, spliced p53 isoform (Delta-p53) transactivates the expression of endogenous p21, resulting in the inhibition of CDK2/cyclin A activity to and attenuate S phase progression [22].

2.3. RNA Helicases Regulate G2/M Phase Transition

In the cell cycle, the G2 phase is the second gap for cells to prepare for mitosis (M phase). During the G2 phase, cyclin A is degraded, but cyclin B is synthesized, resulting in the association of Cdc2 with cyclin B, which is required for the initiation of mitosis. Cyclin B can be phosphorylated at Tyr15 by WEE1, a kinase of the WEE family, resulting in altering equilibria and affecting G2/M transition [23][24]. The initiation of G2 arrest, triggered by DNA damage or inappropriate replication, is important for DNA damage repair, which can be regulated through p53 mediated signaling pathways [25]. In

addition, p21, as the downstream target of p53, is able to inhibit the activity of Cyclin A, Cyclin D, and other cell-cycle-related proteins, including cdc2 [26]. Different RNA helicases are associated with G2/M arrest.

2.4. RNA Helicases Regulate Cytokinesis

Cytokinesis is the last step of the cell cycle in which the cell must devotedly split the chromosomes and cytoplasm to produce two daughter cells with equal contents [27]. RNA helicases are involved in the key steps of cytokinesis, including the assembly and contraction of the contractile network, the formation of the mitotic spindle, and the interaction between the microtubule and cortical actomyosin cytoskeleton [28].

2.5. RNA Helicases Target CDK Inhibitor p21

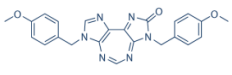
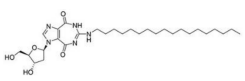
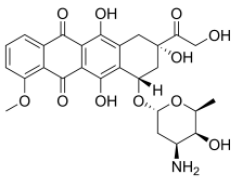
CDK inhibitors (CKIs) are mainly identified in CIP/KIP and INK4 families, which are key regulators of G1, S, and G2 phase transitions during the cell cycle [29]. The CKI inhibitors in the CIP/KIP family, including p21, p27, and p57, target CDK1, CDK2, CDK4, and CDK6. The CKI inhibitors in the INK4 family, including p15, p16, p18, and p19, also targets CDK4 and CDK6. The expression and stability of CKIs are regulated by multiple mechanisms, including transcriptional, post-transcriptional, epigenetic regulation, and ubiquitin-dependent or independent protein degradation. P21 is one of the most studied CDK1 inhibitors, which was first identified as a CDK-interacting protein (CIP1) and wild-type p53-activated factor 1 (WAF1). P21 can bind to cyclin A/CDK2 [30], cyclin E/CDK2 [31], cyclin D/CDK4 [32], and cyclin B/CDK1 complexes [33], resulting in cell cycle arrest in the S phase, G1/S transition, and G2/M transition. We will discuss how p21 is regulated by different RNA helicases.

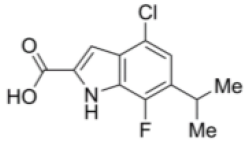
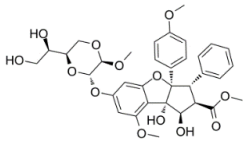
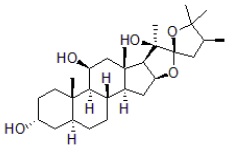
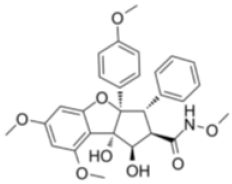
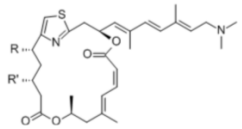
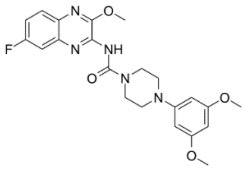
3. Development of RNA Helicase Inhibitors for Clinical Treatment

3.1. Different Targeting Strategies Are Used to Develop Compounds against RNA Helicases

The important roles of RNA helicases in the regulation of the cell cycle, cell proliferation, cellular transformation, apoptosis, and cell adhesion and motility make RNA helicases an active targets of drug development for the treatment of viral infections, neurodegenerative diseases, and cancers. Based on the crystal structures and the mechanism(s) of activity of the enzymes, specific and selective inhibitors for RNA helicases have been designed. In general, inhibitors targeting RNA helicase activity could act via one or more of the mechanisms: (1) inhibition of the ATPase activity of RNA helicases by interference with ATP binding and result in limiting the energy necessary for the unwinding and translocation; (2) inhibition of the helicase activity by competitively occupying the RNA binding site of the RNA helicases; and (3) stabilization of RNA helicases onto RNA, resulting in the inhibition of translation initiation (Table 2).

Table 2. The Structures and Sites of Action of RNA Helicase Inhibitors in Diseases.

RNA Helicases	Inhibitors	Chemical Structure	Mechanisms of Action	Diseases	Model	Toxicity or Tissue-Specific
DDX3	RK-33		Inhibition of helicase activity	Lung cancer, medulloblastoma, prostate cancer, Ewing sarcoma, and colorectal cancer	In vitro, and animal models	No discernable toxicity in animal models
	NZ51		Inhibition of helicase activity	Breast cancer	In vitro	Not clear
	Doxorubicin		Inhibition of ATPase activity	Oral squamous cell carcinoma	In vitro	Cardiotoxicity

RNA Helicases	Inhibitors	Chemical Structure	Mechanisms of Action	Diseases	Model	Toxicity or Tissue-Specific
eIF4A	Compound 18		Inhibition of ATPase activity	Exon junction complex	NA	IC_{50}: 0.97 μmol/L
	Silvestrol		Stabilization of RNA helicase onto RNA	Breast cancer	In vitro	Not toxic in vitro and in vivo at concentrations of effective activity
	Hippuristanol		Inhibition of helicase activity	Leukemia	In vitro	Not clear
	CR-1-31-B		Stabilization of RNA helicase onto RNA	Breast cancer	In vitro	Not clear
	Pateamine A		Regulation of ATPase and RNA helicase activity	Melanoma	In vitro, and animal models	Low toxicity to quiescent cells
DDX6	RX-5902		Inhibition of ATPase activity	TNBC	In vitro, preclinical models of TNBC, phase I study	Not clear

3.2. The Therapeutic Potential of RNA Helicase Inhibitors in the Treatment of Various Disorders

As described above, different inhibitors of RNA helicases have been developed, which may potentially be used in disease treatment [17][34][35]. The DDX3 inhibitor, NZ51, is able to block the ATP-dependent helicase activity of DDX3. NZ51 suppresses DDX3 activity at low micromole concentration and displays anti-proliferative activity by inhibiting cell replication at the G1 phase in aggressive breast cancer cells [12][19]. However, treatment with NZ51 did not significantly reduce tumor growth in breast cancer mouse model [19]. Doxorubicin, an antitumor drug, can inhibit the ATPase activity of DDX3, which shows anticancer activity on human oral squamous cell carcinoma cells. However, the cardiotoxicity is a limitation for doxorubicin in vivo [36]. The DDX3 inhibitors, RK-33, can bind with the ATP-binding domain of DDX3 to block its helicase activity.

Hippuristanol, as a pan eIF4A inhibitor, has been reported to inhibit human T lymphotrophic virus type 1-infected T-cell line and adult T-cell leukemia cell proliferation by promoting cell cycle arrest at the G1 phase and suppressing the expression of cell cycle proteins and cyclin-dependent kinases, and inducing apoptosis by decreasing the expression levels of Bcl-x, baculoviral IAP repeat, containing 3 X-linked inhibitors of apoptosis (xIAP) and caspase 8 and FADD like apoptosis regulator [37][38].

DDX5 (p68) can be phosphorylated at the Y593 site by growth factors, including platelet-derived growth factor, to increase cellular proliferation, epithelial to mesenchymal transition (EMT), malignant transformation, cell migration, and oncogenesis through translocation of β-catenin to nuclear and activation of cyclin D1, c-JUN, and c-MYC [39].

4. RNA Helicases and Phase-Separated Organelles

Recently, several studies have demonstrated that the DEAD-box RNA helicases involved in regulation of liquid–liquid phase separation (LLPS) play a crucial role in the formation of RNA-containing membrane-less organelles, including pericentriolar material (PCM), stress granules (SGs), P bodies, and P granules in *Caenorhabditis elegans* [40].

Pericentriolar material is defined as a matrix of proteins surrounding the two barrel-shaped centrioles during mitosis, which serves as a platform for protein complexes to regulate organelle trafficking, protein degradation, and spindle assembly.

Stress granules are RNPs that assemble in response to environmental stresses such as oxidative stress, heat shock, or osmotic shock. One component of yeast stress granules is Ded1p, also named DDX3 in mammalian. Temperature-driven liquid phase condensation of Ded1p induces the sequestration of housekeeping mRNAs and promotes an expanded heat shock response in program results of the preferential expression of stress proteins at 39 °C [41].

P bodies are the large cytoplasmic granules, which are membrane-less cytoplasmic organelles that form via phase-separation once RNAs and nearby RBPs assemble into ribonuclear particle (RNP) granules. P bodies have all the key characters of LLPS, which are liquid-like, spherical, and dynamic, and can be dissolved by the alcohol 1,6-hexanediol.

P granules are RNA/protein condensates in the germline of *Caenorhabditis elegans.* P granules are membrane-less organelles that may assemble by intracellular phase separation. GLH-1, a germline putative RNA helicase, regulates the formation and disassembly of P granules coupling with distinct steps of its ATPase hydrolysis cycle [42].

DDXs globally promote phase separation in their ATP- and RNA-bound state. ATP hydrolysis induces the release of RNA clients from a DDX, results in the disassembly of RNA-containing membrane-less organelles [40]. The condensates formed by 2NT-DDX4^{YFP}, a recombinant protein, dissolve during mitosis and leads to increasing of noise in protein concentration.

5. Conclusions

RNA helicases are highly conserved enzymes important for RNA metabolism, which are involved in multiple steps of cell cycle regulation (Figure 3). RNA helicases are involved in cell cycle regulation at each phase with different mechanisms of action, including the regulation of (1) pre-mRNA transcription or splicing of some cell cycle regulators, (2) translation of cell cycle stage associated cyclins and CDKs, and (3) transcriptional and post-translational modification of the effectors, such as p21, that are involved in cell cycle progression. For example, DDX3 regulates the expression of cyclin A1, cyclin E1, and CDK2. DHX33 regulates the transcription of many cyclins and CDKs. DDX21 regulates the expression of cyclin D1. DDX56 regulates the expression of WEE1, a G2–M cell cycle checkpoint gene. DDX5 (p68) is involved in the expression of cyclin D1, which is also important for p53 activation. DHX9 regulates the formation of cyclin D–CDK complex. DDX46 regulates G1/S cell cycle arrest. DDX41 is a repressor of CDK inhibitors, such as p21. The effect of RNA helicases on cell cycle progression is cell-type dependent, and targeting RNA helicases with inhibitors should have a significant effect on the control of cell cycle and cell proliferation. Small molecule inhibitors of RNA helicases have already been developed based on the crystal structures and the mechanism(s) of action of these enzymes. These inhibitors have been validated in vitro and in vivo, which may be further tested in different diseases, including cancer and ADPKD, as a potential therapeutic strategy.

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