The multifarious roles of heterogeneous ribonucleoprotein A1 in viral infections

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Summary
Viruses are obligate parasites known to interact with a wide variety of host proteins at different stages of infection. Current antiviral treatments target viral proteins and may be compromised due to the emergence of drug resistant viral strains. Targeting viral-host interactions is now gaining recognition as an alternative approach against viral infections. Recent research has revealed that heterogeneous ribonucleoprotein A1, an RNA-binding protein, plays an essential functional and regulatory role in the life cycle of many viruses. In this review, we summarize the interactions between heterogeneous ribonucleoprotein A1 (hnRNPA1) and multiple viral proteins during the life cycle of RNA and DNA viruses. hnRNPA1 protein levels are modulated differently, in different viruses, which further dictates its stability, function, and intracellular localization. Multiple reports have emphasized that in Sindbis virus, enteroviruses, porcine encephalitis virus, and rhinovirus infection, hnRNPA1 enhances viral replication and survival. However, in others like hepatitis C virus and human T-cell lymphotropic virus, it exerts a protective response. The involvement of hnRNPA1 in viral infections highlights its importance as a central regulator of host and viral gene expression. Understanding the nature of these interactions will increase our understanding of specific viral infections and pathogenesis and eventually aid in the development of novel and robust antiviral intervention strategies.

KEYWORDS
heterogeneous ribonucleoprotein A1, hnRNPA1, replication, RNA binding proteins, role, viruses

1 | INTRODUCTION
Viruses, despite their limited number of genes, utilize many host factors for efficient replication in the host. Depending on the nature of their genetic material, viral proteins interact with a plethora of host proteins that facilitate their infection inside the infected host. Host cellular systems comprise highly complicated and sophisticated networks that consist of interactions between numerous cellular components; viruses hijack these cellular pathways, leading to the reconstruction of modulated networks to meet their requirements for efficient replication and immune suppression.

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Abbreviations: ARV, avian reovirus; CRE, cis-acting replication element; ds, double-stranded; EBV, Epstein-Barr virus; ESS 2, exonic splicing silencer 2; EV-71, enterovirus 71; G and SG RNA, genomic and sub genomic RNA; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus 1; HK-2, hexokinase 2; hnRNAs, heterogeneous nuclear RNAs; hnRNP, heterogeneous nuclear ribonucleoprotein; hnRNPA1, heterogeneous ribonucleoprotein A1; HPV-16, human papillomavirus 16; HRV, human rhinovirus; HTLV-1, human T-cell lymphotropic virus type 1; IG sequence, intergenic sequence; IR-1, internal repeat region 1; IRES, internal ribosome entry site; ITAF, internal trans activating factor; JUNV, Junin virus; LMP-2, latent membrane protein 2; LTR, long terminal repeat; MAPKs, Mitogen-activated protein kinases; MHV, murine hepatitis virus; mRNAs, messenger RNAs; N, nucleocapsid protein; NLS, Nuclear localization sequence; ORF, open reading frame; PEDV, porcine epidemic diarrhea virus; PKC, Protein kinase C; PTMs, Post translational modifications; RBDS, RNA-binding domains; RBPs, RNA-binding proteins; RGG, Arginine-glycine-glycine; RIGs, RNA immunoprecipitations; RNAs, RNA interference; RRM, RNA Recognition motifs; RxRE or XRE, rex response element; S6Ks, Ribosomal S6 kinases; SARS CoV, severe acute respiratory syndrome coronavirus; siRNA, silencing RNA; SL-II, stem loop II; UTR, untranslated region; VSV, vesicular stomatitis virus; Y2H, Yeast two-hybrid screens; (GlcNAc), O-GlcNAcylation (GlcNAc).
Recent technical advances in methodology, including genomewide RNA interference (RNAi) screens, yeast two-hybrid (Y2H) screens, and transcriptional gene expression profiling, have identified hundreds of host proteins involved in viral infections, of which about one in five are RNA-binding proteins (RBPs).\textsuperscript{11-15} The multifaceted role of the host RNA machinery means that RBPs are at the center of host-virus cross-talk. However, a comprehensive understanding of the sizeable network of host proteins interacting with the viral machinery still remains to be elucidated.

The transcripts of protein-coding genes in the nucleus of eukaryotic cells are known as heterogeneous nuclear RNAs (hnRNAs). After being transcribed, cellular pre-mRNAs associate with nuclear proteins to form heterogeneous nuclear ribonucleoprotein (hnRNP) complexes, which function to affect the structure, posttranscriptional processing, or nucleocytoplasmic transport of these mRNAs.\textsuperscript{16,17} They also regulate splicing, nuclear export of mRNAs, telomere biogenesis, DNA repair, transcription, translation, and cell signalling.\textsuperscript{17-19} The hnRNP family comprises of more than 20 evolutionarily conserved proteins, named alphabetically from hnRNPA1-hnRNPU in humans.\textsuperscript{17} All the members of the family share a common modular structure consisting of one or more RNA-binding domains (RBDs) which dictate their interaction with RNA.\textsuperscript{17}

hnRNPA1 is the most abundant RBP in the hnRNP(A/B) subfamily. It affects the expression of many critical genes in the host, at the transcriptional, posttranscriptional, translational, and post-translational level which are responsible for controlling crucial metabolic pathways in the host.\textsuperscript{19-22} The N-terminal domain of the protein encodes two RBDs which are pivotal for RNA specificity and binding (Figure 1). Additionally, a flexible glycine-rich arginine-glycine-glycine (RGG) region known as the RGG box imparts protein and RNA binding features to the protein. Downstream of the RGG box, there is a 38 amino acid (aa) sequence termed the M9 nuclear localisation sequence (NLS) in the glycine (Glyc) rich region, which facilitates bidirectional nucleo-cytoplasmic shuttling of the protein by means of its interaction with the members of importin α/β sub-familys.\textsuperscript{17,23-25} (Figure 1). Transportin-1 interacts with the Glyc-rich region (195-268 aa) of hnRNPA1 by the virtue of its F-peptide (301-318 aa).\textsuperscript{25}

Post-translation modifications (PTMs) in a protein are known to affect their activity and binding affinity. Likewise, several post-translational modifications like phosphorylation, methylation, ubiquitination, and sumoylation dictate the activity and compartmentalization of hnRNPA1 in a cell.\textsuperscript{17} For instance, methylation of arginine residues in the RGG motif may regulate the RNA-binding activity of the protein.\textsuperscript{21,26-28} Similarly, kinases such as protein kinase C (PKC), mitogen-activated protein kinases (MAPKs), and ribosomal S6 kinases (S6Ks) phosphorylate serine residues present at both the N and C terminal of the protein, regulating its function.\textsuperscript{17,21,29-31} PTMs like phosphorylation in the C-terminal region of the protein result in cytoplasmic accumulation of hnRNPA1.\textsuperscript{22,25,30} Contrastingly, the addition of O-GlcNAcylation (GlcNAc) moiety to the serine or threonine aa via β-O-linkage is a commonly occurring, reversible modification which impairs the binding of hnRNPA1 to karyopherin β (Transportin-1).\textsuperscript{25,32} This leads to enhanced nuclear localization of the protein, eventually affecting its activity.\textsuperscript{25}

2 | MULTIPLE ROLES OF HNRNPA1 IN VIRUSES

Based on the polarity of the genome, viruses are categorized as positive sense or negative sense. Depending on their genetic makeup, they need to utilize many RBPs to successfully complete their infection cycle in the host.\textsuperscript{33-35} As the replication of the viral genome takes place in the host cytoplasm or nucleus, they must have a mechanism in place to discriminate between the cellular and viral RNAs present in an infected cell. Moreover, due to their limited coding capacity, they
lack preexisting RNA machinery to ensure successful replication in the host. Owing to all these factors, viruses have strategically evolved to exploit host RNA-binding proteome and evade host RNA degradation mechanisms. hnRNPA1 is an RBP involved at multiple stages post-infection that, depending on the virus in question, has contradictory roles; in some, it promotes viral replication, while in others, it abrogates it. Diverse roles exhibited by the protein are summarized below (Tables 1–4).

### 2.1 Antiviral role of hnRNPA1

By the virtue of advanced techniques like RNAi screen, microarray, forward chemical genetics, proteomic, Y2H screens, and RNA immunoprecipitations (RIPs), the association of hnRNPA1 with multiple promoters, untranslated (UTR) regions, and participation at various stages of viral gene expression has been elucidated (Figure 2). Upon infection of cells by viruses, the genome acts as a template for viral gene transcription and posttranscriptional regulation, thereby facilitating the expression of viral genes.

In human T-cell lymphotropic virus type I (HTLV-1) cell culture model, hnRNPA1 inhibits the binding of the Rex protein to its response element (RxRE or XRE) in 3′ long terminal repeat (LTR) of all viral RNAs. Silencing RNA (siRNA)–mediated knockdown of hnRNPA1 affected the splicing of gag/pol transcripts and increased the binding of Rex to its response element, thereby positively affecting the rate of viral replication. Furthermore, ectopic expression of hnRNPA1 antagonized the posttranscriptional activity of Rex by competitive binding, thereby eliciting an antiviral response against HTLV-1 infection.

Hepatitis C virus (HCV) has a 13.6-kb genome which encodes a single positive sense RNA molecule 9.6 kb in size encoding a polycistronic open reading frame (ORF) flanked by UTR regions at the 5′ and 3′ ends. These regions are pivotal for viral replication. The conserved region at the 3′ end of the ORF is termed the cis-acting replication element (CRE), which is indispensable for viral replication and translation. The conserved structure is responsible for RNA-RNA interactions with various viral and host factors, one of which is hnRNPA1. Additionally, viral RNA-dependent RNA polymerase (NS5B) also interacts with hnRNPA1. Up-regulation of hnRNPA1 in Huh-7 cells, down-regulated HCV RNA synthesis, and 48 hours post-infection coinciding with a surge in HCV RNA synthesis were observed after hnRNPA1 silencing. The authors speculate that since hnRNPA1 binds to both the CRE and viral polymerase, it might compete with the latter, for efficient viral replication thereby exerting an antiviral effect. Viruses in which hnRNPA1 plays an antiviral role are summarized below (Table 1).

#### TABLE 1

| Serial Number | Virus                                      | Genome Type | Cytoplasmic Retention | Functional Implication                                                                 |
|---------------|--------------------------------------------|-------------|-----------------------|---------------------------------------------------------------------------------------|
| 1             | Human T-cell lymphotropic virus (HTLV-1)   | RNA virus (+) | -                     | 1. Regulates posttranscriptional and posttranslational processing of HTLV-1 viral genes. |
|               |                                            |             |                       | 2. Inhibits export of REX-1 associated mRNAs.                                           |
| 2             | Hepatitis C virus (HCV)                     | RNA virus (+) | -                     | 1. hnRNPA1 binds to the 5′ and 3′ nontranslated region (NTR) region of the HCV RNA and viral polymerase, NS5b, thereby regulating viral replication, negatively. |

#### 2.2 Pro-viral role of hnRNPA1

Pro-viral effect was seen in Sindbis virus infection model, wherein hnRNPA1 was redistributed to the cytoplasmic site of viral replication and bound to the 5′ UTR region (5′UTR) of viral RNA, promoting the synthesis of negative-strand RNA (G and SG RNA). Furthermore, a decline in hnRNPA1 expression affected viral RNA synthesis, cap-dependent and cap-independent translation of viral genes.

A similar trend was reported in porcine epidemic diarrhea virus (PEDV) infection, wherein hnRNPA1 co-immunoprecipitated with PEDV nucleocapsid protein (N) during the course of infection. Furthermore, hnRNPA1 also bound to terminal leader sequence and intergenic (IG) sequence important for efficient virus replication.

Levengood et al reported that in enterovirus 71 (EV-71) infection, hnRNPA1 is redistributed to the cytoplasm and interacts with the 5′UTR in the stem loop II (SL-II) region of the internal ribosome entry site (IRES) v- RNA (viral RNA), thereby acting as an internal trans activating factor (ITAF), accentuating IRES-mediated translation of viral genes. Combined knockdown of hnRNPA1 and hnRNPA2B1 greatly impaired viral RNA translation, impeding viral replication. Biological studies also showed that the SL-II domain undergoes a conformational change to assemble a viable hnRNPA1-RNA complex. Mutations or deletions in this region completely impair viral replication.

Cammas et al reported physical binding of hnRNPA1 to the 5′UTR region of human rhinovirus (HRV) IRES. Courteau et al supported this and also showed that cytoplasmic localization of hnRNPA1 controlled and enhanced IRES-mediated translation of viral proteins, thereby acting as an ITAF. Furthermore, down-regulating hnRNPA1 or expressing a cytoplasmic restricted mutant of the protein (hnRNPA1 ΔM9) partially restored the block on viral translation. They also identified the role of hexokinase 2 (HK-2) in controlling the nucleo-cytoplasmic distribution of hnRNPA1.
Chiu et al. reported that in avian reovirus (ARV) infection, non-structural protein p17 is shuttled to and fro from the nucleus in an hnRNPA1-dependent manner. The hnRNPA1 is constantly shuttled to and fro the nucleus by an active import/export mechanism which relies on its interaction with the F-peptide (301-318 aa) of Transportin-1, a member of the importin family. ARV p17 protein interacts with hnRNPA1 and is indirectly shuttled across the nuclear pore complex, alongside the hnRNPA1-transportin-1 cargo. This is supported by site-directed mutagenesis, wherein mutant hnRNPA1195-268 with intact M9 NLS (195-268 aa) retained its binding ability to p17.

**TABLE 2** Summary of reports showing hnRNPA1 as a pro-viral host protein

| Serial Number | Virus                  | Genome Type | Cytoplasmic Retention | Functional Implication                                                                 |
|---------------|------------------------|-------------|-----------------------|----------------------------------------------------------------------------------------|
| 1             | Sindbis virus[^18,37]  | RNA virus (+) | -                     | 1. Binds to 5’UTR, promotes IRES assisted and non-IRES-assisted protein translation. 2. Helps in viral RNA replication (+) and (−) strand. |
| 2             | Epidemic Porcine Diarrhea virus (PEDV[^38]) | RNA virus (+) | -                     | 1. Positively regulates viral replication.                                                |
| 3             | Enterovirus 71 (EV-71)[^39] | RNA virus (+) | -                     | 1. Binds to 5’UTR, promotes IRES-assisted translation of viral genes. 2. Helps in viral replication. |
| 4             | Human rhinovirus (HRV)[^40,41] | RNA virus (+) | Yes                   | 1. Enhances viral replication by promoting IRES-mediated translation.                    |
| 5             | Avian reovirus (ARV)[^42] | ds RNA virus | -                     | 1. Binds to ARV p17 protein and mediates its nucleo-cytoplasmic import/export 2. hnRNPA1 depletion in p17-transfected Vero cells, leads to nuclear retention of p17. 3. Positively regulates viral replication. |

**TABLE 3** Summary of reports with contradicting roles for hnRNPA1

| Serial Number | Virus                  | Genome Type | Cytoplasmic Retention | Functional Implication                                                                 |
|---------------|------------------------|-------------|-----------------------|----------------------------------------------------------------------------------------|
| 1             | Human immunodeficiency virus I (HIV-1)[^43-46] | RNA virus (+) | Yes                   | 1. hnRNPA1 binds to HIV-1 RNA and regulates nucleo-cytoplasmic export and splicing of viral RNA. 2. Maintains cytoplasmic stability of viral mRNA. |
| 2             | SARS corona virus (SARS CoV)[^47,48] | RNA virus (+) | -                     | 1. Involved in the viral RNA synthesis. 2. Interacts with the viral nucleocapsid protein of SARS CoV. |
| 3             | Murine Hepatitis virus (MHV)[^49,50] | RNA virus (+) | -                     | 1. hnRNPA1 enhances the rate of viral replication and IRES-mediated translation of viral proteins. |
| 4             | Junin virus (JUNV)[^51] | RNA virus (−) | Yes                   | 1. Promotes viral RNA transcription and replication in early stages of infection.       |

**TABLE 4** Summary of reports in which the role of hnRNPA1 is not elucidated

| Serial Number | Virus                  | Genome Type | Cytoplasmic Retention | Functional Implication                                                                 |
|---------------|------------------------|-------------|-----------------------|----------------------------------------------------------------------------------------|
| 1             | Epstein-Barr virus (EBV)[^52] | RNA virus (+) | -                     | 1. hnRNPA1 binds to the late membrane protein 2 (LMP2) mRNA assumed to control splicing of this gene in EBV infection. |
| 2             | Human papilloma virus –16 (HPV-16)[^54,55] | DNA virus | -                     | 1. hnRNPA1 is up-regulated in HPV-16 infected cells. 2. It binds to late response element (LRE) mRNA and regulates the expression of virus late response genes. |
| 3             | Vesicular stomatitis virus (VSV)[^54] | RNA virus (−) | -                     | 1. VSV infection promotes hnRNPA1 relocalization in a Rae 1-dependent manner for apoptotic signalling. 2. hnRNPA1 silencing in VSV infection exhibits delayed onset of apoptosis. |
FIGURE 2 Functional role of heterogeneous ribonucleoprotein A1 (hnRNPA1) in viral infections. hnRNPA1 is targeted by viruses to control various stages in their life cycle: (A) replication, (B) transcription, (C) posttranscriptional modification like nuclear export/import, and (D) translation.

whereas mutant hnRNPA1-184 (1-184 aa) lost its capacity to interact with p17, thereby leading to the nuclear accumulation of ARV p17 protein.42 Multiple reports suggest that ARV p17 protein induces autophagy that is mandatory to support efficient replication in the host.74-76 The authors suggest that ARV p17-hnRNPA1 interaction is needed for import and export of the p-17 cargo via the nuclear pore complex (NPC). Additionally, siRNA-mediated knockdown of hnRNPA1 in p17 transfected Vero cells exhibited nuclear retention of p17, 17 to 30 hours posttransfection.42 Furthermore, siRNA-mediated depletion of hnRNPA1 in Vero cells dropped ARV titer, establishing that hnRNPA1 plays a pro-viral role in ARV infection.42

Various viruses in which hnRNPA1 supports viral replication in the host are listed in Table 2.

2.3 Controversial role of hnRNPA1

In the case of human immunodeficiency virus 1 (HIV-1) infection, contradictory results were reported by two different research groups, Monette et al reported a surge in the amount of endogenously expressed hnRNPA1 post-HIV-1 infection, as enhanced hnRNPA1 levels were seen to be favorable for the virus.43 Additionally, HIV v-RNA was immunoprecipitated with hnRNPA1 protein.43,77 A decrease in hnRNPA1 levels down-regulated viral pr55Gag expression, affecting viral replication negatively.43,53 Subsequently, a virus-imposed block on hnRNPA1 import to the nucleus was observed. This phenomenon was linked with decrease in the nuclear pore glycoprotein p62 and transportin-1 levels, post-infection, pivotal for nucleo-cytoplasmic shuttling of hnRNP proteins.43 Cytoplasmic retention of hnRNPA1 favored IRES-mediated translation of viral genes and vice-versa.

In contrast, Zahler et al highlighted the importance of hnRNPA1 in regulating the splicing of many viral genes (viz, Tat), wherein, hnRNPA1 binds to exonic splicing silencer 2 (ESS 2), thereby repressing the splicing of Tat mRNA.44,45 Overexpression of hnRNPA1 in an in vitro system abrogated the expression of TaT, adversely affecting viral replication.43,45,46,78-80

hnRNPA1 is known for its action as a cis-acting element favoring replication and transcription of viral genes. Luo et al reported that the C terminal region of hnRNPA1 has high affinity and directly binds to the SARS_N (Nucleocapsid protein) in severe acute respiratory syndrome coronavirus infection (SARS CoV).81 However, a deletion in the C-terminal region of the protein substantially abrogated viral replication and transcription, suggesting that hnRNPA1 and SARS_N interaction facilitates the binding of other cis- or trans-activating factors, enabling viral transcription and replication to ensue.81

Murine hepatitis virus (MHV) belongs to the genus Betacoronaviruses. hnRNPA1 is up-regulated and localized to the cytoplasm, post-MHV infection.81 It regulates discontinuous viral transcription by binding to negative strand leader and IG sequence indispensable for viral transcription and also mediates the formation of MHV viral ribonucleoprotein complexes.82,83 Furthermore, it also binds to MHV N protein which has multifarious roles in the viral life-cycle and has the ability to bind viral RNA.16,84-86 Remarkably, hnRNPA1 also binds to positive stranded 3’UTR, suggesting a possible role in negative strand RNA synthesis.84 There are conflicting reports about the importance of hnRNPA1 in MHV infection. According to a study by Shi et al, viral RNA synthesis was enhanced after ectopic expression of hnRNPA1; however, a truncation mutant of the protein, lacking the C terminal region responsible for cytoplasmic localization of the protein, had inverse effects.83,87 Another report by Shen et al claimed that CB3 cell lines lacking any detectable expression of the RBP could sustain viral replication, implying that the effect exerted by hnRNPA1 can be substituted by other cellular gene products similar in function to hnRNPA1; however, members of the hnRNP family interact in a similar fashion with MHV RNA in un-infected and virally infected CB3 cells.49,88 Many members of the hnRNPA1 family interact in a similar fashion with MHV RNA in an in vitro system abrogated the expression of TaT, adversely affecting viral replication.43,45,46,78-80

Maeto et al ascribed that hnRNP A/B subfamily (hnRNPA1 and A2) has a different role in acute and persistent Junin virus (JUNV) infections.51 JUNV is a single-stranded, enveloped RNA virus belonging to the Arenaviridae family.57,89 Acute infection by this virus is characterized by enhanced production of viral progeny, whereas, in
persistent infection, there is no infectious viral particle produced.\textsuperscript{90,91} In acute infection, where there is production of viral nucleoprotein (N), hnRNPA1 is overexpressed and cytoplasm localized. This might aid the virus in translation. During persistent infection, hnRNPA1 was predominantly nuclear, supported by experiments using a mutant lacking NLS, as reported by Maeto et al.\textsuperscript{51,90,91} This difference may be linked to the role of this protein in the host whereby cytoplasmic hnRNPA1 negatively regulates the translation of anti-apoptotic proteins like XIAP and APAF1.\textsuperscript{92,93} Furthermore, down-regulation of hnRNPA(A/B) proteins individually abrogates JUNV replication; however, the effect was much more pronounced when both hnRNPA1 and hnRNPA2 were silenced simultaneously.\textsuperscript{51} Moreover, hnRNPA1 was found to co-immunoprecipitate with N protein in acutely infected cells.\textsuperscript{51} Upregulating N protein induced cytoplasmic re-localization of hnRNPA1 in Vero cells,\textsuperscript{51} further pointing towards the role of hnRNPA1 in the JUNV lifecycle.

2.4 Undesignated role for hnRNPA1

In Epstein-Barr virus (EBV) infection, hnRNPA1 has been speculated to regulate the splicing of latent membrane protein 2 (LMP-2) mRNA by its interaction with the intronic region in the LMP2 mRNA in association with hnRNPU and beta actin.\textsuperscript{52} In silico prediction studies using RBPMAP identified the binding of hnRNPA1 to stabilize a non-coding internal repeat region 1 (IR1) of EBV RNA.\textsuperscript{52,94} Additional molecular and biochemical studies aiming towards characterizing the role of this protein in EBV are needed to better understand the importance of hnRNPA1 in the EBV lifecycle.

Human papillomavirus 16 (HPV-16) is the most common sexually transmitted virus. It encodes early and late genes under the control of different promoters. Viral gene expression is regulated at the transcriptional and posttranscriptional level.\textsuperscript{95} hnRNPA1 expression is upregulated in HPV-16 infection.\textsuperscript{96} hnRNPA1 has also been observed to directly bind to splicing silencer RNA elements in HPV-16L1 coding region, thereby inhibiting splicing of HPV-16 late mRNA.\textsuperscript{77,97} Additionally, hnRNPA1 promoted splicing of early HPV mRNAs, thereby promoting enhanced gene expression.\textsuperscript{95,100} However, further studies directing towards modulating the levels of hnRNPA1 are needed to elucidate its role in HPV-16 replication.

In the case of vesicular stomatitis virus (VSV), Lyses et al reported that although hnRNPA1 silencing did not have any major effect on viral replication and growth, HeLa cells in which hnRNPA1 was silenced displayed delayed onset of apoptosis post-virus infection, suggesting that hnRNPA1 may play a protective role by initiating antiviral immune response post-VSV infection.\textsuperscript{54}

3 CONCLUSION AND FUTURE DIRECTIONS

Viruses are known to usurp many host cell proteins for their own benefit.\textsuperscript{1} Successful infection is characterized by sequestering host proteins, concurrently, evading the host-induced immune response.\textsuperscript{1} Owing to their limited genetic capacity, viruses tend to utilize many host proteins. Likewise, hosts have evolved innate and adaptive cellular defense mechanisms to counteract the infection caused by these viruses. The multifaceted nature of hnRNPA1 in the host makes it a lucrative target for many viruses. This review highlights the importance of hnRNPA1 and diverse roles played by this protein in the life cycle of various viruses.

For instance, in Sindbis virus,\textsuperscript{18,37,69} PEDV,\textsuperscript{38} EV-71,\textsuperscript{39} and HRV\textsuperscript{40,41} infections, hnRNPA1 shows a pro-viral effect which may be attributed to the role of this protein as an ITAF, positively regulating IRES mediated translation of viral RNAs. Likewise, in ARV infection, virus exploits the nucleo-cytoplasmic machinery in place for trafficking hnRNPA1 via its interaction with transportin-1 to indirectly translocate p17\textsuperscript{42,76} through the NPC. hnRNPA1 down-regulation, affects virus titer, negatively, implicating towards a supportive role in ARV infection.\textsuperscript{42} Contrastingly, in HTLV-1\textsuperscript{56,59} and HCV-1\textsuperscript{55,58,61,63} life cycle, hnRNPA1 negatively regulates viral replication by controlling the posttranscriptional and translational modification of viral mRNAs. However, in the case of HIV-1,\textsuperscript{43-46} SARS CoV,\textsuperscript{47,48} MHV,\textsuperscript{49,50} and JUNV\textsuperscript{51,89-91} infections, the advantage gained by the virus through its interaction with hnRNPA1 is debatable. This can be linked to the way the host interactome is shaped post-viral infection. For example, depending on the stage of infection, that is, acute or chronic, the localization of hnRNPA1 is modulated and varied effects are exhibited in JUNV cell culture model.\textsuperscript{51}

RBPs have been established as cis- and trans-acting elements, hnRNPA1 acts as a cis-acting element in SARS CoV infection model, controlling viral gene expression.\textsuperscript{81} It also binds SARS nucleocapsid protein, facilitating the binding of other cis- or trans-activating factors, to ensure viral transcription and replication.\textsuperscript{81} In MHV infection, hnRNPA1 binds to positive and negative viral RNA.\textsuperscript{82-84} However, the role of hnRNPA1 in MHV infection is controversial. Viral replication was enhanced post-hnRNPA1 transfection, but in hnRNPA1 silenced cell lines, no retardation in viral replication was observed,\textsuperscript{49,83,87,88} indicating that the effect incurred may be substituted by other isoforms or members of hnRNP family.

In EBV and HPV-16 infections, although hnRNPA1 has been reported to bind to viral RNA,\textsuperscript{52,94,97-99} further studies directed towards how these interactions dictate virus survival need further investigation. Likewise, in VSV infection, hnRNPA1 was not seen to directly affect viral replication but hnRNPA1 silenced cells displayed delayed onset of virus induced apoptotic events.\textsuperscript{54} The varied profile of hnRNPA1 in multiple viruses may also appertain to the diverse replication profile exhibited by these viruses. Similar alterations in related viruses may elicit different consequences for viral replication.

Although all these observations are fascinating, many questions pertaining to the functional implication of hnRNPA1 in the host, post-viral infections, still remain unsolved. Unravelling the complexity and the fate of these hnRNPA1-virus interactions not only enhances our current understanding of the disease biology and pathogenesis but also helps identify crucial nodal points which can be exploited further. Additionally, it will be imperative to utilize the interactions between
viral proteins and hnRNPA1 as tools to identify biomarkers for diagnostic measures and host-based therapeutics.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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