RNA Biology 7:6, 775-787; November/December 2010; © 2010 Landes Bioscience

RNA helicases

Emerging roles in viral replication and the host innate response

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Key words: antiviral state, interferon response, plant and animal viruses, viral gene expression, reverse transcription, assembly

Abbreviations: CARD, caspase activation and recruitment domain; CTE, constitutive transport element; dsRNA, double stranded RNA; dsRBDs, double-stranded RNA binding domains; DUF, domain of unknown function; EJC, exon junction complex; ELISA, enzyme linked immunosorbent assay; EMCV, encephalomyocarditis virus; FMDV, foot and mouth disease virus; HIV-1, human immunodeficiency virus 1; HTLV-1, human T-cell lymphotropic virus type 1; HBV, hepatitis B virus; HDV, hepatitis delta virus; HDAg, hepatitis delta antigen; HCV, hepatitis C virus; Ικκε, IκB kinaseε; IFN, interferon; IPS-1, interferon-β promoter stimulator 1; IRF, interferon regulatory factor; JCV, JC virus; LTR, long terminal repeat; MDA-5, melanoma differentiation associated gene 5; MPMV, Mason-Pfizer monkey virus; Mov10, moloney leukemia virus 10 homolog; NFκβ, nuclear factor κβ; PCE, post-transcriptional control element; PMA, phorbol myristyl acetate; RHA, RNA helicase A; RISC, RNA-induced silencing complex; RNP, ribonucleoprotein; RRE, rev responsive element; RT-PCR, reverse transcriptase-PCR; SF2, superfamily 2; siRNA, small interfering RNA; SV40, simian virus 40; TRBP, TAR RNA binding protein; TBK1, TANK-binding kinase 1; UTR, untranslated region; VSV, vesicular stomatitis virus

RNA helicases serve multiple roles at the virus-host interface. In some situations, RNA helicases are essential host factors to promote viral replication; however, in other cases they serve as a cellular sensor to trigger the antiviral state in response to viral infection. All family members share the conserved ATP-dependent catalytic core linked to different substrate recognition and protein-protein interaction domains. These flanking domains can be shuffled between different helicases to achieve functional diversity. This review summarizes recent studies, This review summarizes recent studies of RNA helicases in virus biology. First, RNA helicases are catalysts of progressive RNA-protein rearrangements that begin at gene transcription and culminate in release of infectious virus. Second, RNA helicases can act as a scaffold for alternative protein-protein interactions that can defeat the antiviral state. The mounting fundamental understanding of RNA helicases is being used to develop selective and efficacious drugs against human and animal pathogens. The analysis of RNA helicases in virus model systems continues to provide insights into virology, cell biology and immunology and has provided fresh perspective to continue unraveling the complexity of virus-host interactions.

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Submitted: 09/10/10; Revised: 11/08/10; Accepted: 11/20/10
DOI: 10.4161/rna.7.6.14249

RNA Helicases: Ubiquitous Players in Gene Expression, Innate Response and Viral Replication

RNA helicases are ubiquitous in plants and animals, and all helicases contain the highly conserved DExH/D ATP-binding domain.[1-5] RNA helicases play essential roles in a broad array of biological processes. During gene expression, RNA helicases catalyze ribonucleoprotein complex (RNP) rearrangements beginning at gene transcription and continuing during the consecutive steps in post-transcriptional gene expression: pre-mRNA splicing, mRNA export, translation and turnover.[6-9] Despite their essential role, the mechanisms used by RNA helicases to mediate RNP rearrangements in gene expression are not fully understood. RNA helicases have been identified in all eukaryotic and prokaryotic cells, but in a minority of virus families.[10] Apparently a sufficiently diverse repertoire of cellular RNA helicase proteins is available to support most viral replication strategies. Their role in viral replication is exerted at two focal points: (1) ATPase-dependent catalytic cofactor for viral replication; (2) cellular sensor to trigger or antagonize, the antiviral state.

Modular domain structure of RNA helicases. Helicases can be classified as RNA or DNA helicases based on the substrate they bind and remodel. The helicase core is comprised of eight conserved motifs (motifs I, Ia, Ib, II, III, IV, V and VI).[2,5,11,12] Along with DNA helicases, RNA helicases can be grouped into 5 superfamilies (SF1-SF5) based on conservation of sequence motifs.[13] Most RNA helicases fall into SF2 and encode the DEAD (amino acid residues Asp-Glu-Ala-Asp), DExH, DExD or DEAH motif,[14] which are named for the residues of their Walker B motif (motif II) that contains the ATP-binding domain.[5,15] SF2 comprises eleven families, five of which are DExH/D helicases

(DEAD box, SKI2-like DExH, RIG-I-like DExH, DEAH/RHA and viral DExH).[14] Identified in all eukaryotes examined, the DExH/D box family members are divergent in the amino acid sequences that flank the helicase core. These flanking residues represent interchangeable domains (**Fig. 1**) that reoccur amongst proteins involved in the full scope of gene expression, and determine interaction with protein cofactors or target RNA.[16] The RNA helicases may exhibit processive activity that affects long stretches of RNA or rearrangement of short oligonucleotides. They may catalyze RNP remodeling or act as nonenzymatic inducers of the antiviral state, as described below.

Induction of the antiviral state. RNA helicases play a prominent role in the cellular response to viral infection. Viral infections are recognized by membrane-bound receptors and cytoplasmic sensors that trigger signaling pathways that operate by cascades of protein interactions. The outcome is the ubiquitinylation, phosphorylation and nuclear translocation of transcription factors that activate expression of interferons, interferon-stimulated genes (ISGs)[17] and inflammatory cytokines.[18] One family of cytosolic sensor is the RIG-I-like receptor (RLR) family, which includes retinoic acid-inducible gene 1 (RIG-I/DDX58) and melanoma differentiation-associated gene 5 (MDA-5).[17] Classified as RIG-I-like DExH family members (DECH variants), these RNA helicases contain amino-terminal caspase activation and recruitment domains (CARD) (**Fig. 1**). Their interaction with viral double-stranded RNA (dsRNA) induces conformational changes that reveal CARD domains for interaction with another CARD-containing adaptor protein, mitochondria antiviral signaling (MAVS; also called interferon-beta promoter stimulator 1, IPS-1) (**Fig. 2**). This leads to activation of the TANK-binding kinase 1 (TBK1)/IκB kinase-ε (IKKε) complex that phosphorylates transcription factors IRF-3 and IRF-7.[19] The phosphorylated IRF-3 and IRF-7 are translocated to the nucleus and activate transcription of antiviral and immunological genes, including interferons (IFNs); IFN-α and IFN-β. Even though RIG-I and MDA-5 encode similar DECH and CARD domains, they recognize different subsets of viral RNA by their divergent structural features or nucleotide composition. RIG-I recognizes free 5' triphosphate structures and short dsRNAs (<1 kb) whereas MDA-5 recognizes longer RNAs (>1 kb in length), such as encephalomyocarditis virus (EMCV) RNA and synthetic poly(I:C) RNA.[17,20] RIG-I and MDA-5 signaling converges at the MAVS/IPS-1 adapter protein, which integrates response to a variety of viral infections.[17] The complete characterization of the ligands of RIG-I and MDA-5 may identify additional ligands and cofactor interactions involved in IRF signaling. For instance, the activity of RIG-I and MDA-5 can be downregulated by another cytoplasmic DExH helicase, LGP2 (Laboratory of Genetics and Physiology 2). LGP2 shares the domain structure of RIG-I and MDA-5 with the exception of the CARD domains (**Fig. 1**). Preferentially-expressed in mammary tissues and tumors,[21] under some circumstances, LGP2 acts to sequester viral double-stranded RNA from RIG-I and MDA-5 and attenuate induction of the antiviral state (**Fig. 2**).[22] In other cases, LGP2 facilitates the induction of the antiviral state, and residues of the ATPase domain of LGP2 are involved in the viral RNA recognition.[20] Results in LGP-2-deficient mice revealed differences in response to two viral infections.[23] Compared to control mice, LGP2-deficient mice exhibited reduced sensitivity to lethal vesicular stomatitis virus (VSV) infection, but increased sensitivity to lethal EMCV infection, which are sensed by RIG-I and MDA-5, respectively. A possible explanation is that LGP2 in mice contributes to regulation of RIG-I or MDA-5 activity.[24] In sum, recognition of viral RNA by RIG-I and MDA-5 induces the innate immune system, whereas LGP2 interferes with the viral RNA recognition and attenuates induction of the antiviral state, at least in some circumstances. The apparent counterbalance of RIG-1 and MDA-5 by LGP2 sets the precedent that RNA helicases may be adapted to attenuate the antiviral state. The results posit that LGP2 participates in a quality control system to monitor proper induction of the antiviral state.

Catalysis of viral gene expression. Viruses are intracellular parasites that hijack cellular RNA helicases to sponsor their replication.[12] Currently, eight cellular RNA helicases have been shown to play a role in viral replication (**Fig. 1**). These are DNA or RNA viruses that synthesize their genome within the nucleus of the host cell.[25] Additionally, three virus families encode viral RNA helicases: Flavivirdae, Poxviridae and the plant Potyvirdae.[12,26,27] The viral RNA helicases share the modular domain structure of cellular helicases, but enjoy intimate contact with the viral RNP. This review will summarize the properties and activity of the 11 cellular and viral RNA helicases that modulate viral replication.

Host-encoded RNA Helicases

Biochemical and genetic analysis of viral replication has identified roles for many host-encoded RNA helicases. Specifically, several helicases have been identified by analyzing global changes in host mRNA expression following viral infection[28,29] and small interfering RNA (siRNA) screens to identify genes required for viral replication.[30] For example, following HIV-1 infection, changes in gene expression are observed for *dhx9*, *ddx10*, *ddx18*, *ddx21*, *ddx23*, *ddx39* and *ddx52*.[28,29] The expression levels of cytosolic sensors *ddx58/RIG-I*, *mda-5* and *lgp-2*, are increased by

Figure 1 (See opposite page). Domain structure of DExH/D helicases involved in viral replication. Upper rectangle: RNA helicases of the RIG-I-like receptor family are components of the innate antiviral response that attenuates viral replication. Lower rectangle: RNA helicases that promote viral replication. Protein sequences were retrieved from the NCBI conserved domains database and domains determined by annotation and query of the Uniprot database. The predicted molecular weight (kDa) and number of amino acid residues (aa) are indicated. Jagged edges indicate interruption by additional sequence or domains. Domains are: CARD, Caspase-activation and recruitment domain; DExDc, DEAD-like helicase superfamily ATP binding domain; HELICc, Helicase superfamily C-term domain associated with DExH/D box proteins; RIG-I_CRD, Regulatory domain of RIG-I; RS/GYR, Arginine/serine, glycine tyrosine-rich domain; dsRBD, Double-stranded RNA binding domain; HA2, Helicase-associated domain of unknown function; DUF, Domain of unknown function; RG-rich, arginine and glycine-rich domain; SPRY, SP1a and RYanodine receptor domain; p68HR, Characteristic of p68-like RNA helicase; Peptidase_S29, serine protease domain with trypsin-like fold; Poty_PP, Observed in polyproteins of the Potyviridae.

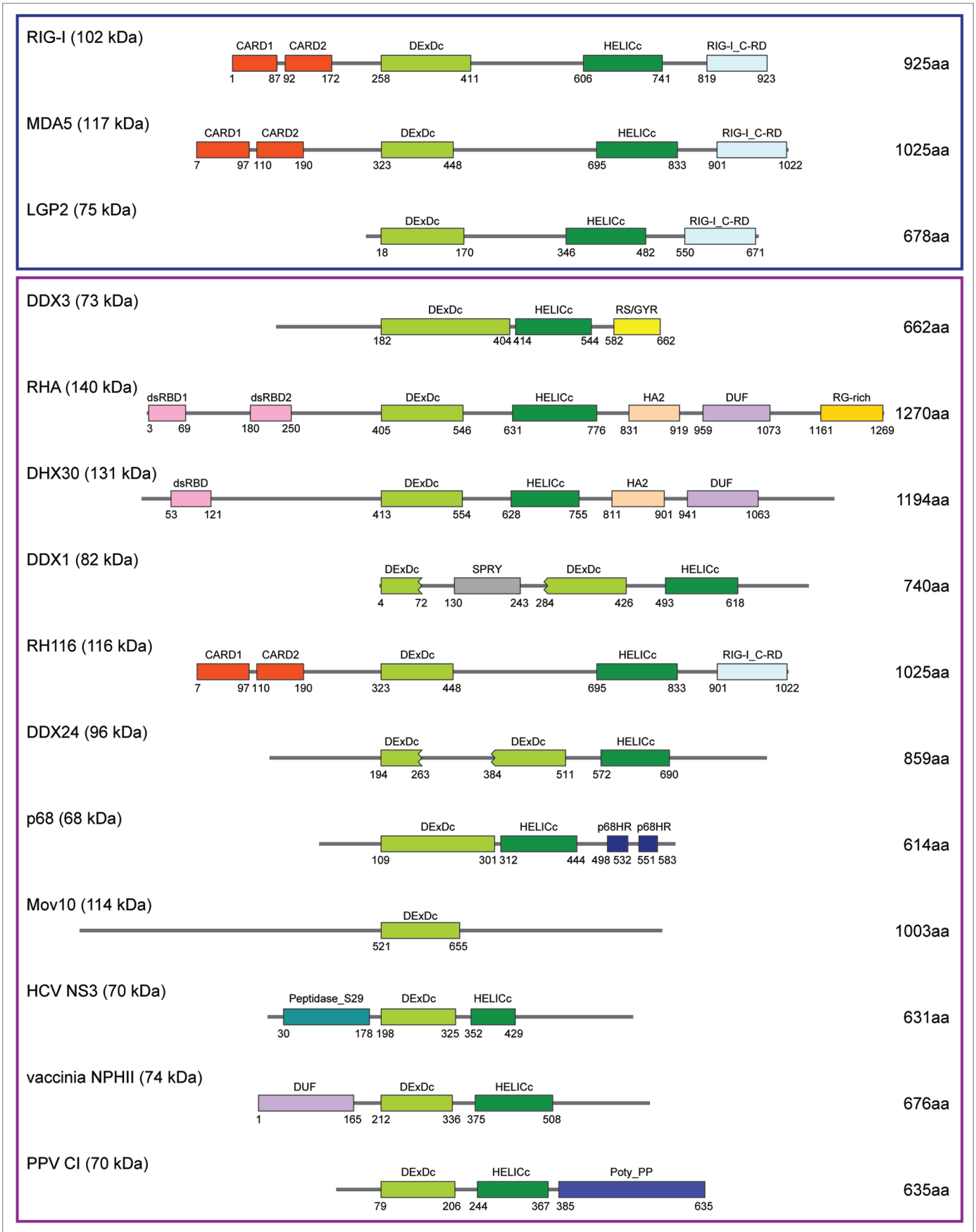

Figure 1. For figure legend, see page 776.

infection with Dengue virus, yellow fever virus, vaccinia virus, Hantaan virus and Sin nombre virus, consistent with induction of the innate antiviral response.[22] The ubiquitous involvement of cellular RNA helicases in virus replication is attributable to their ability to as act a scaffold for alternative protein-protein interactions. While some host-encoded RNA helicases, such as RIG-I and MDA-5, induce the cellular antiviral response and limit viral replication, eight host-encoded helicases have been shown to promote virus replication. The following sections describe the structure of these helicases and their role in the virus life cycle.

DDX3. DDX3 is a 73 kD nucleo-cytoplasmic DEAD helicase that is ubiquitously expressed in a wide range of tissues.[31-33] DDX3 has multiple activities in the cell, which involve ATPase activity and ability to act as a scaffold for alternative protein-protein interactions. The central helicase and DEAD domains are flanked at the N-terminus by a protein-protein interaction domain and a putative nuclear export signal and a glycine-rich C-terminus (**Fig. 1**). DDX3 is highly conserved in metazoans (**Table 1**). Ded1 is the yeast homolog and is essential for general translation initiation.[34] Ded1 was identified in a yeast genetic screen and the ded1-deficiency can be rescued by human DDX3, implicating DDX3 in translation of metazoan RNAs.[34,35] Since then, metazoan DDX3 has been observed to modulate gene expression at the transcriptional and post-transcriptional levels, both of which affect the broader processes of cell growth regulation, apoptosis and the innate response to virus infection.[32,36,37] Members of four virus families use DDX3 to promote their life cycle (**Table 2**).

Retrovirus. Jeang and colleagues identified DDX3 affects HIV-1 posttranscriptional gene expression.[33] The exogenous expression of DDX3 increases production of HIV-1 Gag virion structural protein (5 to 12-fold), while suppression of endogenous DDX3 by antisense RNA decreases Gag production (factor of 13).[33] Northern analysis determined that the overexpression of DDX3 did not change the abundance of the unspliced gag transcript or the ratio of unspliced to spliced viral transcripts. The results indicated that DDX3 did not affect HIV-1 transcription or pre-mRNA processing and is likely to enhance Gag production by increasing the Rev-dependent nuclear export of the unspliced gag transcripts. Consistent with this activity, DDX3 is a binding partner of the CRM1 nuclear export receptor and the HIV-1 viral posttranscriptional trans-activator, Rev.[33]

DDX3 expression is enhanced in a HeLa cell line that expresses HIV-1 Tat.[33] Two possible explanations are that *ddx3* expression is upregulated by the transcriptional trans-activation activity of Tat or the post-transcriptional RNA silencing suppressor activity of Tat, which may attenuate miRNA activity against ddx3.[38,39] Yedavalli et al. explored DDX3 as a target to inhibit HIV-1 replication.[40] Two-ring expanded nucleoside analogs were identified that inhibit DDX3 activity, suppress HIV-1 replication and exhibit insignificant toxicity in cell culture or in mice. These data document that cellular helicases are a feasible target for the development of novel antiretroviral drugs.

Poxvirus. DDX3 promotes the innate response to virus infection by its ability to act as a scaffold for protein-protein interactions.[41-44] DDX3 augments the activity of TBK1/IKKε, which activates IRF-3, IRF-7 and the NFκB transcription factor to stimulate interferon and interferon response genes that induce the antiviral state.[41,42] While the helicase activity of DDX3 is not required, the N-terminal domain of DDX3 is required and associates with IKKε. Notably the same domain is targeted by vaccinia virus K7 protein.[41] The crystal structure of K7 in complex with the N-terminal DDX3 peptide reveals that a hydrophobic cleft of K7 residues engage a thumb-like projection of tandem phenylalanine residues.[45] Presumably this protein-protein interaction prevents DDX3 from engaging IKKε to promote interferon induction. The findings suggest that DDX3 is a prime target for viral manipulation of interferon induction.[41,42]

Flavivirus. Yeast two-hybrid studies initially identified an interaction between DDX3 and the HCV core structural protein.[31,35,46] Subsequently RNA interference verified that DDX3 is important for viral RNA replication in HuH-7 liver cells.[47] The N-terminal residues of DDX3 are important for interaction with the HCV core and DDX3 interaction is significantly reduced by a single alanine substitution in HCV core.[48] However it remains to be determined whether or not the HCV core blocks interaction between DDX3 and IKKε, which would attenuate IRF signalling. Alternatively, HCV core may block interaction between DDX3 and another cellular protein that bolsters replication by another mechanism.

Hepadnavirus. Whereas DDX3 enhances replication of HIV-1 and HCV, DDX3 restricts hepatitis B virus (HBV) replication in both hepatoma and non-hepatoma cells. DDX3 binds to HBV polymerase (Pol), which is responsible for reverse transcription of viral RNA to DNA[49] and is incorporated into nucleocapsid with the pre-genome RNA.[50] DDX3 ATPase activity, but not helicase activity, is necessary for the inhibitory effect on HBV reverse transcription, which posits that inhibition of viral DNA synthesis occurs at a step following ATP hydrolysis, but prior to RNA unwinding.[50] In addition to catalyzing reverse transcription, HBV Pol exhibits an immune modulatory role that is attributed to disrupted IRF signaling.[50] Similar to vaccinia virus K7, HBV Pol disrupts the interaction between DDX3 and IKKε. The results suggest that DDX3 is manipulated to evade IFN induction at the expense of viral reverse transcription. The identification of DDX3 residues essential for the interaction with HBV Pol may provide another selective target for small molecule inhibitors to impair virus replication.

RNA helicase A (RHA)/DHX9. Human RHA/DHX9 is an SF2 DEIH helicase that is the homolog of bovine nuclear DNA helicase II and *Drosophila melanogaster* Maleless.[51-53] RHA is the largest and most complex of the helicases involved in viral replication (140 kDa and six domains) (**Fig. 1**). RHA executes protein-protein interactions that impact the continuum of gene expression, beginning at transcription and culminating in mRNA translation and influence cell growth and apoptosis, and the innate response to virus infection.[3,54-59] RHA contains two double-stranded RNA binding domains (dsRBDs) of conserved α-β-β-β-α topology; the DEIH helicase core; the domain of unknown function (DUF), which is conserved in Ago2; the helicase-associated domain 2 (HA2) of a diversity of RNA helicases; a nuclear transport domain that is recognized by importin-α; and the carboxyl-terminal arginine and glycine-rich residues that

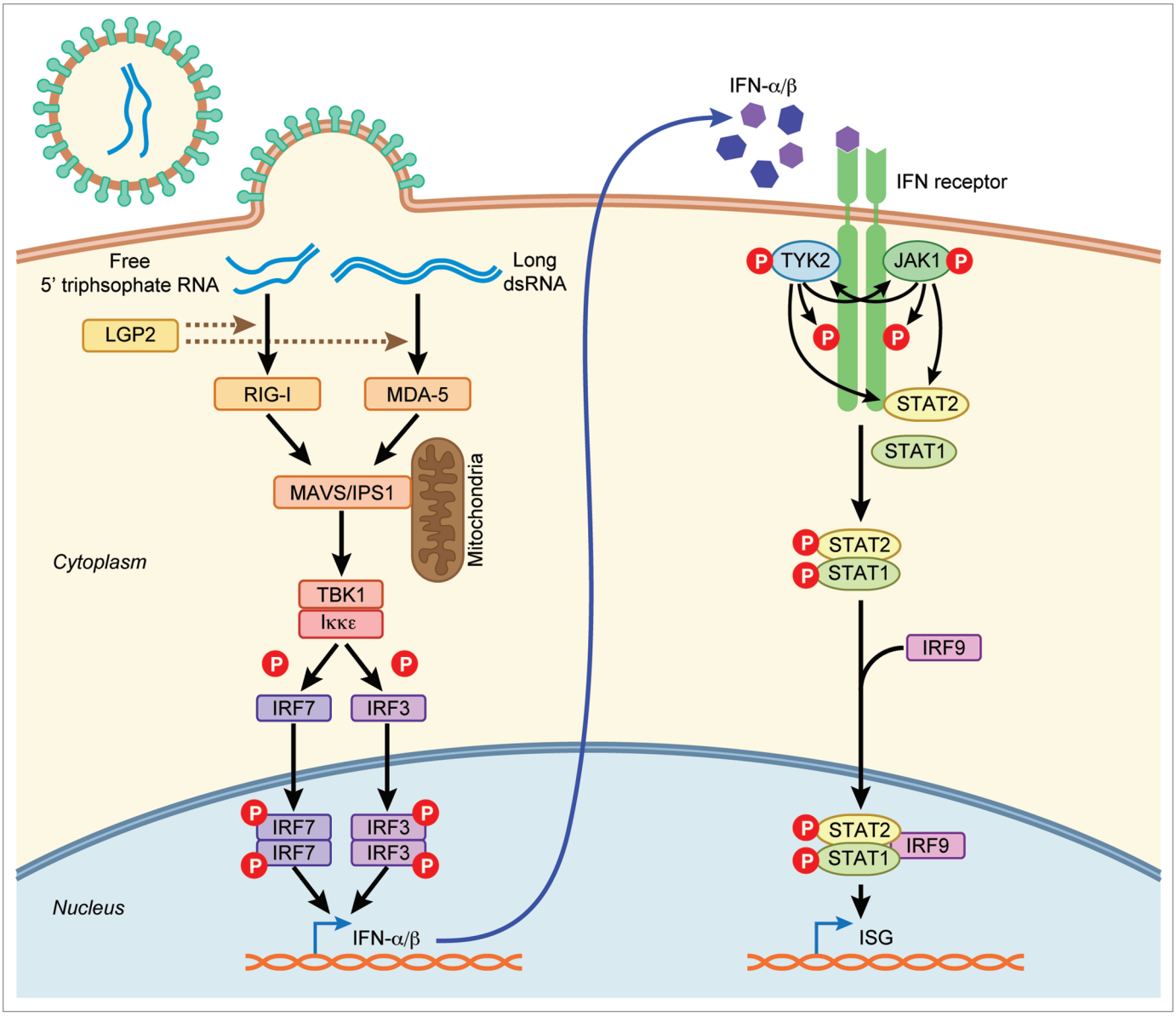

Figure 2. RNA helicases of the RIG-I-like receptor (RLR) family play a crucial role in the innate antiviral response. RLR family members, retinoic acid-inducible gene 1 (RIG-I/DDX58) and melanoma differentiation-associated gene 5 (MDA-5) are cytoplasmic sensors that detect viral RNA and trigger induction of the antiviral state. RIG-I and MDA-1 recognize viral RNA as foreign by features including free 5' triphosphate ends, short double-stranded RNA (dsRNA) and long dsRNA (≥1 kb), respectively. RLR family member, laboratory of genetics and physiology 2 (LGP2) can antagonize this activity (dashed line) by regulation that is poorly understood. Interaction with their RNA ligands induces conformational changes in RIG-I and MDA-5 that favor interaction with mitochondria antiviral signaling (MAVS), also called interferon-beta promoter stimulator 1 (IPS-1). MAVS/IPS-1 activates the TANK-binding kinase 1 (TBK1)/IκB kinase-ε (IKKε) complex, which phosphorylate IFN-regulatory factor (IRF)-3, IRF-7 and NFκB (not shown). The IRFs dimerize, translocate to the nucleus and bind to target genes. Transcriptional activation of interferon (IFN) genes leads to production of IFNs (α and β), which are secreted from the cell. IFN binding to the IFN receptor activates the janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. The JAK and tyrosine kinase 2 (TYK2) phosphorylate one another, the receptor and STAT2. STAT2 binds STAT1 and triggers phosphorylation and STAT1/2 dimerization. The STAT heterodimer translocates to the nucleus with IRF-9. They activate transcription of interferon stimulated genes (ISG), which generate the anti-viral state that attenuates viral replication.

are recognized by PRMT1 methylase.[60,61] RHA is prominently nuclear[62] and interacts with RNA polymerase II and transcription factors and coactivators that modulate gene transcription.[63-65] In the cytoplasm, RHA interacts with structural features of the 5' untranslated region (UTR) of the junD mRNA to facilitate efficient cap-dependent translation of this protooncogene.[57,66,67] In sum, virus interaction with RHA may be advantageous for efficient expression of viral genes. Furthermore, the impact of RHA on cellular gene expression may produce cell growth conditions that are advantageous for the viral life cycle. Members of three virus families use RHA to promote their replicative cycle.

Table 1. Significant conservation is observed amongst RNA helicases involved in virus biology

DExD/H family member	Amino acid identity (%) relative to human homolog[a]																		
	Pan troglodytes	*Mus musculus*	*Rattus norvegicus*	*Canis lupis familiaris*	*Bos taurus*	*Gallus gallus*	*Danio rerio*	*Drosophila melanogaster*	*Anopheles gambiae*	*Caenorhabditis elegans*	*Plasmodium falciparum*	*Schizosaccharomyces pombe*	*Schizosaccharomyces cerevisiae*	*Kluyveromyces lactis*	*Eremothecium gossypii*	*Magnaporthe grisea*	*Neurospora crassa*	*Arabidopsis thaliana*	*Oryza sativa*
DDX3	-[b]	99	99	99	99	94	-	61	51	-	54	-	54	-	-	-	-	55	46
RHA/DHX9	-	90	90	95	95	-	-	53	53	45	-	-	-	-	-	-	-	-	-
DHX30	99	98	98	98	98	79	53	-	-	-	-	-	-	-	-	-	-	-	-
DDX1	100	98	98	98	97	93	85	61	63	50	36	-	-	-	-	-	-	-	-
RH116	-	80	80	83	84	63	58	-	-	-	-	-	-	-	-	-	-	-	-
DDX24	99	80	82	85	84	60	54	41	43	39	-	40	36	37	36	36	36	37	39
P68/DDX5	-	99	99	100	100	91	86	60	62	56	56	58	58	59	57	60	61	60	44
Mov10	100	91	92	95	92	51	47	-	-	-	-	-	-	-	-	-	-	47	49

[a]Protein sequences were retrieved from the NCBI HomoloGene and BLAST databases, date 30 June 2010. The percentage of amino acid identity relative to the human homolog was determined. [b]Homolog not annotated in database.

Retrovirus. RHA overexpression has been suggested to increase retrovirus gene transcription, the ratio of spliced to unspliced viral transcripts[68,69] and nuclear export of unspliced RNA.[62,70] However downregulation experiments with siRNAs and quantitative RNA analysis determined RHA is not required for retrovirus transcription, RNA splicing or nuclear export, but that RHA is necessary for retrovirus translation.[57,71-73] RHA selectively interacts with structural features of the 5' UTR of many retroviruses and overexpression of RHA increases their translation.[57,71-73] RHA interaction with the 5' UTR increases polysome association and requires the ATP-binding activity of the DEIH helicase domain.[57,73] The molecular basis of RHA translation activity is catalytic rearrangement of the RNP to facilitate ribosome scanning and translation initiation, and possibly and protein-protein interaction that secures a circular polysome for efficient translation reinitiation.[57] In sum, RHA is necessary for efficient translation of many retroviruses including HIV-1 (**Fig. 3**).

In the case of the simian Mason-Pfizer monkey virus (MPMV), RHA interacts with the 5' UTR to facilitate translation.[74] Additionally, RHA interacts with the 3' UTR of MPMV in a region necessary for nuclear export of the unspliced viral transcript.[70] This region is designated the constitutive transport element (CTE)[62] and facilitates nuclear export by recruiting the TAP nuclear export receptor.[75] Conceivably RHA interacts with MPMV RNA in the nucleus and facilitates consecutive remodeling of the viral RNP necessary for nuclear export and subsequent translation in the cytoplasm.[76]

Studies on HIV-1 determined that RHA promotes the infectivity of progeny virions[77] (**Fig. 3**). Molecular analysis of the defect determined that RHA in the virus producer cells fosters the reverse transcription activity of the progeny virions[77] (**Fig. 3**). Kleiman and colleagues determined the defect is attributable to reduced annealing of tRNA to viral RNA (40% of control) during the virion assembly process.[133] Furthermore, RHA is incorporated into the progeny virions, possibly through interaction with the nucleocapsid domain of Gag,[77] the HIV-1 RNA or an adapter protein.[73] RHA-deficient virions are less infectious to Hela-based TZM-bl reporter cells[77] and primary T lymphocytes.[73] The defect is attributed, in part, to reduced reverse transcription[77] but may also involve replication steps that are downstream of reverse transcription. In sum, RHA appears to be involved in multiple steps in the retroviral life cycle.

Flavivirus. Behrens and colleagues identified that RHA binds to the 5' and 3' UTRs of bovine viral diarrhea virus RNA and affects viral replication.[78] Two other proteins that contain the conserved dsRBD (NF-45 and NF-90/NFAR-1) facilitate viral replication. These findings suggest the dsRBD may be acting as a scaffold to secure the viral RNA in a configuration helpful to replication of the bovine diarrheal virus.

To investigate possible importance of RHA in a human flavivirus, He et al. studied HCV replicon cells using RHA downregulation strategies. A lentivector-based inducible RNA interference system administered partial RHA downregulation. Partial RHA downregulation produced a gradual reduction of HCV RNA and protein over 21 days, as measured by RT-PCR and immunoblot, respectively.[79] The results suggest RHA is a necessary host factor for HCV in replicon cells.

Picornavirus. Recent study of foot and mouth disease virus (FMDV) determined that RHA downregulation decreases viral replication.[80] In infected cells, RHA co-precipitates FMDV replication proteins, 2C and 3A.[80] Furthermore, FMDV infection changes the subcellular localization of RHA from prominently nuclear and a uniform distribution, to prominently cytoplasmic and a punctuate distribution. Similar to results in retroviruses and bovine diarrheal virus,[57,73,78] RHA interacts with terminal regions of FMDV RNA. Together the results posit the model that FMDV uses RHA to promote viral RNA replication and to facilitate viral protein synthesis. The authors speculate that FMDV

Table 2. Overview of the role of cellular helicases in replication cycle of indicated virus

RNA helicase	Virus	Role in replication cycle
DDX3	HIV-1	Binds CRM1 and HIV-1 Rev and increases Gag protein production
	Vaccinia virus	Interacts with vaccinia virus K7 protein, which blocks transcriptional activation of the interferon responsive genes
	Hepatitis B virus (HBV)	Restricts viral replication by binding to HBV Polymerase and inhibiting reverse transcription of HBV RNA to DNA
	Hepatitis C virus (HCV)	Important for HCV RNA replication
RHA	Retroviruses: HIV-1, human T-cell leukemia virus type 1, bovine leukemia virus, spleen necrosis virus, feline leukemia virus, Mason-Pfizer monkey virus (MPMV)	Associates with post-transcriptional control element (PCE) in the 5' untranslated region and facilitates translation of the transcript Facilitates annealing of tRNA to viral RNA during virus assembly Incorporated into HIV-1 virions and facilitates virion infectivity
	MPMV	Associates with the constitutive transport element (CTE) in the 3' UTR that binds the TAP nuclear export receptor; may augment release of CTE-containing RNA from the nuclear pore complex
	Bovine viral diarrhea virus	Binds to the 5' and 3' termini of viral RHA; enhances replication
	HCV	Required for HCV replication
	Foot and mouth disease virus	Binds to the 5' and 3' termini of viral RHA; enhances replication
DHX30	HIV-1	Overexpression increases steady state HIV-1 RNA and decreases virion RNA in progeny virions
DDX1	HIV-1	Interacts with HIV-1 Rev; affects nuclear export of unspliced reporter mRNA
	JC virus	Binds the JC virus transcriptional control region; facilitates productive expression of early and late JCV transcripts
	Infectious bronchitis virus	Interacts with coronavirus non-structural protein 14 and colocalizes with the viral RNA
RH116	HIV-1	Overexpression increases steady state HIV-1 mRNA
DDX24	HIV-1	Interacts with HIV-1 Gag; downregulation modestly reduces nuclear export of unspliced HIV-1 mRNA; reduces viral RNA in virions; reduces the RNA infectivity of progeny virions
p68	HCV	Interacts with HCV NS5B; required for transcription of negative strand viral RNA
Mov10	Hepatitis delta virus	Required for viral replication
	Retroviruses: HIV-1, simian influenza virus, murine leukemia virus, feline immunodeficiency virus, equine infectious anemia virus	Activity as antiviral restriction factor
	HIV-1	Interacts with HIV-1 Gag, packaged into virions and affects proteolytic processing; overexpression or downregulation reduces infectivity of progeny virions

uses RHA to connect the 5' and 3' UTRs to switch between viral RNA replication to viral protein synthesis, which may occur on a circular polysome.[80]

In summary, RHA interacts with the terminal regions of many viral RNAs. Future analysis is warranted to determine the domain(s) of RHA required for interaction with viral RNA and test the possibility that similar residues are required across several virus families. This fundamental investigation will be informative to development of antiviral therapy that selectively discriminates between the cellular and viral RNA targets of RHA.

DHX30. To date a single virus, HIV-1, has been shown to interact with DHX30 (isoform 2).[81] DHX30 is a 131 kDa protein with the conserved ATP-dependent helicase domain (DEVH variant) followed by the DUF domain and HA2 domain and one dsRBD at the amino-terminus (**Fig. 1**). The DHX30 domain structure is highly similar to RHA. Similar to results with RHA, overexpression of DHX30 increases expression of the HIV-1 provirus (2 to 3-fold) and an HIV-1 LTR luciferase reporter (1.5–4 fold), and this activity is eliminated by a DEVH mutation.[81] In distinction from RHA, DHX30 overexpression decreased viral RNA packaging into progeny virions (factor of ~10 as measured by RT-real time PCR on equivalent particle-associated Gag), suggesting proper trafficking of HIV-1 RNA between the cytoplasm and virions was disrupted (**Fig. 3**). The authors speculated that DHX30 might cause a modification of the packaging signal by binding to the 5' UTR. As expected, the reduction in viral RNA packaging correlated with reduced infectivity of progeny virions (by a factor of 6). Downregulation of DHX30 did not produce an effect on HIV-1 gene expression,[81] which is likely attributable to redundant activity by RHA. RHA is abundantly expressed in many types of animal cells and displays high sequence identity with DHX30 in basic residues that direct RHA interaction with retrovirus RNA.[134] Domain exchange experiments between DHX30 and RHA will be instrumental to understand the specificity and potential functional redundancy of these RNA helicases.

DDX1. Members of three virus families exhibit interaction with DDX1 (**Table 2**). DDX1 is an 82 kDa ATP-dependent

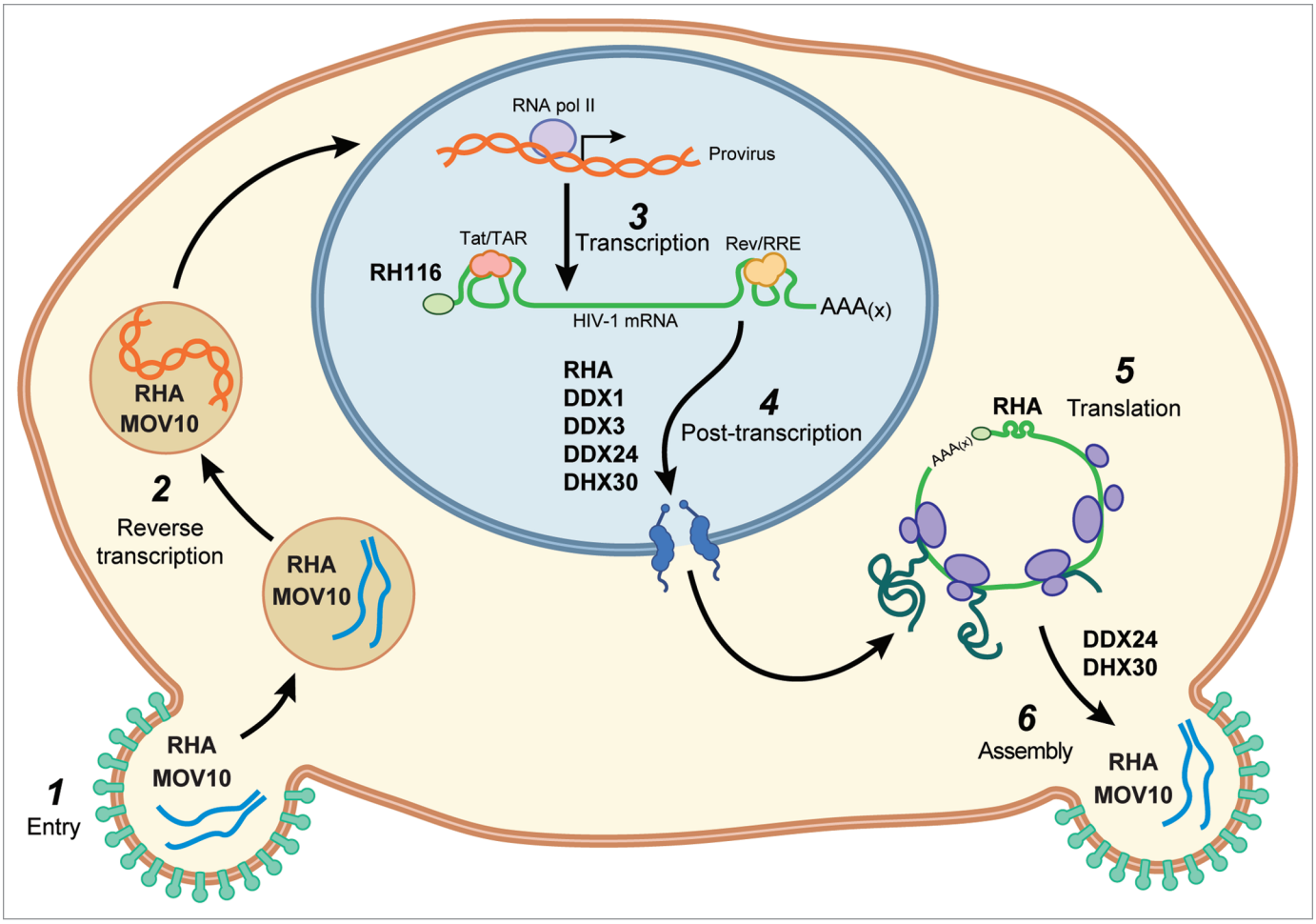

Figure 3. Cellular helicases involved in HIV-1 replication. DExH/D helicases with a known function in HIV-1 replication are indicated beside the corresponding step in the replication cycle of HIV-1: (1) Receptor-mediated entry; (2) Reverse transcription of viral genomic RNA to DNA and integration into host chromosome to render the provirus; (3) Transcription of HIV-1 provirus and accumulation of viral mRNA; (4) Post-transcription includes RNA processing and export from the nucleus; (5) Translation of viral transcripts on polysomes; (6) Assembly of viral structural and enzymatic proteins and unspliced viral transcript into progeny virions that bud from the plasma membrane.

DEAD box family member that contains a SPRY domain (**Fig. 1**). DDX1 exhibits affinity for poly(A) RNA, heterogenous nuclear ribonucleoprotein K and cleavage stimulatory CSTF-64, which suggests DDX1 contributes to proper 3' end maturation of mRNAs.[82,83]

Retrovirus. In common with DDX3, RHA and DHX30, DDX1 activity affects HIV-1 replication (**Fig. 3**). Yeast and mammalian two hybrid systems identified DDX1 interacts with HIV-1 Rev.[84] DDX1 downregulation reduces the activity of an HIV-1 Rev/RRE-dependent luciferase reporter gene, and RT-PCR determined that nuclear export of unspliced reporter mRNA was impaired. The reduced Rev/RRE activity correlated with disordered Rev subcellular distribution in nucleus and nucleolus,[85] consistent with an important role for this host factor in HIV-1 biology. While DDX1 is upregulated in neuroblastoma and retinoblastoma cell lines and tumors,[86] expression in astrocytes is low. Astrocytes are nonpermissive for HIV-1 replication and ectopic expression of DDX1 is sufficient to complement the defect in HIV-1 replication.[85] The findings that DDX1 facilitates Rev/RRE activity and is a rate-limiting factor for HIV-1 replication in astrocytes indicates that DDX1 is a required host factor for HIV-1 replication.[87]

Polyoma virus. DDX1 also modulates cell specificity of the human polyoma virus, JC virus.[88] DDX1 expression is high in cells susceptible to JC virus infection and low in nonpermissive cells; exogenous DDX1 expression renders nonpermissive cells susceptible to JC virus infection. DDX1 and CSTF64 bind the JC virus transcriptional control region and the outcome is productive expression and accumulation of early and late JC virus transcripts. By contrast, downregulation of DDX1 impairs JC virus gene expression. The results are likely attributable to impaired 3' end processing that culminates in the decay of viral transcripts.

Coronavirus. Yeast 2-hybrid screens determined DDX1 interacts with coronavirus nonstructural protein 14.[89] Vero cells infected with infectious bronchititis virus exhibited transit of DDX1 from the nucleus to the cytoplasm and colocalization with the coronaviral RNA.[89] Mutation of DDX1 DEAD motif to AAAA eliminated the colocalization and the replication

of coronavirus, indicating a necessary role for the ATPase-dependent helicase activity of DDX1.[89] The results suggest that DDX1 is important for efficient coronavirus replication.

RH116. RH116 has been observed to affect replication of one virus to date, HIV-1 (**Table 2**). RH116 is a 116 kDa amino acid interferon-induced helicase (DECH variant). Assigned to the RIG-I like DExH box helicase family, RH116 contains two CARD domains (**Fig. 1**) and exhibits nuclear accumulation. RH116 is 99.5% identical to MDA-5 and recapitulates its inhibition of cellular proliferation.[90] RH116 was identified by a differential display RT-PCR screen for cofactors required for suppression of HIV-1 infection by the synthetic immunomodulator, Murabutide.[90] The overexpression of RH116 increases HIV-1 replication in HeLa-CD4 cells coincident with nuclear accumulation of endogenous RH116.[90] A possible explanation for this observation is squelching of a cofactor needed for the antiviral activity of RH116. The remarkable amino acid identity with MDA-5 suggests that RH116 is a cytosolic sensor for HIV-1 under some circumstances. These findings warrant new investigations into the control of RH116 gene expression, the cofactors that control the subcellular localization of RH116 and the effect of RH116 on IRF signaling activity during HIV-1 infection of lymphocytes.

DDX24. DDX24 is a 96 kDa DEAD box helicase that lacks other conserved motifs (**Fig. 1**) and exhibits amino acid content that is dissimilar to typical DEAD box family members.[91] Proteomic analysis identified DDX24 coprecipitates with HIV-1 Gag. This interaction is mediated by the Gag nucleocapsid domain and is disrupted by RNase, indicating that the interaction is RNA-dependent.[77] DDX24 also coprecipitates with HIV-1 Rev.[25] The downregulation of DDX24 changes the subcellular localization of Rev from nucleolar to nuclear and moderately increases Rev/RRE-dependent nuclear export of unspliced HIV-1 mRNA (2–3 fold).[25] Despite the increase of viral transcript in the cytoplasm, the infectivity of HIV-1 progeny virions was reduced on Hela-based TZM-bl reporter cells. Real time PCR determined reduced abundance of virion-associated RNA, which is sufficient to account for the reduction in titer.[25] In sum, DDX24 appears to be important for proper trafficking of the viral RNA for assembly into virions (**Table 2 and Fig. 3**).

P68/DDX5. p68 is a DEAD box helicase that contains a p68HR domain that is characteristic of p68-like RNA helicases (**Fig. 1**). Named for its molecular weight of 68 kDa, p68 cross reacts with monoclonal antibody to SV40 large-T antigen (pAB204 epitope), which suggests these proteins display a similar epitope.[92-94] In common with SV40 large-T antigen, p68 affects cellular proliferation and tumor development, and mechanistically p68 intersects the processes of transcriptional regulation, RNA splicing and the processing of pre-ribosomal RNA.[95-100] Using results from a yeast two-hybrid screen, Goh et. al. determined that p68 interacts with HCV NS5B RNA-dependent RNA polymerase.[101] Expression of NS5B of HCV changes the subcellular localization of endogenous p68 from the nucleus to the cytoplasm,[101] similar to the effect of FMDV on RHA.[80] Downregulation of p68 reduces the transcription of negative strand HCV RNA. Taken together, p68 is an important host factor for HCV at the level of HCV gene expression (**Table 2**).

Mov10. Moloney leukemia virus 10 homolog (Mov10) contains a putative SF1 helicase (DEAG variant) and lack other defined domains (**Fig. 1**). Mov10 appears to be heavily post-translationally modified because of substantial difference between the predicted and observed molecular weights (114 kDa and 130 kDa, respectively). Mov10 is required for RNA interference-mediated gene silencing by RNA-induced silencing complex (RISC);[102,103] however RNA interference is successfully employed to test the effect of Mov10 on virus replication (below). Mov10 is expressed in a variety of cell types including lymphocytes and embryonic stem cells.[104,105] Mov10 in HeLa cells coprecipitates with RISC components Ago1 and Ago2 and colocalizes with Ago proteins in cytoplasmic processing bodies.[102] Virus interaction with Mov10 has the potential to interface with antiviral RNA silencing and influence the viral replication efficiency.

Hepatitis delta virus (HDV, unassigned family). The downregulation of Mov10 or the Mov10 binding partner, Ago2, is sufficient to reduce HDV replication.[106] HDV replication requires RNA-directed transcription and host RNA-dependent RNA polymerase catalytic activity. In principle, these processes are similar to RNA-directed RISC loading to miRNA target RNA and RNA-dependent catalytic activity of RISC. We posit a corollary model in which Mov10 facilitates remodeling of the incoming viral RNA to produce a transcription initiation competent RNP.

Retrovirus. The downregulation of endogenous Mov10 reduces HIV-1 infectivity. However, exogenous expression of Mov10 in primary or transformed cells severely reduces infectivity of progeny virions.[103,104,107] These non-reciprocal results suggest an appropriate balance of Mov10 and cofactors is responsible for control of virus replication. Recently published studies determined Mov10 is a restriction factor against several retroviruses: simian influenza virus, murine leukemia virus, feline immunodeficiency virus, equine infectious anemia virus and HIV-1.[103,104,107] Mov10 of human, simian and murine origin exhibit antiretroviral activity, consistent with their significant conservation among various species[103] (**Table 1**). HIV-1 infection of human cell lines (A3.01, CEM-T4, CEM-SS) reduces endogenous Mov10,[103] which is reminiscent of virus-associated degradation of the APOBEC3G restriction factor by Vif.[108] Mov10 interacts with APOBEC3G in primary $CD4^+$ T cells and 293T cells, although Vif does not downregulate Mov10 activity.[104]

Similar to DHX30, Mov10 interacts with the nucleocapsid domain of HIV-1 Gag in an RNA-dependent manner and is packaged in virions (**Fig. 3**). Restriction occurs at an early, post-entry step in viral replication that occurs before reverse transcription is initiated (**Fig. 3**). Results from producer cells indicate that proteolytic processing of nascent virions is reduced,[107] which may indicate defective viral core uncoating or translocation to the nucleus. The issue remains uncertain of whether or not the anti-HIV activity requires ATPase-dependent helicase activity of Mov10. Mutation of the DEAG helicase domain eliminated anti-HIV-1 activity in one study,[103] but not in another investigation.[104] Both studies used 293T cells to produce virus, but they employed different cells to measure virus titer: osteosarcoma HOS-derived HIV GFP GHOST reporter cells and HeLa, respectively. The use of different target cells may contribute to the conflicting

outcomes. The restriction activity of Mov10 in species from mouse to man and against many retroviruses raises the possibility that Mov10 restricts replication of other viral families. Either way, deciphering the fundamental mechanisms of Mov10 activity may provide a target for development of selective anti-viral molecules.

Virus-Encoded Helicases

While most viruses do not encode their own helicase, 3 virus families encode a viral helicase. The viral helicases display the familiar domain structure of cellular helicases (**Fig. 1**). The viral helicases are essential for the replication of these viruses and in some cases are emerging targets for anti-viral therapy (see below). This section focuses on properties of the viral RNA helicases.

HCV nonstructural protein 3 (NS3). HCV encodes a single open reading frame that is translated to a 3,000 amino acid polyprotein and cleaved into 10 mature proteins. NS3 is a 70 kDa DExH box protein (DECH variant) that resembles SF2 family helicases.[10,109] NS3 contains five domains: two N-terminal domains that comprise a protease and three distal domains that comprise the helicase[10,110] (**Fig. 1**). Until recently, the NS3 helicase and protease domains were considered functionally independent, however, new data indicate the protease domain exhibits a positive charge that enhances the interaction of the helicase domain with RNA.[111,112] NS3 RNA helicase activity is essential for HCV replication and is not replaced by cellular helicases.[112,113] NS3 RNA helicase affects two steps in the HCV replication cycle. During RNA-dependent RNA replication, NS3 is required to unwind the double-stranded RNA intermediate, which may enable movement of HCV NS5b polymerase.[110,114,115] Second, NS3 assists in virus assembly and is likely attributable to ability to act as a scaffold for interaction with viral or cellular cofactors. Point mutation of the NS3 helicase domain (both subdomains) demonstrated a role for NS3 helicase in infectious virus assembly, independent of a role in HCV RNA replication.[116] Homologous NS3 proteins are encoded by two other Flaviviruses, yellow fever virus and dengue virus.[14] In sum, NS3 helicase activity is essential for Flavivirus replication and is a potential therapeutic target against the significant human pathogen, HCV.

HCV affects nearly 180 million people worldwide and is responsible for about 50–75% of liver cancer cases.[110,117] Current therapy against HCV is ineffective in about 20% and 60% of patients chronically infected with HCV genotypes 2 and 3 and genotype 1, respectively.[118] HCV helicase has been actively pursued as a target to inhibit HCV.[119,120] Several studies to identify small molecule, nucleic acid and antibody inhibitors of HCV NS3 have been described in detail[10,110] and clinical trials have involved combinations to target HCV protease and polymerase.[110] The continued mechanistic investigation of NS3 and ready availability of a cache of candidate compounds are essential tools to develop an efficacious treatment for HCV infection.

Vaccinia virus nucleoside triphosphate phosphohydrolase II (NPH-II). Vaccinia virus encodes a 74 kDa helicase that contains a DEVH ATP binding domain and a DUF domain, and is designated nucleoside triphosphate phosphohydrolase II (NPH-II) (**Fig. 1**). NPH-II is an RNA-dependent NTPase that is activated by single-stranded RNA, and can hydrolyze all four ribonucleoside triphosphates.[121] Homology is observed between the helicase domain of NPH-II, three yeast PRP splicing proteins (PRP16, PRP2 and PRP22), RHA/DHX9 and the Drosophila homolog Maleless.[122] NPH-II unwinds RNA substrates or RNA-DNA hybrids in a processive and directional fashion with a small step size of around 6 base pairs.[123]

Essential for vaccinia virus replication, NPH-II is incorporated into the vaccinia virion.[122] Fathi and Condit uncovered several temperature sensitive mutations of NPH-II that generate non-infectious progeny virions at non-permissive temperature.[124,125] Gross and colleagues determined the temperature sensitive mutations produced defects in early transcription of the DNA template.[126] DNA-mediated marker rescue of NPH-II temperature sensitive viruses revealed the ATPase and helicase activity of NPH-II are essential for vaccinia virus replication.[127] Mutations that block RNA unwinding without significantly affecting the ATPase activity are lethal, possibly by promoting genomic instability. The authors posited that NPH-II facilitates productive viral transcription by preventing R loop formation behind the elongating RNA polymerase, which otherwise may result in genomic instability.[128] Homologous NPHII proteins are encoded by Poxviridae members variola virus and fowlpox virus.[14] In sum, NPH-II provides essential function(s) in the viral life cycle, which apparently are lacking from cellular RNA helicases or cannot be provided in an accessible configuration. NPH-2 viral RNA helicase activity is a potential therapeutic target to attenuate poxvirus replication and pathogenesis.

Plum pox virus cylindrical inclusion protein (CI). Plum pox virus (PPV) CI is a 70 kDa DExH box RNA helicase (DECH variant) that contains the Poty_potyviridae polyprotein domain (PP) (**Fig. 1**). PPV is a member of the Potyviridae, which is the most numerous group of plant viruses. Of unknown function, Poty_PP is ~300 amino acids, rich in basic residues and conserved in polypeptides across Potyviridae. CI protein is produced by cleavage of the viral polyprotein and exhibits NTP-dependent helicase activity.[129] PPV CI helicase activity was the first reported for an RNA virus.[129] CI is a catalyst necessary for viral replication and a scaffold to promote the spread of the virus from cell to cell, and these functions are genetically separable.[130-132] DECH helicase and NTPase mutations disrupt viral replication.[130] Mutations that impair viral cell-to-cell spread retain helicase and NTPase activity[132] but impair necessary virus-host protein interactions. Homologs of CI are encoded by potyviruses tobacco-mosaic virus and the lilly-mottle virus,[14] which suggests CI activity is conserved among PPV.

Perspectives on the Future Directions

The study of RNA helicases is fueling fundamental understanding of cell biology and the virus-host interface. The versatile roles of RNA helicases in virus biology are attributable to the linkage of the conserved catalytic domain to different substrate recognition domains. This modular configuration is similar in principle

to the separable domains of transcription factors: activation domain and DNA binding domain. The functional versatility of RNA helicases encompasses their well-characterized roles as cytosolic receptors to recognize viral infection and trigger activation of the antiviral state, to control of gene expression that results in proper utilization of the viral RNA for translation and assembly into virions, to their manipulation by viral proteins to block induction of the antiviral state.

This fundamental information has generated fresh perspectives to address new open issues of significant potential impact on cell biology, immunology and viral pathogenesis. Future aims include: (1) to determine the complete list of ligands that trigger the antiviral state and definition of their biophysical requirements for productive interaction; (2) to define all of the RNA helicases that interface with viral gene products to manipulate the antiviral state, and their molecular mechanism; (3) to characterize the features of cellular helicases and viral helicases that determine selective interaction with RNA substrates; (iv) to execute effective strategic application of the fundamental knowledge of RNA helicases to identify anti-viral drugs with minimum toxicity to human and animal patients. In closing, recent achievements to understand the basic science of RNA helicases are being applied to develop selective, efficacious inhibitors of significant human pathogens, HCV and HIV-1. The continued progress to define the molecular mechanisms of RNA helicases at the virus-host interface is rocket-fuel to attain efficacious drugs against human and animal pathogens.

Acknowledgements

We thank Mr. Tim Vojt for illustration, Dr. Paula Pitha and Reviewers for their helpful comments. The authors appreciate the support of Glenn Barber Predoctoral Fellowship, College of Veterinary Medicine, Ohio State University to A.R. and NIH NCI P30CA100730 and RO1CA108882 to K.B.L.

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