

ADVANCED REVIEW

RNA regulatory processes in RNA virus biology

Shaun T. Cross | Daniel Michalski | Megan R. Miller | Jeffrey Wilusz 

Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, Colorado

Correspondence

Jeffrey Wilusz, Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO 80523.

Email: jeffrey.wilusz@colostate.edu

Funding information

National Institute of Allergy and Infectious Diseases, Grant/Award Numbers: AI123136, AI39497; National Science Foundation, Grant/Award Number: 5325000

Abstract

Numerous post-transcriptional RNA processes play a major role in regulating the quantity, quality and diversity of gene expression in the cell. These include RNA processing events such as capping, splicing, polyadenylation and modification, but also aspects such as RNA localization, decay, translation, and non-coding RNA-associated regulation. The interface between the transcripts of RNA viruses and the various RNA regulatory processes in the cell, therefore, has high potential to significantly impact virus gene expression, regulation, cytopathology and pathogenesis. Furthermore, understanding RNA biology from the perspective of an RNA virus can shed considerable light on the broad impact of these post-transcriptional processes in cell biology. Thus the goal of this article is to provide an overview of the richness of cellular RNA biology and how RNA viruses use, usurp and/or avoid the associated machinery to impact the outcome of infection.

This article is categorized under:

RNA in Disease and Development > RNA in Disease

KEYWORDS

capping, non-coding RNAs, polyadenylation, RNA decay, RNA export, RNA methylation, RNA virus, RNA virus-host interactions, splicing, translation, virus

1 | OVERVIEW OF RNA BIOLOGY AND RNA VIRUSES

Post-transcriptional processes play a major role in gene expression. No RNA transcript is synthesized in a “ready-to-use” fashion by a DNA-dependent RNA polymerase in the cell. All primary transcripts undergo some form of processing in their maturation. Messenger RNAs made by RNA polymerase II, for example, must be capped at their 5′ end, spliced to remove introns, and cleaved/polyadenylated at their 3′ ends to serve as effective mRNAs. Many transcripts also undergo RNA editing or base methylations to further fine tune their RNA sequence/base composition/structure. Furthermore, RNAs must be properly localized in the cell for effective gene expression. RNA degradation rates play a major role in regulating the levels of specific transcripts. Translation rates are also regulated. To add to this growing complexity, there is a large number of small and long non-coding RNAs in the cell that undoubtedly also influence aspects of gene expression in a very significant way. Thus to truly understand how gene expression is regulated, one needs to fully consider all aspects of a transcript's post-transcriptional fate.

Transcripts made by RNA viruses can be significantly impacted by these various aspects of RNA biology that are occurring in the cell. Understanding how viral RNAs interface with and/or avoid these cellular processes can shed considerable light on both virus biology as well as cell biology. Thus it is the goal of this article to provide an overview of how RNA viruses are influenced by RNA regulatory processes.

2 | RNA SPLICING AND RNA VIRUSES

Transcribed pre-mRNAs require at least three post-transcriptional modifications to become mature mRNA transcripts capable of being exported from the nucleus and translated into proteins in the cytoplasm. These post-transcriptional processing events include 5'-capping, splicing, and 3'-polyadenylation. Cellular pre-mRNAs typically contain multiple exons and introns. Splicing is a molecular process whereby introns are removed from the pre-mRNA, leaving the exons ligated together to form the mature mRNA transcript. To generate diversity in eukaryotes, various exons within the pre-mRNA can be spliced together in unique combinations, a process termed alternative splicing. Alternative splicing is a general phenomenon in eukaryotic genomes, and ~95% of genes possessing multiple exons in humans are alternatively spliced, creating numerous isoforms of a given protein (Pan, Shai, Lee, Frey, & Blencowe, 2008). Alternative splicing of pre-mRNA is an important regulatory pathway that contributes to the spatiotemporal control of gene expression and generates functional diversification of proteins (Lopez, 1998).

2.1 | Alternative RNA splicing and RNA viruses

Unlike most cellular pre-mRNAs which contain one or more introns, most transcripts generated by RNA viruses possess no introns. Influenza viruses and Borna disease virus are among the rare classes of RNA viruses that generate pre-mRNAs that undergo splicing (Fournier et al., 2014). RNA viruses that utilize splicing as a component of their strategy of gene expression all have a nuclear aspect to their life cycle as their transcripts must be present in this cellular compartment to usurp the cellular RNA splicing machinery (Chua, Schmid, Perez, Langlois, & Tenoever, 2013; Dubois, Terrier, & Rosa-Calatrava, 2014; Tsai et al., 2013). The genome of influenza A virus is comprised of eight single-stranded negative RNA segments that encode 10 main viral proteins and numerous other auxiliary proteins. The two smallest viral RNAs, M and NS, undergo splicing. The M segment can generate the unspliced M1 mRNA transcript and the spliced M2 mRNA transcript (Figure 1a). M1 encodes the M1 matrix protein and M2 an ion channel protein. Alternatively spliced transcripts of the M pre-mRNA encode a small polypeptide of unknown function (Shih, Suen, Chen, & Chang, 1998), and for some viral strains alternative splicing of M generates variant M42 of the M2 ion channel (Wise et al., 2012). Likewise, the NS segment can generate the unspliced NS1 mRNA transcript and the spliced NS2 mRNA. These transcripts encode two multifunctional proteins. NS1 encodes the non-structural NS1 protein, which acts (among other things) as an interferon antagonist, countering the cellular antiviral responses. NS2 encodes the NS2/NEP protein, which has dual roles both in viral genome replication and nuclear export of newly synthesized viral RNPs (Fournier et al., 2014). Alternative splicing of the NS RNA generates a transcript encoding a truncated

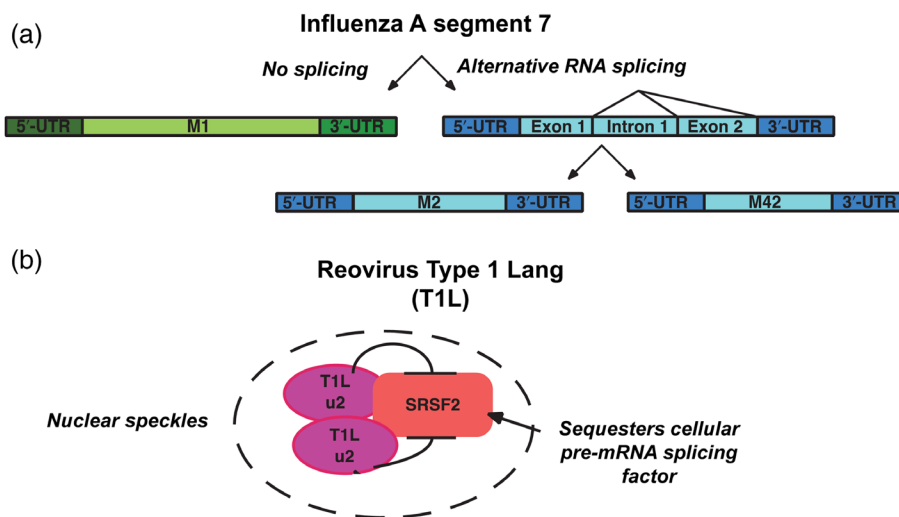


FIGURE 1 RNA viruses can use and/or usurp cellular RNA splicing during infection. Panel a. Two segments of influenza A viral RNA are processed by the cellular RNA splicing machinery to increase the coding capacity of viral genome. Illustrated here is segment 7 which can generate mRNAs that remain unspliced to provide a transcript to generate the viral M1 protein or can be alternatively spliced to yield several other products, including mRNAs to generate the M2 and M42 proteins as illustrated here. Panel b. While no transcripts of the cytoplasmic reoviruses are directly spliced by the cellular machinery, the reovirus T1L strain does generate the μ 2 protein which sequesters the alternative splicing factor SRSF2 in nuclear speckles and causes dysregulation of cellular mRNA splicing

version of NS1 termed NS3. This alternatively spliced transcript has been reported to exist for some viral strains (Selman, Dankar, Forbes, Jia, & Brown, 2012).

2.2 | The influence of cytoplasmic RNA viruses on nuclear RNA splicing

Mammalian reoviruses are double-stranded RNA (dsRNA) nonenveloped viruses that replicate in membrane-associated cytoplasmic viral factories (de Fernández et al., 2014). Reovirus strain Type 1 Lang (T1L) has been shown to repress interferon (IFN)- β signaling while Type 3 Dearing (T3D) does not (Zurney, Kobayashi, Holm, Dermody, & Sherry, 2009). The different influence of the two strains on IFN- β signaling is determined by the M1 gene encoding the reovirus μ 2 protein (Irvin et al., 2012). The μ 2 protein from the T3D strain contains a serine at position 208 while the T1L strain contains a proline at this position. A minor capsid protein, μ 2 protein is highly expressed in infected cells and has RNA binding (Wise et al., 2012) and NTPase activities (Kim, Parker, Murray, & Nibert, 2004; Kobayashi, Ooms, Chappell, & Dermody, 2009). It also determines virus strain-specific differences in the morphology of viral factories via its ability to bind and stabilize microtubules (Parker, Broering, Kim, Higgins, & Nibert, 2002). μ 2 localizes mainly to viral factories upon infection (Broering, Parker, Joyce, Kim, & Nibert, 2002), but it can also be observed diffusely throughout the cytoplasm and nucleus (Mbisa, Becker, Zou, Dermody, & Brown, 2000). Recently it has been shown that μ 2 from T1L and reovirus recombinants encoding the T1L μ 2 amino acid polymorphism form a complex with the pre-mRNA splicing factor SRSF2 in nuclear speckles, interchromatin domains that are highly enriched in splicing factors (Figure 1b) (Rivera-Serrano, Fritch, Scholl, & Sherry, 2017). T1L thus has demonstrated an ability to alter splicing of cellular transcripts. Depletion of SRSF2 also leads to enhanced reovirus replication and cytopathic effects, indicating that T1L μ 2 influences splicing of cellular mRNAs in a manner benefitting the virus. This suggests that antagonism of the splicing factor SRSF2 by a cytoplasmic RNA virus has global consequences within the cell.

It is highly possible that other cytoplasmic viruses may influence nuclear RNA splicing events. Alphaviruses, for example, sequester the cellular HuR protein and relocalize it the cytoplasm during infection (Barnhart, Moon, Emch, Wilusz, & Wilusz, 2013; Sokoloski et al., 2010). This results in a disruption of alternative splicing patterns that are normally regulated by the HuR protein (Sokoloski et al., 2010). Thus the impact of RNA viruses on cellular RNA splicing patterns is an interesting and likely highly fruitful area for future study.

3 | POLYADENYLATION AND RNA VIRUSES

Polyadenylation is a two-step process that occurs co-transcriptionally on all nonhistone mRNAs in the cell. First, the pre-mRNA undergoes endonucleolytic cleavage at a site downstream of an AAUAAA hexanucleotide (Shi & Manley, 2015). After cleavage, poly(A) polymerase (PAP) adds adenosine residues to the newly formed 3' terminus. This addition of a poly(A) tail is facilitated by poly(A) binding protein 2 (PABP2), which increases the affinity between PAP and the RNA, resulting in increased processivity in the enzymatic process (Eckmann, Rammelt, & Wahle, 2011). Global analyses of gene expression have documented the large extent of alternative polyadenylation and its potential role as a major regulator of gene expression (Tian & Manley, 2017). The poly(A) tail functions in RNA export, stability and translation initiation (Curinha, Oliveira Braz, Pereira-Castro, Cruz, & Moreira, 2014; Fuke & Ohno, 2008). Thus, many RNA viruses have evolved a strategy to put a poly(A) tail on the 3' end of their transcripts. Key questions surrounding polyadenylation of RNA viruses include: What is the mechanism of polyadenylation, particularly since many RNA viruses are cytoplasmic and cannot effectively usurp the standard nuclear cellular poly(A) machinery; and how do RNA viruses that do not polyadenylate their 3' ends compensate for the lack of a poly(A) tail?

3.1 | Generation of poly(a) tails on cytoplasmic viruses

Generally speaking, RNA viruses add a poly(A) tail to their transcripts using their own encoded RNA dependent RNA polymerase (RdRp) by one of two mechanisms. As seen in picornaviruses, viral poly(A) tails can be synthesized using a poly(U) stretch on the 5' end of the template strand (Figure 2a) (Kempf & Barton, 2015; Steil, Kempf, & Barton, 2010). Long poly(U) stretches can also be found at the ends of the template for the synthesis of plus strands in alphaviruses and coronaviruses as well. Alternatively, poly(A) tails can be made by the viral RdRp stuttering over a short U tract (Figure 2b). Good examples of this stuttering mechanism can be seen throughout the negative sense RNA viruses, including rhabdoviruses (Barr, Whelan, & Wertz, 2002), filoviruses (Volchkova, Vorac, Repiquet-Paire, Lawrence, & Volchkov, 2015), paramyxoviruses (Hausmann, Garcin, Delenda, & Kolakofsky, 1999), and orthomyxoviruses (Poon, Pritlove, Fodor, & Brownlee, 1999). Interestingly, there have been several reports that indicate the polyadenylation event in RNA viruses may be regulated. The usage of the RNA

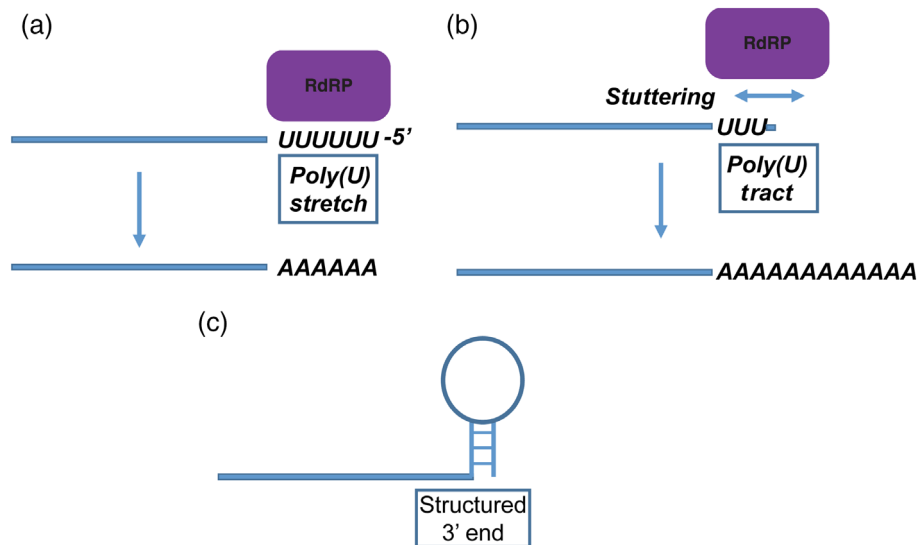


FIGURE 2 Three major approaches used by RNA viruses to generate the 3' ends of viral mRNAs. Panel a. Template-dependent poly(A) formation. Some viruses (e.g., picornaviruses) possess a poly(U) stretch at the 5' end of their negative strand RNA template that can be directly copied by the viral RdRP to generate a poly(A) tail on the viral mRNAs. Panel b. Reliance on a stuttering RdRP to generate a poly(A) tail. Some viruses (e.g., rhabdoviruses) contain short U-rich tracts near the 5' end of genes on the negative sense strand that serves a slippery site for the viral RdRP to stutter upon, thus generating a poly(A) tail on the positive-sense mRNA product. Panel c. Termination with a large structure at the 3' end precludes the need for a poly(A) tail. Finally, other viruses (e.g., flaviviruses) have a large hairpin structure at their 3' end which serves the purpose of a poly(A) tail to protect the RNAs from 3'-5' exonucleases as well as promote translation

editing site in the GP gene of Ebola viruses appears to be regulated by alternative polyadenylation (Volchkova et al., 2015). Mutational analyses suggest that there is a functional link between 5' capping and 3' polyadenylation by the vesicular stomatitis virus (VSV) L protein (Li, Rahmeh, Brusic, & Whelan, 2009). There is also variation in the size of poly(A) tails that could have biological relevance. Among the picornaviruses, encephalomyocarditis virus (EMCV) transcripts have a relatively short ~20 base poly(A) tail as opposed to polioviruses/rhinoviruses which have longer (~60 base) poly(A) tails (Kempf & Barton, 2015). Coronavirus poly(A) tails have also been demonstrated to show small variations in length throughout infection (Wu, Ke, Liao, & Chang, 2013). These differences in the size of the poly(A) tail may reflect differences in viral mRNA translatability or relative stability. Finally, several RNA viruses have been shown to be able to use cellular poly(A) polymerase activities to repair/generate poly(A) tails (Liu et al., 2008).

3.2 | Nonpolyadenylated cytoplasmic RNA viruses—alternative strategies for 3' end formation

RNA viruses that do not generate polyadenylated transcripts still have to ensure that their RNAs are protected from exonucleolytic digestion and function effectively in translation. Host cell histone mRNAs are naturally nonpolyadenylated, thus this is clearly achievable (Romeo & Schümperli, 2016). RNA viruses with nonpolyadenylated 3' ends (e.g., flaviviruses, bunyaviruses, etc.) all contain large 3' terminal structures that likely serve as effective structural impediments to 3'-5' exonucleases (Figure 2c) (Ibrahim, Wilusz, & Wilusz, 2008). Thus these terminal structures make a significant contribution to viral RNA stability—but how do they also compensate for the lack of poly(A) binding protein on their 3' ends? In order to mimic the role of the poly(A) tail in translation initiation, the reovirus NSP3 protein has a higher affinity for eIFG4 than cellular PABP2 (Gratia et al., 2015). Transcripts from another family of nonpolyadenylated RNA virus, flaviviruses, contain 3' UTR elements that coordinate with the 5' sequences to mediate efficient translation as well as bind PABP2 in a poly(A)-independent fashion (Chiu, Kinney, & Dreher, 2005; Polacek, Friebe, & Harries, 2009).

3.3 | The influence of RNA viruses on cellular Polyadenylation and 3' end processing

Finally, RNA viruses can also have a dramatic impact on cellular polyadenylation. Influenza virus, for example, inhibits pre-mRNA cleavage and uses its NS1 protein to target the cellular PABP2 factor (Chen, Li, & Krug, 1999; Shimizu, Iguchi, Gomyou, & Ono, 1998). Alphavirus RNAs use a high affinity binding site in their 3' UTR to bind and cause the relocalization

of the predominantly nuclear HuR protein (Barnhart et al., 2013; Dickson et al., 2012). This results in the dysregulation of polyadenylation at sites normally regulated by HuR. Finally, it has been recently demonstrated that VSV infection causes dramatic changes in alternative polyadenylation site usage on cellular mRNAs (Jia et al., 2017). This may have implications regarding cellular innate immune responses to the virus.

4 | CAPPING AND RNA VIRUSES

Given the critical nature of mRNA capping for translation and stability, many RNA viruses have also adapted this RNA modification to enhance their gene expression. Viral RNA caps must be as “host-like” as possible to avoid degradation of the viral transcripts as well as avert viral clearance from host cells by the immune system due to signaling of the innate immune system by improperly capped transcripts. Interestingly, the routes by which the capping of viral transcripts are achieved are rather dissimilar across all RNA viruses. For example, some viruses have encoded specific enzymes that mimic host capping mechanisms (Ogino & Ogino, 2017), while others have evolved ways to steal caps from cellular mRNAs (Hopkins et al., 2013). It is important to understand the mechanisms/dynamics associated with viral RNA capping as it is an attractive target for development of novel antiviral therapeutics.

Capping of cellular mRNAs occurs co-transcriptionally on short nascent RNAs in the nucleus, although there have been reports of cytoplasmic recapping of RNAs (Kiss et al., 2016; Moteki & Price, 2002). Transcripts made by RNA Polymerase II are initially generated with a 5' triphosphate (pppRNA). An RNA triphosphatase activity in the complex of capping enzymes then cleaves the γ -phosphate on the nascent RNA transcript, leaving a diphosphate intermediate (ppRNA). Following the cleavage, RNA guanylyltransferase (GTase) activity transfers a GMP to the ppRNA to form a G cap. The cap is matured by methylation on the seventh position, forming the m7G “cap 0” structure (Moteki & Price, 2002) and the transcript is subsequently methylated at the 2' O position of the ribose to form a cap 1 structure.

4.1 | Capping enzymes of RNA viruses

While most capping enzymes encoded by RNA viruses follow the overall enzymatic blueprint set out by the cellular capping machinery, there is one interesting nuance in some viral enzymes in terms of the source of the phosphates in the final 7mGpppN cap structure. VSV encodes for an enzymatic domain in the multifunctional L protein known as GDP polyribonucleotidyltransferase (PRNTase) which is responsible for generating a fully methylated cap on viral mRNA. In short, PRNTase forms a covalent bond with the viral mRNA via a monophosphate (p) on the 5' end (as opposed to a ppN 5' end like the cellular enzyme). This PRNTase-pRNA intermediate is transferred to GDP (rather than GMP like cellular transcripts). The GDP for capping is generated by the L proteins GTPase activity on GTP. The resulting GpppRNA is further modified, becoming first an m7G cap 0, followed by 2'-O methylation of the first base (cap 1). Through the use of GDP analogues, the PRNTase domain was shown to recognize the C2-amino group and either the 2' or 3' hydroxyl group of GDP to facilitate this novel mechanism of cap formation (Li, Wang, & Whelan, 2006; Ogino & Ogino, 2017; Ogino, Yadav, & Banerjee, 2010).

In addition to the enzymatic pathway difference noted above, viral capping enzymes in general are structurally different enough from their host cell counterparts that they are an attractive candidate for antiviral development (Kiss et al., 2016). One example of this is with the flavivirus NS5 capping enzyme (Bullard et al., 2015; El Sahili & Lescar, 2017; Han & Lee, 2017). Small molecule inhibitors targeting multiple areas of the NS5 methyltransferase (MTase), including the SAM/SAH binding pocket, cap binding pocket and allosteric regulatory domains have been described [(Benmansour et al., 2017; Brecher et al., 2015; Coutard et al., 2014; Idrus, Tambunan, & Zubaidi, 2012; Lim et al., 2011; Milani et al., 2009); reviewed in (Decroly & Canard, 2017)]. Inhibition of the ZIKV MTase has also been proposed as an antiviral strategy for that emerging pathogen (Coutard et al., 2017). Interestingly, inhibiting viral MTases has shown favorable results in attenuating multiple viruses that have the potential to be used as vaccines (Li et al., 2013; Zhang, Wei, Zhang, Cai, & Niewiesk, 2014).

4.2 | Viral cap snatching

Rather than encoding for enzymes that build caps for their RNA, some viruses steal a cap from host transcripts in a process known as cap snatching. This strategy is used by several families of RNA viruses that contain segmented genomes, including the *Bunyaviridae* (e.g., Hantavirus), *Arenaviridae* (e.g., Lassa fever virus) and the *Orthomyxoviridae* (e.g., influenza viruses) (Reguera et al., 2016; Rosenthal et al., 2017; Sikora, Rocheleau, Brown, & Pelchat, 2017). The virus encodes for a protein(s) that has an endonuclease domain, such as the L protein of *Bunyaviridae* or the heterotrimer of PA, PB1, and PB2 of influenza

virus (with the endonuclease activity in the PA subunit). This viral endoribonuclease cuts close to the 5' cap of host RNA transcripts, most commonly occurring ~15 nucleotides downstream of the cap, but the cut site can vary by 10 to 20 nucleotides. This capped RNA fragment then acts as a primer for transcription (Cheng & Mir, 2012; Dias et al., 2009; Reguera, Weber, & Cusack, 2010).

As opposed to most RNA viruses, influenza A virus (IAV) replicates in the nucleus. Interestingly, high throughput sequencing of the 5' end of IAV transcripts has revealed that IAV preferentially steals caps from noncoding RNAs, specifically small nuclear RNAs (snRNA) and the promoter associated capped small RNAs (csRNA) (Gu et al., 2015). In addition to preferentially cap snatching from snRNAs, there was a bias towards stealing caps from the splicing-associated U1 and U2 snRNAs (Gu et al., 2015). It will be interesting to see in the future how modulation of the levels of these noncoding RNAs plays a role in IAV infection.

Bunyaviruses replicate in the cytoplasm and must actively compete with host mRNA decapping machinery to find and steal 5' caps from cellular mRNAs (Cheng & Mir, 2012; Reguera et al., 2010). These viruses use the viral nucleocapsid (N) protein to find and direct capped host transcripts into cellular P bodies until used by the viral RNA dependent RNA polymerase (RdRp). The preferential mRNAs that are targeted by bunyaviruses appear to be cell cycle-associated mRNAs that have been marked for destruction by the host decapping enzyme Dcp2. Knock down or over-expression of the cellular Dcp2 enzyme leads to either increased or decreased bunyavirus replication respectively (Hopkins et al., 2013). Phosphorylation of Dcp2 can also upregulate enzymatic activity and further inhibit bunyavirus replication. These studies clearly indicate that capping/decapping is an important front in the molecular arms race for defense against certain viral infections.

4.3 | Host recognition of viral caps/5' ends

Nuances in the 5' ends/caps of viral RNAs are also used by cellular innate immune mechanisms to target and eliminate virally-derived nucleic acid in the cell. While the presence of a 5' cap effectively masks an RNA from recognition as foreign, viral capping may not be 100% efficient and viral transcripts often have structured ends which can be detected by the cellular nucleic acid surveillance machinery. One of the best characterized of these pathways involves RIG-I, a protein which uses its C terminal domain to recognize viral RNA via either the presence of 5'-triphosphate on nascent transcripts or blunt-ended dsRNA (Domain et al., 2010; Wang et al., 2010). Upon recognition of viral 5' ends with “noncellular” structural configurations, RIG-I becomes activated via a conformational change and signals the cell to begin interferon production. A good example of how the terminal structural features of viral RNAs can influence RIG-I can be found in influenza viruses where the 5' and 3' ends of individual transcripts form a partial duplex (known as a panhandle) with each other. RIG-I has a very high affinity for this structural feature and thus the panhandle effectively stimulates interferon production even though influenza virus does not have a 5'-PPP attached to the blunt-ended dsRNA (Lee, Kim, et al., 2016).

It was previously believed that to protect themselves from recognition by RIG-I, RNA viruses could merely attach a m7G “cap 0” structure to their RNAs. However, recent research has illustrated that this cap 0 structure alone does not prevent recognition by the cellular innate immune system. Surprisingly, RNAs with a cap 0 structure have a similar ability to activate RIG-I as does an RNA containing a 5' triphosphate. However, RNAs that contain a cap 1 structure, one in which the first base of the transcript also contains a 2'-O ribose methylation, do not activate RIG-I (Devarkar et al., 2016). The presence or absence of this 2'-O-methylation cap 1 on transcripts is also monitored by the MDA5 protein which also triggers an interferon response—primarily mediated by IFIT proteins, when this RNA modification is missing (Daffis et al., 2010; Lee, Kim, et al., 2016; Schlee et al., 2009; Züst et al., 2011). MDA5 activation involves a conformational change and induction of tetramer formation, similar to RIG-I. To avoid detection by this cellular surveillance mechanisms, viruses encode specific 2'-O-methyltransferases (MTases) that are conserved in virus families, such as flaviviruses and recently roniviruses (Egloff, Benarroch, Selisko, Romette, & Canard, 2002; Zeng et al., 2016). Further research into the structural features of these MTases may reveal characteristics about the enzyme domains allowing for novel antiviral therapies that can target multiple viruses in a single family (Coutard et al., 2017).

5 | RNA METHYLATION AND RNA VIRUSES

N6-methyladenosine (m6A) methylation is one of the most abundant modifications that occurs to RNA in the cell (Fu, Dominianni, Rechavi, & He, 2014). m6A methylation has effects on both structural and functional roles of RNA. The methylation of RNA is a dynamic process that consists of proteins known as “writers,” “erasers,” and “readers.” Writers are responsible for methylation, erasers are responsible for de-methylation, and readers serve as effector proteins in recognizing the m6A

methylation for biological function. Mapping of the transcriptome for m6A methylation has demonstrated that the modification often occurs at preferential locations that can also be well-conserved. Thus the importance of this RNA modification for the regulation of cellular gene expression is becoming clearer (Dominissini et al., 2012; Schwartz et al., 2012). Interestingly, m6A methylation has recently been shown to occur on viral transcripts and has the potential to induce antiviral or proviral effects on viral replication. Furthermore, the studies of m6A writer, eraser, and reader proteins on cytoplasmic RNA viruses have helped to confirm the presence of these proteins in the cytoplasm (Gokhale et al., 2016), which was suggested by previous work (Chen et al., 2015; Lin, Choe, Du, Triboulet, & Gregory, 2016).

5.1 | Antiviral effects of m6A methylation

Knock down of the m6A writer proteins (methyltransferases) METTL3 and METTL 14 increases the replication of hepatitis C virus (HCV) (Gokhale et al., 2016). On the other hand, when the eraser protein (de-methyltransferase) FTO was knocked down, viral replication decreased. Knock down of m6A reader proteins, the YTH domain family proteins (YTHDF), increased viral replication late in infection. The YTHDF proteins were also shown to have competitive, antagonistic effects against the HCV core protein, which is responsible for viral packaging (Gokhale et al., 2016). Similar antiviral effects of m6A modification on viral RNAs were recently duplicated in another member of the *Flaviviridae*, Zika virus (ZIKV) (Lichinchi et al., 2016). These results strongly suggest that tagging of viral RNAs with an m6A modification may be part of the cellular arsenal of strategies to minimize the impact of viral infection.

5.2 | Proviral effects of m6A methylation

The role of m6A modifications in RNA virus infections, however, does not appear to be straightforward. Mapping of m6A modification sites across HCV and ZIKV genomes showed highly conserved targeted sequences (Gokhale et al., 2016; Lichinchi et al., 2016). Given the capability of RNA viruses to evolve quickly under selective pressures, it seems unusual that they would maintain these m6A methylation targets if the modification solely led to antiviral effects. RNA viruses may maintain these regions to prevent activation of the immune system via toll-like receptors and RIG-I (Durbin, Wang, Marcotrigiano, & Gehrke, 2016; Karikó, Buckstein, Ni, & Weissman, 2005). It should also be noted that host cells appear to be able to sense and react to viral infection by changing m6A methylation status of cellular transcripts (Lichinchi et al., 2016). In the case of HCV, m6A methylations may actually increase viral fitness by slowing replication and facilitating the characteristic slow, persistent infection strategy favored by the virus (Gokhale et al., 2016). Finally, the patterns of m6A vary between different ZIKV lineages (Lichinchi et al., 2016). As different lineages provide varying levels of pathogenicity (Weaver et al., 2016), regulation of m6A could theoretically be contributing to these differences. Clearly, further research into the role of m6A in cellular and viral gene regulation is needed to define this interesting new aspect of host-virus RNA interplay.

6 | RNA EDITING ON RNA VIRUS TRANSCRIPTS

Viral genomes display some of the highest genomic mutational frequencies known. Mutational patterns in viral genomes do not occur randomly, rather certain nucleotide mutations always occur more frequently than others, a phenomenon known as directional mutational pressure. The source of such unequal viral mutation rates is largely due to error-prone polymerases. RNA editing can be simply defined as the addition or substitution of RNA bases that were not originally encoded by the genome. RNA editing in paramyxoviruses, for example, occurs co-transcriptionally when the RNA-dependent-RNA polymerase (RdRp) interacts with a *cis*-acting sequence element (3'-UAAUUUUUCCCC) in the genome that causes a stuttering of the polymerase (Figure 3a). This "stuttering" mechanism is responsible for editing the RNA via the addition of up to 6 G's at a single RNA editing site (Iseni et al., 2002). Interestingly, RNA editing could also be done via cellular enzymes in a completely post-transcriptional process.

One cellular means of carrying out RNA editing is via the double-stranded RNA-specific adenosine deaminase (ADAR) enzymes (Figure 3b) (George, John, & Samuel, 2014). Humans possess three major ADAR isoforms: ADAR1-p150, ADAR1-p110, and ADAR2. ADAR enzymes facilitate adenosine deamination to inosine, which is biologically relevant since inosine behaves like guanosine and can base-pair with cysteine. During viral replication, the cysteine-inosine base-pairing will lead to guanosine being incorporated in place of inosine, ultimately leading to adenosine to guanosine transition mutations. The expression level of ADAR often increases as the cell detects increasing levels of foreign RNA. Interestingly, several viruses of the family *Flaviviridae*, including Hepatitis C virus, Bovine viral diarrhea virus, and Dengue virus, can stimulate

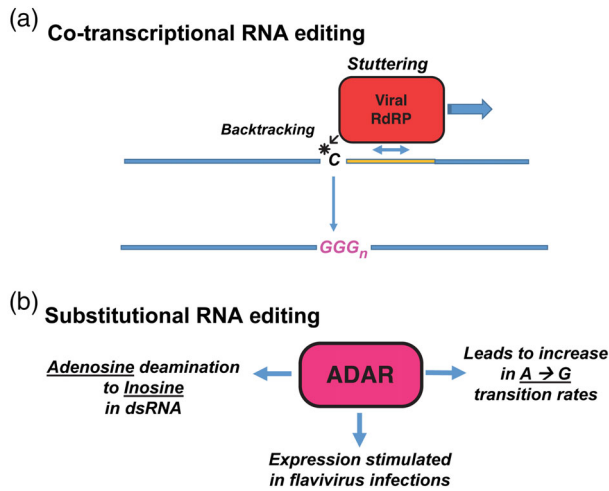


FIGURE 3 RNA editing of RNA virus transcripts. Panel a. Select mRNAs generated by paramyxoviruses and filoviruses can contain an additional one to ~8 G residues due to slippage/stuttering of the viral RdRp in certain regions during transcription. Panel b. The cell possesses inducible RNA deaminases such as ADAR that can deaminate adenosine residues to inosines. These enzymes can increase the mutation rate of RNA viruses and thus can affect viral fitness and evolution

ADAR expression, while many other virus families do not (Khrustalev, Khrustaleva, Sharma, & Giri, 2017). The consequence of ADAR editing of viral RNA is an increase in A to G transition rates (Liu et al., 2015). Studies on human metapneumovirus suggest that high levels of viral RNA editing may lead to the production of increased levels of defective interfering particles (van den Hoogen et al., 2014). The increased proportion of G's that results from ADAR editing might also have a positive effect on virus biology, enabling, for example, viral RNAs to form stronger or novel secondary structures given the higher stability of G-C base pairing. Finally, RNA editing strategies like ADAR enzymes do not act uniformly along the length of viral RNA genome, thus directional mutational pressure and subsequently genomic mutational rates are not constant. An emerging hypothesis is that stalling of either the viral RdRp or cellular ribosomes on viral RNAs is associated with mutational pressure, perhaps by enabling RNA editing enzymes like ADAR to act on viral RNAs (Khrustalev et al., 2017).

7 | RNA NUCLEAR EXPORT AND RNA VIRUSES

Export of RNA from the nucleus is a key step in mRNA synthesis. In order to be exported, mRNA generally must be fully processed and packaged it into a messenger ribonucleoprotein (mRNPs) (Bindereif & Green, 1986). The majority of mRNA export is mediated by the nonkaryopherin heterodimer Nxf1 and Nxt1, although some are exported by the karyopherin chromosome region maintenance 1 (CRM1) (Aibara, Katahira, Valkov, & Stewart, 2015; Brownawell & Macara, 2002; Delaleau & Borden, 2015). The mRNA is trafficked through the nuclear pore complexes (NPCs) to the cytoplasm (Allen, Cronshaw, Bagley, & Goldberg, 2000). For the small number of RNA viruses that transcribe in the nucleus, viral mRNA export is best characterized for influenza virus.

Influenza virus transcripts use both the Nxf1-Nxt1 heterodimer and CRM1 pathways to move from the nucleus into the cytoplasm. Interestingly, the virus appears to have multiple, perhaps even redundant strategies to ensure the effective export of its transcripts to the cytoplasm. Influenza virus manipulates the host Nxf1 factor to transport a defined subset of its mRNAs to the cytoplasm (Larsen et al., 2014). NP, NA and HA mRNAs use Nxf1, but PA, PB1 and PB2 mRNAs do not. Late in infection, influenza virus activates caspase activity which causes enlargement of nuclear pores. This permits the passive transport of the viral ribonucleoprotein (vRNP) via the CRM1 export pathway (Mühlbauer et al., 2015). The influenza NS2 protein also has been reported to interact with CRM1, perhaps further enhancing nuclear export of viral mRNAs (Elton et al., 2001; Wang, Zhou, & Du, 2014). In addition, the viral MI protein has also been implicated in nuclear export of vRNPs through CRM1 (Brunotte et al., 2014). Recently, the MI and PB2 viral proteins have been implicated in the subnuclear movement of viral mRNAs, perhaps as a precursor to effective viral RNA export (Ando et al., 2016). Nucleolin also influences the subnuclear trafficking of vRNPs (Terrier et al., 2016). Influenza virus also recruits/hijacks the DExD/H-box RNA helicase DDX19, that remodel viral mRNA and perhaps also contribute to efficient export (Diot et al., 2016; Fuller-Pace, 2006).

7.1 | Disruption of nuclear RNA export by cytoplasmic RNA viruses

Cytoplasmic RNA viruses can also take steps to block the export of cellular mRNAs from the nucleus. The nonstructural protein 5 (NS5) of dengue virus and other flaviviruses is shuttled between the cytoplasm and nucleus where it may influence CRM-mediated nuclear export (Rawlinson, Pryor, Wright, & Jans, 2009). Porcine reproductive and respiratory syndrome virus

(PRRSV) uses its nsp1 β protein to induce accumulation of host mRNAs in the nucleus during infection (Han, Ke, Zhang, & Yoo, 2017). Expression of the NS_S gene of the bunyavirus Rift Valley Fever Virus also induces nuclear accumulation of cellular mRNAs (Copeland, Van Deusen, & Schmaljohn, 2015). 2A protease encoded by enteroviruses can cleave components of the nuclear pore complex, altering RNA export kinetics in infected cells (Park, Schweers, & Gustin, 2015).

Given the importance of viral RNP nuclear export, this process has recently received attention as a possible target for antiviral therapies (Kakisaka et al., 2015). While targeting host proteins is in some ways attractive since there is less probability of viral resistance, this therapeutic avenue should be pursued with caution due to potential consequences on normal host cell functions.

8 | TRANSLATION AND RNA VIRUSES

Translation initiation in eukaryotic cells is a highly regulated process (Aitken & Lorsch, 2012). It involves 12 or more initiation factor proteins to direct the ribosomal subunits and Met-tRNA_i^{Met} over the AUG start codon. Key initial steps include the formation of a preinitiation complex (PIC) combined with the formation of the ternary complex (TC) (eIF2, GTP, and Met-tRNA_i^{Met}). The PIC then interacts with the 40S ribosomal subunit and scans the mRNA for the AUG start codon. Once the AUG is found, several initiation factors are released, allowing for the binding of the 60S ribosomal subunit, forming the 80S complex that initiates translation. Not surprisingly, RNA viruses have evolved ways to manipulate this process to favor translation of their mRNAs.

8.1 | Viral IRES elements

Some viral genomes encode an alternative translation initiation mechanism known as internal ribosome entry sites (IRES) that bypass the need for 5' cap recognition by translation factors. These elements were found in the 1980's, first in picornaviruses followed by Hepatitis C Virus (HCV) (Pelletier & Sonenberg, 1988; Pestova, Shatsky, Fletcher, Jackson, & Hellen, 1998). IRES elements are located in the 5' UTRs of transcripts and form extensive secondary and tertiary structures that recruit the host translational machinery. IRES elements can be classified into three types based upon their secondary structure and initiation factors that they selectively recruit (Pacheco, Serrano, & Fernandez, 2008).

We'll focus on the type III IRES located in the HCV positive strand RNA to illustrate the state of the art in our mechanistic understanding of how these elements function (Jaafar, Oguro, Nakamura, & Kieft, 2016). As outlined in Figure 4, the HCV IRES recruits an intermediate of the PIC that includes eIF1, eIF1A, and eIF3 and forms in the absence of the ternary complex (TC). Binding to the IRES displaces eIF1 from the PIC and leads to one of two pathways to initiate translation depending on eIF2 availability in the cell. If eIF2 is in an active state, the TC is transferred to the IRES-PIC complex, causing the IRES to undergo a conformational change. eIF2 would then hydrolyze GTP and leave, followed by binding of eIF5B to the complex. In an eIF2 inactive state, it is proposed that Met-tRNA_i^{Met} can bind either directly without the need of a delivery factor and then is stabilized in the complex by eIF1A and eIF5B, or is delivered to the complex by either eIF1A or eIF5B. After Met-tRNA_i^{Met} binding occurs in either of the two pathways, eIF1A and eIF5B proceed to then assist in the final codon-anti-codon verification and ribosomal subunit joining steps (Jaafar et al., 2016).

IRES elements and associated structures have the capability of being targeted by antivirals. A recent study illustrated the potential of siRNA as an antiviral therapeutic against HCV. The capacity of the HCV IRES to form secondary and tertiary structures can naturally preclude siRNAs from binding to many target sequences. Using an siRNA tiling technique, a handful of siRNAs were found to be effective in disrupting the HCV IRES and HCV replication (Moon, Lee, Kim, Cho, & Lee, 2016).

8.2 | NonIRES-mediated cap independent mechanisms of viral translation

Curiously, some viruses are translated in a cap-independent manner that does not involve an IRES element. Notably, members of the norovirus family have a cap-like protein known as VPg that interacts with the HEAT-1 domain of the initiation factor eIF4G via its C-terminal region. VPg, however, is also still capable of binding to eIF4E and it is proposed that this interaction potentially regulates host response to the viral infection (Chung et al., 2014; Leen, Sorgeloos, Correia, & Chaudhry, 2016). Norovirus-encoded protease targets several translation factors for decay, thus tipping the balance of translation initiation to favor viral mRNAs (Emmott, Sorgeloos, Caddy, & Heesom, 2017). Because of the conserved nature of using the HEAT-1

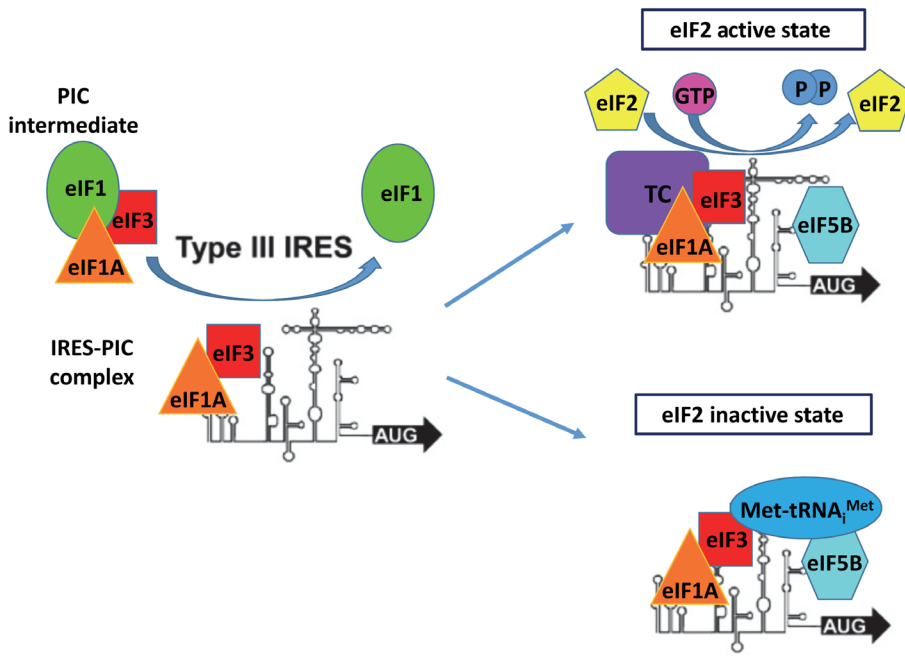


FIGURE 4 An overview of HCV IRES-dependent translation. The HCV IRES is classified as “Type III” and recruits a preinitiation complex (PIC) that includes eIF1, eIF1A, and eIF3. Binding to the HCV IRES causes displacement of eIF1. Translation initiation then proceeds by one of two pathways depending on the state (active or inactive) of eIF2 in the cell. For more information, see the accompanying text in section 8.1

domain for binding by VPg in the norovirus family (Leen et al., 2016), small molecules could be selected to disrupt the VPg-eIF4G complex as possible antivirals.

8.3 | Virus manipulation of stress granules

In an effort to reduce viral translation, the cell induces an innate immunity pathway triggered by dsRNA leading to the formation of stress granules (SG). SG are membrane-less aggregates of stalled translation preinitiation complexes that form in the cytoplasm (Protter & Parker, 2016). To maintain the highest fidelity of viral translation, viruses have developed methods to interfere with this pathway. Some viruses, such as Ebola virus, have encoded proteins (VP35) to interfere and inhibit the function of G3BP1, a host protein that helps drive SG formation (Le Sage et al., 2017). Other viruses, such as Semliki Forest virus, sequester G3BP1 via nsP3 to its replication complex, preventing SG formation and enhancing viral replication (Panas et al., 2012). Additional viruses, such as flaviviruses, have been shown to modulate the translational landscape of the cell and prevent SG formation even though the exact mechanism has yet to be revealed (Haneke, Lohmann, Bartenschlager, & Fackler, 2017). The commonality of SG disruption in RNA virus infections, as well as the plethora of mechanisms through which SG formation is modulated, indicate its strategic importance for maintaining efficient viral replication and translation. Interestingly, not all RNA viruses target SGs for disruption. Rabies virus does not have mechanisms to modulate SG assembly and possibly uses them to maintain a healthy equilibrium of mRNA/translation for viral replication (Blondel, Nikolic, & Civas, 2016).

8.4 | miRNA regulation of RNA virus translation

MicroRNAs (miRNAs) are 21–23 nucleotide long RNAs that have the capacity to control many cellular processes and are commonly produced in many eukaryotic organisms. The function of miRNAs relies on their ability to either degrade mRNA and/or inhibit translation. Interestingly, cellular miRNAs can sometimes effectively target viral RNA genomes. Thus several RNA viruses have evolved synonymous mutations (Enterovirus 71) (Zheng et al., 2013) or deletions (neurotropic flaviviruses) (Heiss, Maximova, Thach, Speicher, & Pletnev, 2012) to avoid recognition and repression of viral gene expression by host cell miRNA. In addition to blocking translation, miRNAs can at times also promote gene expression (Vasudevan, 2012). It has been shown that miR-122 is responsible for stabilization of HCV RNA as well as influencing the balance between how much RNA is translated and how much is involved in replication synthesis (Masaki et al., 2015; Mengardi et al., 2017). MicroRNAs let-7 and miR-17 are also responsible for enhanced translation in bovine viral diarrhea virus (BVDV) (Scheel et al., 2016).

9 | RNA STABILITY/DEGRADATION AND RNA VIRUSES

RNA degradation is a tightly controlled and regulated process that, in coordination with transcription, is essential for maintaining the homeostasis of cellular gene expression (Schoenberg & Maquat, 2012). Messenger RNA decay is largely initiated by removal of the poly(A) tail (deadenylation) followed by degradation of the body of the transcript by one of two exonucleolytic pathways. The 5' to 3' RNA degradation pathway is initiated via decapping proteins responsible for removing the 5' cap structure on mRNA transcripts (Hsu & Stevens, 1993). The RNA exosome is a cellular machine that is largely responsible for the 3' to 5' decay pathway (Chekanova et al., 2007). Distinct forms of the RNA exosome exist in the cytoplasm and nucleus, associating with specific protein cofactors unique to each subcellular compartment (Staals et al., 2010). Numerous RNA binding proteins have been implicated in regulating RNA decay, including HuR (Grammatikakis, Abdelmohsen, & Gorospe, 2017), TTP (Wells, Perera, & Blackshear, 2017), AUF1 (White, Matsangos, & Wilson, 2017), and others. These proteins can target mRNAs to multiple degradation pathways. Finally, inducible ribonucleases and the RNAi machinery all feed their products into cellular RNA decay pathways (Drappier & Michiels, 2015).

RNA decay plays a major role in controlling both the quantity and quality of RNA transcripts in the cytoplasm. Thus it is not surprising that RNA viruses have developed ways to successfully interface with the cellular RNA decay machinery (Figure 5). The goal of this section is to provide an overview of some this interplay.

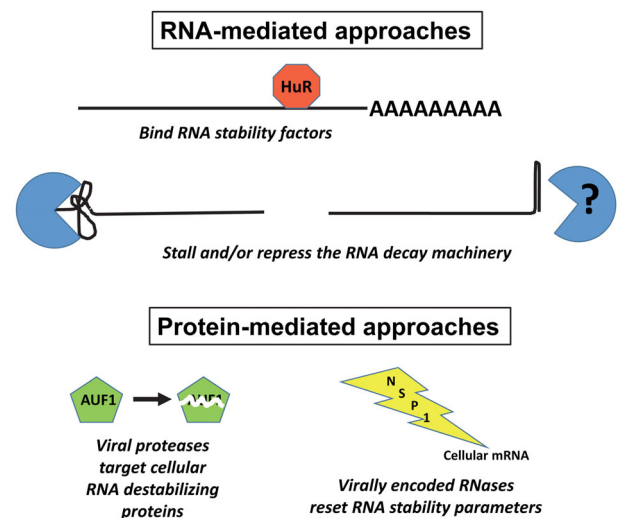
Many viruses target the cellular regulators of RNA decay to successfully navigate around the cellular RNA decay machinery. All alphaviruses contain a high affinity binding site for the cellular HuR protein in their 3' UTR (Barnhart et al., 2013; Sokoloski et al., 2010). HuR binds and stabilizes viral transcripts—and the sequestration of a large amount of HuR by alphavirus RNAs causes a dysregulation of mRNAs normally influenced by binding of this RNA stability factor (Sokoloski et al., 2010). Polioviruses target and cleave the cellular RNA regulatory factor AUF-1 (Ullmer & Semler, 2016).

RNA viruses must also successfully evade specialized RNA quality control pathways. UPF1, Smg5 and Smg 7, key components of the nonsense-mediated RNA decay pathway, are clear restriction factors for numerous RNA viruses (Balistreri, Bognanni, & Mühlemann, 2017). Finally, bringing in their own exonuclease is another strategy employed by RNA viruses. Coronaviruses encode the nsp1 protein and a highly active endoribonuclease (Endo U; nsp15) that essentially reprograms RNA decay in the cytoplasm of infected cells to allow for downregulation of cellular defense mechanisms and effective viral replication (Kindler et al., 2017). This might simply shut down quality control pathways in the cell due to the plethora of new decay products that overwhelms the machinery.

9.1 | Direct targeting of the major RNA decay machinery by RNA viruses

Several RNA viruses are capable of stalling and sequestering the 5' to 3' exonuclease XRN1. Flaviviruses are single-stranded positive-sense RNA viruses that are responsible for a number of serious human diseases (Moon et al., 2012; Moon et al., 2015). A unique feature of all flaviviruses studied thus far is the formation of small subgenomic flavivirus RNA (sF₂RNA) representing the 3' UTR of the viral genomic RNA by stalling of the cytoplasmic 5'-3' exoribonuclease XRN1 (Pijlman et al., 2008). XRN1 becomes stalled and ultimately sequestered on flavivirus UTRs when it encounters a knot-like three helix

FIGURE 5 Major approaches used by RNA viruses to confound the cellular RNA decay machinery. RNA viruses effectively subvert the cellular RNA decay machinery by a variety of mechanisms. Top Panel: RNA-mediated mechanisms include the use of high affinity binding sites to sequester and usurp cellular RNA stabilizing factors (e.g., alphaviruses) as well as the use of complex RNA structures to prevent binding or repress RNA exonucleases (e.g., flaviviruses). Bottom Panel: RNA viruses (e.g., polioviruses) can also encode proteases that can selectively cleave cellular factors involved in RNA decay. Alternatively RNA viruses like coronaviruses encode nonstructural proteins that facilitate massive degradation of cellular RNA that somehow gives viral RNAs a competitive advantage



junction structure (Akiyama et al., 2016; Chapman et al., 2014; Chapman, Moon, Wilusz, & Kieft, 2014; Funk et al., 2010; Silva, Pereira, Dalebout, Spaan, & Bredenbeek, 2010). Stalling of XRN1 on viral UTRs leads to the functional repression of the enzyme—which surprisingly also downregulates decapping and deadenylation activities in infected cells (Moon et al., 2012; Moon, Blackinton, et al., 2015). This results in the up-regulation of numerous short-lived cellular mRNAs which may have a significant impact on viral cytopathology and pathogenesis (Moon et al., 2012; Moon, Blackinton, et al., 2015). Other virus families may also target XRN1 and other components of the 5'-3' pathway to confound the RNA decay machinery. XRN1 and DCPI1a/2, for example, are degraded during a poliovirus infection (Dougherty, White, & Lloyd, 2011).

A variety of cellular factors, including ZAP (Guo, Carroll, Macdonald, Goff, & Gao, 2004), may recruit the exosome to RNA viruses. The Trf–Air–Mtr4 polyadenylation (TRAMP) complex consists of a set of cofactors that aid in degrading targeted RNA substrates via the nuclear RNA exosome (LaCava et al., 2005). It was recently shown that the TRAMP complex participates in viral defense within the cell's cytoplasm (Molleston et al., 2016). The underlying mechanisms of TRAMP complex component export to the cytoplasm and subsequent targeting of viral 3' UTRs have yet to be elucidated.

10 | CYTOPLASMIC RNA GRANULES AND RNA VIRUS INFECTION

Under conditions of stress host cells will increase the formation two types of cytoplasmic granules: processing bodies (P bodies) and stress granules. These are membrane-less, dynamic structures that may be the result of liquid phase transitions induced by disordered regions of RNA binding proteins (Protter & Parker, 2016). P bodies are cytoplasm foci that accumulate translationally repressed mRNPs along with multiple proteins/enzymes involved in mRNA decay (Emara & Brinton, 2007; Shah, Zhang, Ramachandran, & Herman, 2013; Ward et al., 2011; Yang, Yu, Gulick, Bloch, & Bloch, 2006). While they may not necessarily be sites of active RNA decay (Hu, Sweet, Chamnongpol, Baker, & Coller, 2009), P bodies are associated with a role in mRNA surveillance and decay (Lavut & Raveh, 2012). Stress granules are most likely involved in storing mRNAs that were stalled in translation initiation and it is suggested that this aids in protection of genomic information during stress (Frydryskova et al., 2016; Shah et al., 2013; Ward et al., 2011). As outlined below, viral infections can significantly influence P body and stress granule formation.

The role of cellular P body formation and function has been explored for a number of RNA viruses. In general, it appears that RNA viruses may initially promote/induce the formation of P bodies to benefit viral gene expression and then repress P body formation at later times post infection either directly or indirectly. This duality of effects of viral infections on P bodies can make elucidating their overall impact on virus biology difficult. P body formation is significantly affected in HCV infection, however the impact of P bodies on HCV replication efficiency is not clear (Pérez-Vilaró, Scheller, Saludes, & Díez, 2012). Depletion of select P-body proteins decreases HCV gene expression (Pager, Schütz, Abraham, Luo, & Sarnow, 2013), and West Nile virus (WNV) and dengue virus (DENV) flaviviruses have been shown to enhance their replication by interacting with P bodies (Chahar, Chen, & Manjunath, 2013; Ward et al., 2011). However, late in infection, flaviviruses appear to inhibit P body assembly (Emara & Brinton, 2007). Influenza A virus NS1 protein interacts with RAP55-containing P bodies, restricting the accumulation of NP proteins to P bodies and promotes viral replication (Mok et al., 2012; Yang et al., 2006). Polioviruses use proteases and other virally-encoded proteins to disperse P bodies late in infection (Dougherty, Tsai, & Lloyd, 2015). P bodies are also dispersed during infection by the dsRNA-containing rotaviruses (Bhowmick, Mukherjee, Patra, & Chawla-Sarkar, 2015).

Two major stress granule proteins, TIA-1 and G3BP1, are major targets of RNA viruses during infection. West Nile and dengue viral RNAs sequester TIA-1 and interfere with stress granule formation during infection (Mok et al., 2012). RNAs from another flavivirus, tick-borne encephalitis virus, also binds TIA-1 to regulate translation from viral RNAs with minimal effects on overall G3BP1-containing stress granule formation (Albornoz, Carletti, Corazza, & Marcello, 2014). Rabies virus infections induce stress granule formation near viral factories in Negri bodies which appears to have a weak antiviral effect as TIA-1 can block viral translation (Blondel et al., 2016). Overall, G3BP1-enriched stress granules are induced during some RNA viral infections with both positive and negative effects on viral replication (Albornoz et al., 2014; Amorim, Temzi, Griffin, & Moulard, 2017; Bhowmick et al., 2015; Chahar et al., 2013; Courtney, Scherbik, Stockman, & Brinton, 2012; Dougherty et al., 2015; Frydryskova et al., 2016; Hou et al., 2017; Hu et al., 2009; Kim et al., 2016; Lavut & Raveh, 2012; Mok et al., 2012; Nelson et al., 2016; Pager et al., 2013; Panas et al., 2012; Pérez-Vilaró et al., 2012; Rabouw et al., 2016; Sage et al., 2016; Scholte et al., 2015; Xia, Chen, Xu, et al., 2015; Zhou et al., 2017). Taken together these data show the need to effectively address the knowledge gap of the impact of stress granules on RNA virus infections.

11 | NON-CODING RNA REGULATION AND RNA VIRUSES

Non-coding RNAs (ncRNAs) are a large class of transcripts that are not used as templates for productive translation and represent the vast majority of RNAs in cells (Fortes & Morris, 2016). RNAs such as ribosomal RNAs (rRNA), transfer RNAs (tRNA), microRNAs (miRNA), small nuclear RNAs (snRNA), small nucleolar RNAs (snoRNA) and long ncRNA (lncRNA) are among the members of this large and diverse family of non-coding transcripts. They have a plethora of roles in cell biology, however much remains to be discovered about these transcripts, particularly in terms of lncRNA function. LncRNAs are classified as non-coding transcripts longer than 200 nucleotides and they often interact with proteins, DNA and/or other RNAs to aid in the regulation of gene expression (Fortes & Morris, 2016).

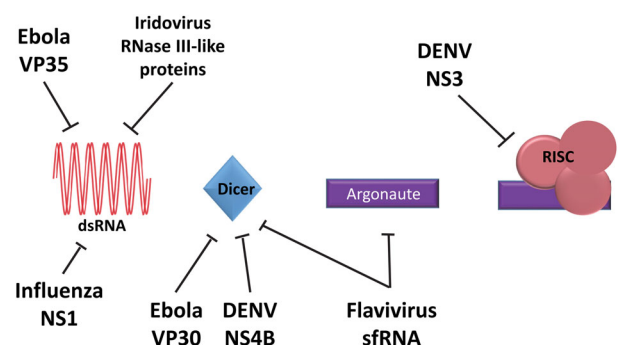
11.1 | RNA interference pathways and RNA viruses

Small RNAs such as miRNAs (~22 nucleotides) or PIWI-associated RNAs (piRNAs) (~24–30 bases) associate with proteins of the Argonaute family and play important roles in RNA silencing and post-transcriptional regulation (Ghosh, Mallick, & Chakrabarti, 2009). The ability of the RNA interference pathway, including the generation of small interfering (si)RNAs and microRNAs, to silence viral RNA is a major part of antiviral innate defense mechanisms in plants and insects (Blair & Olson, 2015; Szittyá & Burgyán, 2013). The relevance of RNAi to antiviral responses in mammals is unclear (Cullen, Cherry, & tenOever, 2013; Li et al., 2016). Many viruses generate suppressors of the cellular RNAi machinery which function through interactions with RNAi components or by sequestering viral double-stranded RNA (Figure 6) (Bivalkar-Mehla et al., 2011). Interestingly, flaviviruses produce subgenomic flavivirus (sf)RNAs that can interact with cellular RNAi machinery of mosquitoes (Goertz et al., 2016; Gokhale & Horner, 2017; Moon et al., 2015; Schnettler et al., 2012). The strategy of using non-coding RNAs to evade the RNAi response is not limited to flaviviruses. Semliki Forest virus appears to produce a viral RNA decoy to aid in evading the RNAi response (Siu et al., 2011). Viral proteins are also generated that interfere with the RNAi machinery. The NS4B and NS3 proteins of dengue virus interfere with RNAi pathways in insect cells (Kakumani et al., 2013; Kakumani et al., 2015). Several plant and animal viruses generate an RNase III-like enzyme that inhibits both the siRNA and miRNA pathways (Weinheimer et al., 2015). The NS1 protein of influenza virus can suppress the cellular RNAi machinery (Li, Basavappa, et al., 2016). Additionally, Ebola virus proteins VP30 and VP35 interfere with RNAi pathways (Fabozzi, Nabel, Dolan, & Sullivan, 2011; Pleet, DeMarino, Lepene, Aman, & Kashanchi, 2017). Clearly the interaction of RNA viruses with the cellular RNAi pathways represents an excellent example of the molecular arms race that has evolved between host and pathogen.

11.2 | Long non-coding RNAs and RNA viruses

Our understanding of the generation and role of small and long-non-coding RNAs in RNA virus infections is currently rapidly developing (Li, Weng, Shih, & Brewer, 2016). Changes in the expression of cellular lncRNAs, for example, have been associated with flavivirus infections. DENV infection of mosquitoes causes an increase in cellular lncRNA production, some of which are associated with suppression of viral replication (Etebari, Asad, Zhang, & Asgari, 2016). Interestingly, RNA viruses can also manipulate the expression of cellular lncRNAs to favor their replication. For example, HCV infections induce production of eosinophil granule ontogeny transcript (EGOT) and other cellular lncRNAs that function as negative regulators of the interferon response (Carnero et al., 2016; Nishitsuji et al., 2016). In addition, influenza A virus can also induce the host VIN lncRNA that enhances viral replication (Winterling et al., 2014). Infection of mice with a variety of RNA viruses,

FIGURE 6 Examples of mechanisms RNA viruses use to suppress RNA interference. RNA viruses target various components of the host cell RNAi machinery as part of the molecular arms race to effectively establish infection. Double-stranded RNA (dsRNA) is sequestered (e.g., by Ebola VP35 or Influenza A virus NS1) or degraded (e.g., by virally-encoded RNase III-like enzymes) to inhibit the RNAi machinery from detecting this key substrate. Cellular enzymes like dicer or argonaute are bound and repressed by viral proteins (e.g., Ebola VP30 or Dengue virus NS4B) or viral RNAs (e.g., flavivirus sfRNA). Finally, DENV NS3 protein interacts with hsc70, impacting the assembly of the RISC effector complex



including Japanese encephalitis virus, rabies virus and SARS-CoV also results in induction of lncRNA, although the impact of these lncRNA on the viral infection remains unexplored (Peng et al., 2010). Clearly the interface of RNA viruses with cellular lncRNAs is a fertile area for future research.

RNA viruses also generate their own lncRNAs that assist in replication and virus-host interactions. Antigenome replicative intermediates that are generated as part of the replication pathway of RNA viruses are an excellent example of a non-coding transcript that plays a pivotal role in viral infections. As discussed above, arthropod-borne flaviviruses generate a ~400–500 base non-coding RNA from their 3' untranslated regions that plays a role in RNAi suppression as well as modulating the cellular RNA decay machinery (Filomatori, Carballada, Aguirre, Pallarés, et al., 2017; Roby, Pijlman, Wilusz, & Khromykh, 2014). Future endeavors to further determine the role of non-coding RNAs in virus biology should be a very fruitful area of investigation.

12 | RNA “SPONGING” AND RNA VIRUSES

Noncoding RNAs, such as long non-coding RNA (lncRNA), have shown the ability to regulate the availability/function of gene products through sequestration of other RNA or proteins in a process known as “sponging.” In eukaryotic cells, a class of competing endogenous RNAs (ceRNA) have been characterized as being able to interfere with miRNA regulation (Lin et al., 2017; Zhang, Guo, Ma, Ma, & Xue, 2017). Additionally, cases of host RNA sequestering proteins have been illustrated that can lead to disease, such as the case of myotonic dystrophy, where excessive CUG triplet repeats in the 3' UTR of the DMPK mRNA bind and sequester muscleblind like 1 (MBNL1) (Lee, Li, et al., 2013). Given the nature of viruses to adapt and evolve to mimic host-like pathways, they likely use protein or RNA sponging as a major strategy in host-virus interactions. Below are a few examples of where this is occurring.

12.1 | RNA–RNA sponging

The sponging of cellular miRNAs has been well-described for the transcripts of several DNA viruses (Cazalla, Yario, & Steitz, 2010; Liu et al., 2013). To date, the best example of miRNA sponging in RNA virus biology is associated with HCV where an interaction with cellular miR-122 is essential for genome stability (Figure 7a) (Wilson & Huys, 2013). However, the sequestration of miR-122 by the large number of HCV plus stranded RNAs has impact on the expression of cellular genes that are normally regulated by miR-122. In some cases, these alterations in gene expression can promote viral replication. An up-regulation of STAT3 in HCV infection, for example, represses an interferon (IFN) type I response (Xiong et al., 2015). The global effects of de-repression of miR-122 target genes in HCV have been documented via high-throughput sequencing and cross-linking immunoprecipitation (HITS-CLIP) procedures (Luna et al., 2015). Other viruses besides HCV also disrupt cellular miRNA regulatory pathways. The sequestration of miR-17 by the 3' UTR of numerous pestivirus RNAs induced a global

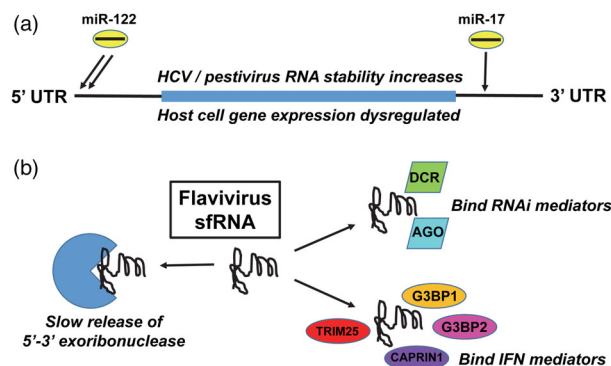


FIGURE 7 Sponging of cellular factors by RNA virus transcripts. Panel a: Sponging of cellular miRNAs by members of the *Flaviviridae*. HCV uses sequences in its 5' UTR to sponge miR-122 while bovine viral diarrhea virus and other pestiviruses use 3' UTR sequences to sponge miR-17. In both cases, miR sponging increases viral RNA stability while dysregulating aspects of cellular gene expression normally influenced by the small RNAs. Panel b: Insect-borne flaviviruses contain a knot-like structure in the 3' UTR region of their mRNA that generates a stable RNA decay intermediate called sfRNA. The sfRNA not only effectively represses the exoribonuclease that generates it due to slow release of the stalled enzyme, but also sponges key proteins involved in the RNA interference and interferon pathways, resulting in the repression of these key aspects of cellular anti-viral defense

de-repression of miR-17 gene targets (Figure 7a) (Scheel et al., 2016). It will be interesting to examine the capacity of other viral genomic RNAs to act as sponges for select cellular miRNAs or other transcripts.

12.2 | RNA-protein sponging

Viral RNAs can also effectively sponge host proteins, leading to benefits for viral replication and possibly contributing to host cell pathogenesis. Subgenomic flavivirus RNA (sflRNA) is a ~400–500 base noncoding RNA derived from the 3' UTR region of insect-borne flaviviruses, such as Dengue Virus (DENV) and Zika Virus (ZIKV) (Roby et al., 2014). The production of sflRNA is not due to an internal promoter, but rather the RNA represents a stable decay intermediate that is generated by the cellular 5'-3' exoribonuclease XRN1 stalling at a knot-like three-helix junction RNA structure (Chapman, Costantino, et al., 2014). DENV sflRNAs have been shown to interact with almost 200 cellular proteins (Figure 7b)—including three that are essential for production of interferon stimulated proteins (G3BP1, G3BP2, and CAPRIN1) (Garneau et al., 2008) as well as one that blocks RIG-I activation (TRIM25) (Manokaran et al., 2016). ZIKV sflRNA was also shown to interfere with RIG-I mediated type I interferon responses, perhaps through a similar mechanism (Donald et al., 2016). Flavivirus sflRNAs have also been shown to interact with Dicer and Argonaute proteins and interfere with RNAi responses (Moon, Dodd, et al., 2015; Schnettler et al., 2012).

Another conserved example of protein sponging by a group of RNA viruses can be found in the alphaviruses of the *Togaviridae* family. The 3' UTR region of Sindbis virus (SINV) contains a U-rich region that interacts with the cellular protein HuR with high affinity (Barnhart et al., 2013). The binding of HuR protein by viral RNA leads to the stabilization of SINV RNAs by preventing deadenylation and decay (Garneau et al., 2008; Sokoloski et al., 2010). The sequestration or sponging of large amounts of HuR protein by alphavirus 3' UTRs causes the protein to relocalize from the nucleus to the cytoplasm in infected cells (Sokoloski et al., 2010). Besides adding stability to the viral RNA, sponging of HuR leads to disruption of post-transcription regulation of host genes via destabilization of transcripts and dysregulation of splicing and polyadenylation (Barnhart et al., 2013; Dickson et al., 2012). The dysregulation of host homeostasis perhaps creates a new cellular landscape driven by the virus to favor its replication and contributes to virus-induced cytopathology.

12.3 | Antiviral treatments involving RNA sponging

There is growing evidence that the sponging strategy can be engineered to be used against viruses to develop novel antiviral techniques. HCV replication, for example, can be inhibited by RNA aptamers that bind to HCV NS5B RNA replicase protein with high affinity. This aptamer can also decrease HCV replication in vivo without off-target effects or activation of the innate immune system (Lee, Lee, et al., 2013). Finally, efforts are also well under way to develop antiviral RNA sponges. A miR-122 antagonist effectively inhibits HCV replication, and is currently being evaluated as a novel antiviral therapeutic (Elmén, Lindow, et al., 2008; Lindow, Silahtaroglu, et al., 2008; Ottosen et al., 2015).

13 | SUMMARY/FUTURE DIRECTIONS

The interplay between RNA viruses and post-transcriptional processes is clearly extensive and highly relevant to virus biology and pathogenesis. Three fundamental themes emerge from the examples we have outlined above. First, the interplay of viruses and cellular RNA biology is clearly part of the molecular arms race between the host cell and the invading pathogen. By impacting fundamental aspects of gene expression through altered post-transcriptional pathways, invading RNA viruses significantly decrease the ability of the cell to alter its gene expression to respond to the pathogen. RNA viruses can target a wide range of aspects of post-transcriptional including nuclear pre-mRNA processing, modulation of cellular capping or subcellular localization of cellular mRNAs, and/or usurping translation and mRNA decay to favor virus gene expression. Cellular efforts to disfavor the use of these post-transcriptional pathways by viruses—many of which undoubtedly are yet to be discovered—are part of the innate defense mechanism of the cell to infection.

The second theme is the simple but fundamental notion that RNA viruses must rely on host cell functions to further their own replication. The relatively small size of the RNA virus genome precludes encoding many proteins that are needed to regulate viral gene expression, including the post-transcriptional processing and fate of viral transcripts. As we increase our appreciation of the mechanistic depth of impact of RNA biology on virus replication, we gain new insights into not only virus biology but also potential avenues for the targeting of antiviral therapeutics.

The final theme is one of the excitement that lies in future discoveries in this area. There is, for example, significant insights to be gained into novel aspects of cellular RNA biology through the study of RNA virus-cell interactions. Over their evolution, viruses and viral RNAs have experimented and developed highly effective ways to usurp and/or avoid aspects of cellular post-transcriptional regulation. Understanding this interplay from a detailed mechanistic perspective is thus likely to be very valuable for the field. In addition, challenging questions in RNA biology, such as what are the components and structure of a bona fide messenger RNP, may be best answered by studying abundant viral mRNAs and then extending these discoveries to cellular transcripts. Thus the interdisciplinary collaboration between cell biologists and virologists should continue to prove very fruitful in the near future.

ACKNOWLEDGMENTS

RNA/virology research in the Wilusz laboratory is funded by awards GM114247, AI123136, and AI139497 from the National Institutes of Health to J.W. S.T.C received fellowship support from the National Science Foundation (NRT Grant No. 1450032). M.R.M. received support as a National Science Foundation Graduate Fellow (Grant No. 5325000).

CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

RELATED WIREs ARTICLES

[Unconventional RNA-binding proteins step into the virus-host battlefield](#)
[Viral internal ribosomal entry sites: Four classes for one goal](#)
[The evolving world of small RNAs from RNA viruses](#)

ORCID

Jeffrey Wilusz  <https://orcid.org/0000-0001-8535-3435>

FURTHER READING

Bidet, K., Dadlani, D., & Garcia-Blanco, M. A. (2014). G3BP1, G3BP2 and CAPRIN1 are required for translation of interferon stimulated mRNAs and are targeted by a Dengue virus non-coding RNA. *PLoS Pathogens*, *10*(7), e1004242. <https://doi.org/10.1371/journal.ppat.1004242>
Issur, M., Picard-Jean, F., & Bisailon, M. (2011). The RNA capping machinery as an anti-infective target. *WIREs RNA*, *2*(2), 184–192.

REFERENCES

- Aibara, S., Katahira, J., Valkov, E., & Stewart, M. (2015). The principal mRNA nuclear export factor NXF1:NXT1 forms a symmetric binding platform that facilitates export of retroviral CTE-RNA. *Nucleic Acids Research*, *43*(3), 1883–1893.
- Aitken, C. E., & Lorsch, J. R. (2012). A mechanistic overview of translation initiation in eukaryotes. *Nature Structural Molecular Biology*, *19*(6), 568–576.
- Akiyama, B. M., Laurence, H. M., Massey, A. R., Costantino, D. A., Xie, X., Yang, Y., ... Kieft, J. S. (2016). Zika virus produces noncoding RNAs using a multi-pseudoknot structure that confounds a cellular exonuclease. *Science*, *354*(6316), 1148–1152.
- Albornoz, A., Carletti, T., Corazza, G., & Marcello, A. (2014). The stress granule component TIA-1 binds tick-borne encephalitis virus RNA and is recruited to perinuclear sites of viral replication to inhibit viral translation. *Journal of Virology*, *88*(12), 6611–6622.
- Allen, T., Cronshaw, J., Bagley, S., & Goldberg, M. (2000). The nuclear pore complex: Mediator of translocation between nucleus and cytoplasm. *Journal of Cell Science*, *113*, 1651–1659.
- Amorim, R., Temzi, A., Griffin, B. D., & Moulund, A. J. (2017). Zika virus inhibits eIF2 α -dependent stress granule assembly. *PLoS Neglected Tropical Diseases*, *11*(7), e0005775. <https://doi.org/10.1371/journal.pntd.0005775>
- Ando, T., Yamyoshi, S., Tomita, Y., Watanabe, S., Watanabe, T., & Kawaoka, Y. (2016). The host protein CLUH participates in the subnuclear transport of influenza virus ribonucleoprotein complexes. *Nature Microbiology*, *1*(8), 16062. <https://doi.org/10.1038/nmicrobiol.2016.62>
- Balistreri, G., Bognanni, C., & Mühlemann, O. (2017). Viruse escape and manipulation of cellular nonsense-mediated mRNA decay. *Viruses*, *9*(1), E24. <https://doi.org/10.3390/v9010024>

- Barnhart, M. D., Moon, S. L., Emch, A. W., Wilusz, C. J., & Wilusz, J. (2013). Changes in cellular mRNA stability, splicing, and polyadenylation through HuR protein sequestration by a cytoplasmic RNA virus. *Cell Reports*, 5(4), 909–917.
- Barr, J. N., Whelan, S. P., & Wertz, G. W. (2002). Transcriptional control of the RNA-dependent RNA polymerase of vesicular stomatitis virus. *Biochimica et Biophysica Acta*, 1577(2), 337–353.
- Benmansour, F., Trist, I., Coutard, B., Decroly, E., Querat, G., Brancale, A., & Barral, K. (2017). Discovery of novel dengue virus NS5 methyltransferase non-nucleoside inhibitors by fragment-based drug design. *European Journal of Medicinal Chemistry*, 125, 865–880.
- Bhowmick, R., Mukherjee, A., Patra, U., & Chawla-Sarkar, M. (2015). Rotavirus disrupts cytoplasmic P bodies during infection. *Virus Research*, 210, 344–354.
- Bindereif, A., & Green, M. R. (1986). Ribonucleoprotein complex formation during pre-mRNA splicing in vitro. *Molecular and Cellular Biology*, 6(7), 2582–2592.
- Bivalkar-Mehla, S., Vakharia, J., Mehla, R., Abreha, M., Kanwar, J. R., Tikoo, A., & Chauhan, A. (2011). Viral RNA silencing suppressors (RSS): Novel strategy of viruses to ablate the host RNA interference (RNAi) defense system. *Virus Research*, 155(1), 1–9.
- Blair, C. D., & Olson, K. E. (2015). The role of RNA interference (RNAi) in arbovirus-vector interactions. *Viruses*, 7(2), 820–843.
- Blondel, D., Nikolic, J., & Civas, A. (2016). Rabies virus infection induces the formation of stress granules closely connected to the viral factories. *PLoS Pathogens*, 12(10), e1005942. <https://doi.org/10.1371/journal.ppat.1005942>
- Brecher, M., Chen, H., Liu, B., Banavali, N. K., Jones, S. A., Zhang, J., ... Li, H. (2015). Novel broad spectrum inhibitors targeting the flavivirus methyltransferase. *PLoS One*, 10(6), e0130062. <https://doi.org/10.1371/journal.pone.0130062>
- Broering, T. J., Parker, J. S. L., Joyce, P. L., Kim, J., & Nibert, M. L. (2002). Mammalian reovirus nonstructural protein microNS forms large inclusions and colocalizes with reovirus microtubule-associated protein micro2 in transfected cells. *Journal of Virology*, 76(16), 8285–8297.
- Brownawell, A. M., & Macara, I. G. (2002). Exportin-5, a novel karyopherin, mediates nuclear export of double-stranded RNA binding proteins. *Journal of Cell Biology*, 156(1), 53–64.
- Brunotte, L., Flies, J., Bolte, H., Reuther, P., Vreede, F., & Schwemmler, M. (2014). The nuclear export protein of H5N1 influenza A viruses recruits Matrix 1 (M1) protein to the viral ribonucleoprotein to mediate nuclear export. *The Journal of Biological Chemistry*, 289(29), 20067–20077.
- Bullard, K. M., Gullberg, R. C., Soltani, E., Steel, J. J., Geiss, B. J., & Keenan, S. M. (2015). Murine efficacy and pharmacokinetic evaluation of the flaviviral NS5 capping enzyme 2-thioxothiazolidin-4-one inhibitor BG-323. *PLoS One*, 10(6), e0130083. <https://doi.org/10.1371/journal.pone.0130083>
- Carnero, E., Barriocanal, M., Prior, C., Unfried, P., Segura, V., Guruceaga, E., ... Fortes, P. (2016). Long noncoding RNA EGOT negatively affects the antiviral response and favors HCV replication. *EMBO Reports*, 17(7), 1013–1028.
- Cazalla, D., Yario, T., & Steitz, J. (2010). Down-regulation of a host microRNA by Herpesvirus saimiri noncoding RNA. *Science*, 328(6), 1563–1566.
- Chahar, H. S., Chen, S., & Manjunath, N. (2013). P-body components LSM1, GW182, DDX3, DDX6 and XRN1 are recruited to WNV replication sites and positively regulate viral replication. *Virology*, 436(1), 1–7.
- Chapman, E. G., Costantino, D. A., Rabe, J. L., Moon, S. L., Wilusz, J., Nix, J. C., & Kieft, J. S. (2014). The structural basis of pathogenic subgenomic flavivirus RNA (sfRNA) production. *Science*, 344(4), 307–310.
- Chapman, E. G., Moon, S. L., Wilusz, J., & Kieft, J. S. (2014). RNA structures that resist degradation by Xrn1 produce a pathogenic Dengue virus RNA. *eLife*, 3, e01892. <https://doi.org/10.7554/eLife.01892>
- Chekanova, J. A., Gregory, B. D., Reverdatto, S. V., Chen, H., Kumar, R., Hooker, T., ... Belostotsky, D. A. (2007). Genome-wide high-resolution mapping of exosome substrates reveals hidden features in the Arabidopsis transcriptome. *Cell*, 131(7), 1340–1353.
- Chen, T., Hao, Y., Zhang, Y., Li, M., Wang, M., Han, W., ... Zhou, Q. (2015). m6A RNA methylation is regulated by microRNAs and promotes reprogramming to pluripotency. *Cell Stem Cell*, 16(3), 289–301.
- Chen, Z., Li, Y., & Krug, R. M. (1999). Influenza A virus NS1 protein targets poly(A)-binding protein II of the cellular 3'-end processing machinery. *The EMBO Journal*, 18(8), 2273–2283.
- Cheng, E., & Mir, M. A. (2012). Signatures of host mRNA 5' terminus for efficient hantavirus cap snatching. *Journal of Virology*, 86(18), 10173–10185.
- Chiu, W. W., Kinney, R. M., & Dreher, T. W. (2005). Control of translation by the 5'- and 3'-terminal regions of the dengue virus genome. *Journal of Virology*, 79(13), 8303–8315.
- Chua, M. A., Schmid, S., Perez, J. T., Langlois, R. A., & Tenoever, B. R. (2013). Influenza A virus utilizes suboptimal splicing to coordinate the timing of infection. *Cell Reports*, 3(1), 23–29.
- Chung, L., Bailey, D., Leen, E. N., Emmott, E. P., Chaudhry, Y., Roberts, L. O., ... Goodfellow, I. G. (2014). Norovirus translation requires an interaction between the C terminus of the genome-linked viral protein VPg and eukaryotic translation initiation factor 4G. *The Journal of Biological Chemistry*, 289(31), 21738–21750.
- Copeland, A. M., Van Deusen, N. M., & Schmaljohn, C. S. (2015). Rift Valley fever virus NSS gene expression correlates with a defect in nuclear mRNA export. *Virology*, 486, 88–93.
- Courtney, S. C., Scherbik, S. V., Stockman, B. M., & Brinton, M. A. (2012). West Nile virus infections suppress early viral RNA synthesis and avoid inducing the cell stress granule response. *Journal of Virology*, 86(7), 3647–3657.
- Coutard, B., Barral, K., Lichière, J., Selisko, B., Martin, B., Aoudi, W., ... Decroly, E. (2017). Zika virus Methyltransferase: Structure and functions for drug design perspectives. *Journal of Virology*, 91(5), e02202-16. <https://doi.org/10.1128/JVI.02202-16>
- Coutard, B., Decroly, E., Li, C., Sharff, A., Lescar, J., Bricogne, G., & Barral, K. (2014). Assessment of Dengue virus helicase and methyltransferase as targets for fragment-based drug discovery. *Antiviral Research*, 106, 61–70.

- Cullen, B. R., Cherry, S., & tenOever, B. R. (2013). Is RNA interference a physiologically relevant innate antiviral immune response in mammals? *Cell Host & Microbe*, *14*(4), 374–378.
- Curinha, A., Oliveira Braz, S., Pereira-Castro, I., Cruz, A., & Moreira, A. (2014). Implications of polyadenylation in health and disease. *Nucleus*, *5*(6), 508–519.
- Daffis, S., Szretter, K. J., Schriewer, J., Li, J., Youn, S., Errett, J., ... Diamond, M. S. (2010). 2'-O methylation of the viral mRNA cap evades host restriction by IFIT family members. *Nature*, *468*, 452–456.
- de Fernández Castro, I., Zamora, P. F., Ooms, L., Fernández, J. J., Lai, C. M.-H., Mainou, B. A., ... Risco, C. (2014). Reovirus forms neo-organelles for progeny particle assembly within reorganized cell membranes. *mBio*, *5*(1), e00931–13. <https://doi.org/10.1128/mBio.00931-13>
- Decroly, E., & Canard, B. (2017). Biochemical principles and inhibitors to interfere with viral capping pathways. *Current Opinion in Virology*, *24*, 87–96.
- Delaleau, M., & Borden, K. L. B. (2015). Multiple export mechanisms for mRNAs. *Cell*, *4*(3), 452–473.
- Devarkar, S. C., Wang, C., Miller, M. T., Ramanathan, A., Jiang, F., & Khan, A. G. (2016). Structural basis for m7G recognition and 2'-O-methyl discrimination in capped RNAs by the innate immune receptor RIG-I. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(3), 596–601.
- Dias, A., Bouvier, D., Crépin, T., McCarthy, A. A., Hart, D. J., Baudin, F., ... Ruigrok, R. W. H. (2009). The cap-snatching endonuclease of influenza virus polymerase resides in the PA subunit. *Nature*, *458*(7240), 914–918.
- Dickson, A. M., Anderson, J. R., Barnhart, M. D., Sokoloski, K. J., Oko, L., Opyrchal, M., ... Wilusz, J. (2012). Dephosphorylation of HuR protein during alphavirus infection is associated with HuR relocalization to the cytoplasm. *The Journal of Biological Chemistry*, *287*(43), 36229–36238.
- Diot, C., Fournier, G., Dos Santos, M., Magnus, J., Komarova, A., van der Werf S., Munier S., Naffakh N. (2016) Influenza A virus polymerase recruits the RNA helicase DDX19 to promote the nuclear export of viral mRNAs. *Scientific Reports*, *6*, 33763. <http://doi.org/10.1038/srep33763>
- Domain, R. C., Lu, C., Xu, H., Brooks, M. T., Hou, T. Y., Hu, F., ... Li, P. (2010). The structural basis of 5' triphosphate double-stranded RNA recognition by RIG-I C terminal domain. *Structure/Folding and Design*, *18*(8), 1032–1043.
- Dominiisni, D., Moshitch-Moshkovitz, S., Schwartz, S., Salmon-Divon, M., Ungar, L., Osenberg, S., ... Rechavi, G. (2012). Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq. *Nature*, *485*(7397), 201–206.
- Donald, C. L., Brennan, B., Cumberworth, S. L., Rezelj, V., Clark, J., Cordeiro, M. T., ... Kohl, A. (2016). Full genome sequence and sRNA interferon antagonist activity of Zika virus from Recife, Brazil. *PLoS Neglected Tropical Diseases*, *10*(10), e0005048. <https://doi.org/10.1371/journal.pntd.0005048>
- Dougherty, J. D., Tsai, W. C., & Lloyd, R. E. (2015). Multiple poliovirus proteins repress cytoplasmic RNA granules. *Viruses*, *7*(12), 6127–6140.
- Dougherty, J. D., White, J. P., & Lloyd, R. E. (2011). Poliovirus-mediated disruption of cytoplasmic processing bodies. *Journal of Virology*, *85*(1), 64–75.
- Drappier, M., & Michiels, T. (2015). Inhibition of the OAS/RNase L pathway by viruses. *Current Opinion in Virology*, *15*, 19–26.
- Dubois, J., Terrier, O., & Rosa-Calatrava, M. (2014). Influenza viruses and mRNA splicing: doing more with less. *mBio*, *5*(3), e00070–e00014. <https://doi.org/10.1128/mBio.00070-14>
- Durbin, A. F., Wang, C., Marcotrigiano, J., & Gehrke, L. (2016). RNAs containing modified nucleotides fail to trigger RIG-I conformational changes for innate immune signaling. *mBio*, *7*(5), 1–11.
- Eckmann, C. R., Rammelt, C., & Wahle, E. (2011). Control of poly(A) tail length. *WIREs RNA*, *2*(3), 348–361.
- Egloff, M., Benarroch, D., Selisko, B., Romette, J., & Canard, B. (2002). An RNA cap (nucleoside-2'-O-) -methyltransferase in the flavivirus RNA polymerase NS5: Crystal structure and functional characterization. *The EMBO Journal*, *21*(11), 2757–2768.
- Elmén, J., Lindow, M., Schütz, S., Lawrence, M., Petri, A., Obad, S., ... Kauppinen, S. (2008). LNA-mediated microRNA silencing in non-human primates. *Nature*, *452*(4), 1–5.
- El Sahili, A., & Lescar, J. (2017). Dengue virus non-structural protein 5. *Viruses*, *9*(4), E91. <https://doi.org/10.3390/v9040091>
- Elton, D., Simpson-Holley, M., Archer, K., Medcalf, L., Hallam, R., McCauley, J., & Digard, P. (2001). Interaction of the influenza virus nucleoprotein with the cellular CRM-1 mediated nuclear export pathway. *Journal of Virology*, *75*(1), 408–419.
- Emara, M., & Brinton, M. (2007). Interaction of TIA-1/TIAR with West Nile and dengue virus products in infected cells interferes with stress granule formation and processing body assembly. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(21), 9041–8046.
- Emmott, E., Sorgeloos, F., Caddy, S. L., & Heesom, K. (2017). Norovirus-mediated modification of the translational landscape via virus and host-induced cleavage of translation initiation factors. *Molecular and Cellular Proteomics*, *16*(4 suppl 1), S215–S229. <https://doi.org/10.1074/mcp.M116.062448>
- Etebari, K., Asad, S., Zhang, G., & Asgari, S. (2016). Identification of *Aedes aegypti* long intergenic non-coding RNAs and their association with *Wolbachia* and Dengue virus infection. *PLoS Neglected Tropical Diseases*, *10*(10), e0005069. <https://doi.org/10.1371/journal.pntd.0005069>
- Fabozzi, G., Nabel, C. S., Dolan, M. A., & Sullivan, N. J. (2011). Ebola virus proteins suppress the effects of small interfering RNA by direct interaction with the mammalian RNA interference pathway. *Journal of Virology*, *85*(6), 2512–2523.
- Filomatori, C. V., Carballeda, J. M., Villordo, S. M., Aguirre, S., Pallarés, H. M., Maestre, A. M., ... Gamarnik, A. V. (2017). Dengue virus genomic variation associated with mosquito adaptation defines the pattern of viral non-coding RNAs and fitness in human cells. *PLoS Pathogens*, *13*(3), e1006265. <https://doi.org/10.1371/journal.ppat.1006265>
- Fortes, P., & Morris, K. (2016). Long noncoding RNAs in viral infections. *Virus Research*, *212*, 1–11.
- Fournier, G., Chiang, C., Munier, S., Tomoiu, A., Demeret, C., Vidalain, P.-O., ... Naffakh, N. (2014). Recruitment of RED-SMU1 complex by Influenza A Virus RNA polymerase to control Viral mRNA splicing. *PLoS Pathogens*, *10*(6), e1004164. <https://doi.org/10.1371/journal.ppat.1004164>

- Frydryskova, K., Masek, T., Borcin, K., Mrvova, S., Venturi, V., & Pospisek, M. (2016). Distinct recruitment of human eIF4E isoforms to processing bodies and stress granules. *BMC Molecular Biology*, *17*(1), 21. <https://doi.org/10.1186/s12867-016-0072-x>
- Fu, Y., Dominissini, D., Rechavi, G., & He, C. (2014). Gene expression regulation mediated through reversible m6A RNA methylation. *Nature Reviews Genetics*, *15*(5), 293–306.
- Fuke, H., & Ohno, M. (2008). Role of poly (A) tail as an identity element for mRNA nuclear export. *Nucleic Acids Research*, *36*(3), 1037–1049.
- Fuller-Pace, F. V. (2006). DExD/H box RNA helicases: Multifunctional proteins with important roles in transcriptional regulation. *Nucleic Acids Research*, *34*(15), 4206–4215.
- Funk, A., Truong, K., Nagasaki, T., Torres, S., Floden, N., Balmori Melian, E., ... Khromykh, A. A. (2010). RNA structures required for production of subgenomic flavivirus RNA. *Journal of Virology*, *84*(21), 11407–11417.
- Gameau, N. L., Sokolowski, K. J., Opyrchal, M., Neff, C. P., Wilusz, C. J., & Wilusz, J. (2008). The 3' untranslated region of Sindbis virus represses deadenylation of viral transcripts in mosquito and mammalian cells. *Journal of Virology*, *82*(2), 880–892.
- George, C. X., John, L., & Samuel, C. E. (2014). An RNA editor, adenosine deaminase acting on double-stranded RNA (ADAR1). *Journal of Interferon & Cytokine Research*, *34*(6), 437–446.
- Ghosh, Z., Mallick, B., & Chakrabarti, J. (2009). Cellular versus viral microRNAs in host–virus interaction. *Nucleic Acids Research*, *37*(4), 1035–1048.
- Goertz, G., Fros, J., Miesen, P., Vogels, C., van der Bent, M., Geertsema, C., ... Pijlman, G. P. (2016). Noncoding subgenomic flavivirus RNA is processed by the mosquito RNA interference machinery and determines West Nile virus transmission by *Culex pipiens* mosquitoes. *Journal of Virology*, *90*(22), 10145–10159.
- Gokhale, N. S., & Horner, S. M. (2017). Knotty Zika virus blocks exonuclease to produce subgenomic flaviviral RNAs. *Cell Host & Microbe*, *21*(1), 1–2.
- Gokhale, N. S., McIntyre, A. B., McFadden, M. J., Roder, A. E., Kennedy, E. M., Gandara, J. A., ... Horner, S. M. (2016). N6-Methyladenosine in Flaviviridae Viral RNA Genomes Regulates Infection. *Cell Host and Microbe*, *20*(5), 654–665.
- Grammatikakis, I., Abdelmohsen, K., & Gorospe, M. (2017). Posttranslational control of HuR function. *WIREs RNA*, *8*(1), e1372. <https://doi.org/10.1002/wrna.1372>
- Gratia, M., Sarot, E., Vende, P., Charpilienne, A., Baron, C. H., Duarte, M., ... Poncet, D. (2015). Rotavirus NSP3 is a translational surrogate of the poly(A) binding protein-poly(A) complex. *Journal of Virology*, *89*(17), 8773–8782.
- Gu, W., Gallagher, G. R., Dai, W., Liu, P., Li, R., Trombly, M. I., ... Finberg, R. W. (2015). Influenza A virus preferentially snatches noncoding RNA caps. *RNA*, *21*(12), 2067–2075.
- Guo, X., Carroll, J. W., Macdonald, M. R., Goff, S. P., & Gao, G. (2004). The zinc finger antiviral protein directly binds to specific viral mRNAs through the CCCCH zinc finger motifs. *Journal of Virology*, *78*(23), 12781–12787.
- Han, M., Ke, H., Zhang, Q., & Yoo, D. (2017). Nuclear imprisonment of host cellular mRNA by nsp1 β protein of porcine reproductive and respiratory syndrome virus. *Virology*, *505*, 42–55.
- Han, S. R., & Lee, S. (2017). Inhibition of Japanese encephalitis virus (JEV) replication by specific RNA aptamer against JEV methyltransferase. *Biochemical and Biophysical Research Communications*, *483*(1), 687–693.
- Haneke, K., Lohmann, V., Bartenschlager, R., & Fackler, O. T. (2017). Flavivirus infection uncouples translation suppression from cellular stress responses. *mBio*, *8*(1), e02150-16. <https://doi.org/10.1128/mBio.02150-16>
- Hausmann, S., Garcin, D., Delenda, C., & Kolakofsky, D. (1999). The versatility of paramyxovirus RNA polymerase stuttering. *Journal of Virology*, *73*(7), 5568–5576.
- Heiss, B. L., Maximova, O. A., Thach, D. C., Speicher, J. M., & Pletnev, A. G. (2012). MicroRNA targeting of neurotropic flavivirus: Effective control of virus escape and reversion to neurovirulent phenotype. *Journal of Virology*, *86*(10), 5647–5659.
- Hopkins, K. C., Mclane, L. M., Maqbool, T., Panda, D., Gordesky-Gold, B., & Cherry, S. (2013). A genome-wide RNAi screen reveals that mRNA decapping restricts bunyaviral replication by limiting the pools of Dcp2-accessible targets for cap-snatching. *Genes and Development*, *27*(13), 1511–1525.
- Hou, S., Kumar, A., Xu, Z., Airo, A. M., Stryapunina, I., Wong, C. P., ... Hobman, T. C. (2017). Zika virus hijacks stress granule proteins and modulates the host stress response. *Journal of Virology*, *91*, e00474-17. <https://doi.org/10.1128/JVI.00474-17>
- Hsu, C. L., & Stevens, A. (1993). Yeast cells lacking 5'→3' exonuclease 1 contain mRNA species that are poly(A) deficient and partially lack the 5' cap structure. *Molecular and Cellular Biology*, *13*(8), 4826–4835.
- Hu, W., Sweet, T. J., Chamnongpol, S., Baker, K. E., & Collier, J. (2009). Co-translational mRNA decay in *Saccharomyces cerevisiae*. *Nature*, *461*(7261), 225–229.
- Ibrahim, H., Wilusz, J., & Wilusz, C. J. (2008). RNA recognition by 3'-to-5' exonucleases: The substrate perspective. *Biochimica et Biophysica Acta*, *1779*(4), 256–265.
- Idrus, S., Tambunan, U. S., & Zubaidi, A. A. (2012). Designing cyclopentapeptide inhibitor as potential antiviral drug for dengue virus ns5 methyltransferase. *Bioinformatics*, *8*(8), 348–352. <https://doi.org/10.6026/97320630008348>
- Irvin, S. C., Zurney, J., Ooms, L. S., Chappell, J. D., Dermody, T. S., & Sherry, B. (2012). A single-amino-acid polymorphism in reovirus protein μ 2 determines repression of interferon signaling and modulates myocarditis. *Journal of Virology*, *86*(4), 2302–2311.
- Iseni, F., Baudin, F., Garcin, D., Marq, J.-B., Ruigrok, R. W. H., & Kolakofsky, D. (2002). Chemical modification of nucleotide bases and mRNA editing depend on hexamer or nucleoprotein phase in Sendai virus nucleocapsids. *RNA*, *8*(8), 1056–1067.
- Jaafar, Z. A., Oguro, A., Nakamura, Y., & Kieft, J. S. (2016). Translation initiation by the hepatitis C virus IRES requires eIF1A and ribosomal complex remodeling. *eLife*, *5*, e21198. <https://doi.org/10.7554/eLife.21198>

- Jia, X., Yuan, S., Wang, Y., Fu, Y., Ge, Y., Ge, Y., ... Xu, A. (2017). The role of alternative polyadenylation in the antiviral innate immune response. *Nature Communications*, 8, 14605. <https://doi.org/10.1038/ncomms14605>
- Kakisaka, M., Sasaki, Y., Yamada, K., Kondoh, Y., Hikono, H., Osada H., Tomii K., Saito T., Aida Y. (2015) A novel antiviral target structure involved in the RNA binding, dimerization, and nuclear export functions of the influenza A virus nucleoprotein. *PLoS Pathogens*, 11 (7), e1005062. <http://doi.org/10.1371/journal.ppat.1005062>
- Kakumani, P. K., Ponia, S. S., S. R. K., Sood, V., Chinnappan, M., Banerjee, A. C., ... Bhatnagar, R. K. (2013). Role of RNA interference (RNAi) in Dengue virus replication and identification of NS4B as an RNAi suppressor. *Journal of Virology*, 87(16), 8870–8883.
- Kakumani, P. K., Rajgokul, K. S., Ponia, S. S., Kaur, I., Mahanty, S., Medigeshi, G. R., ... Bhatnagar, R. K. (2015). Dengue NS3, an RNAi suppressor, modulates the human miRNA pathways through its interacting partner. *The Biochemical Journal*, 471(1), 89–99.
- Karikó, K., Buckstein, M., Ni, H., & Weissman, D. (2005). Suppression of RNA recognition by toll-like receptors: The impact of nucleoside modification and the evolutionary origin of RNA. *Immunity*, 23, 165–175.
- Kempf, B. J., & Barton, D. J. (2015). Picornavirus RNA polyadenylation by 3D(pol), the viral RNA-dependent RNA polymerase. *Virus Research*, 206, 3–11.
- Khrustalev, V. V., Khrustaleva, T. A., Sharma, N., & Giri, R. (2017). Mutational pressure in Zika virus: Local ADAR-editing areas associated with pauses in translation and replication. *Frontiers in Cellular and Infection Microbiology*, 7, 44. <https://doi.org/10.3389/fcimb.2017.00044>
- Kim, D. Y., Reynaud, J. M., Rasaloukaya, A., Akhrymuk, I., Mobley, J. A., Frolov, I., & Frolova, E. I. (2016). New world and old world alphaviruses have evolved to exploit different components of stress granules, FXR and G3BP proteins, for assembly of viral replication complexes. *PLoS Pathogens*, 12(8), e1005810. <https://doi.org/10.1371/journal.ppat.1005810>
- Kim, J., Parker, J. S. L., Murray, K. E., & Nibert, M. L. (2004). Nucleoside and RNA triphosphatase activities of orthoreovirus transcriptase cofactor mu2. *Journal of Biological Chemistry*, 279(6), 4394–4403.
- Kindler, E., Gil-Cruz, C., Spanier, J., Li, Y., Wilhelm, J., Rabouw, H. H., ... Thiel, V. (2017). Early endonuclease-mediated evasion of RNA sensing ensures efficient coronavirus replication. *PLoS Pathogens*, 13(2), e1006195. <https://doi.org/10.1371/journal.ppat.1006195>
- Kiss, D. L., Oman, K. M., Dougherty, J. A., Mukherjee, C., Bundschuh, R., & Schoenberg, D. R. (2016). Cap homeostasis is independent of poly(A) tail length. *Nucleic Acids Research*, 44(1), 304–314.
- Kobayashi, T., Ooms, L. S., Chappell, J. D., & Dermody, T. S. (2009). Identification of functional domains in reovirus replication proteins muNS and mu2. *Journal of Virology*, 83(7), 2892–2906.
- LaCava, J., Houseley, J., Saveanu, C., Petfalski, E., Thompson, E., Jacquier, A., & Tollervey, D. (2005). RNA degradation by the exosome is promoted by a nuclear polyadenylation complex. *Cell*, 121(5), 713–724.
- Larsen, S., Bui, S., Perez, V., Mohammad, A., Medina-Ramirez, H., & Newcomb, L. L. (2014). Influenza polymerase encoding mRNAs utilize atypical mRNA nuclear export. *Virology Journal*, 11, 154. <https://doi.org/10.1186/1743-422X-11-154>
- Lavut, A., & Raveh, D. (2012). Sequestration of highly expressed mRNAs in cytoplasmic granules, P-bodies, and stress granules enhances cell viability. *PLoS Genetics*, 8(2), e1002527. <https://doi.org/10.1371/journal.pgen.1002527>
- Le Sage, V., Cinti, A., McCarthy, S., Amorim, R., Rao, S., Daino, G. L., ... Moulard, A. J. (2017). Ebola virus VP35 blocks stress granule assembly. *Virology*, 502, 73–83.
- Lee, C. H., Lee, Y. J., Kim, J. H., Lim, J. H., Kim, J., Haw, W., ... Lee, S. W. (2013). Inhibition of hepatitis C virus (HCV) replication by specific RNA aptamers against HCV NS5B RNA replicase. *Journal of Virology*, 87(12), 7064–7074.
- Lee, K., Li, M., Manchanda, M., Batra, R., Charizanis, K., Mohan, A., ... Swanson, M. S. (2013). Compound loss of muscleblind—Like function in myotonic dystrophy. *EMBO Molecular Medicine*, 5(12), 1887–1900.
- Lee, M., Kim, H., Park, E., Lee, J., Kim, K., Lim, K., ... Choi, B. S. (2016). Structural features of influenza A virus panhandle RNA enabling the activation of RIG-I independently of 5'-triphosphate. *Nucleic Acids Research*, 44(17), 8407–8416.
- Leen, E. N., Sorgeloos, F., Correia, S., & Chaudhry, Y. (2016). A conserved interaction between a C-terminal motif in norovirus VPg and the HEAT-1 domain of eIF4G is essential for translation initiation. *PLoS Pathogens*, 12(1), e1005379. <https://doi.org/10.1371/journal.ppat.1005379>
- Li, J., Rahmeh, A., Brusci, V., & Whelan, S. P. (2009). Opposing effects of inhibiting cap addition and cap methylation on polyadenylation during vesicular stomatitis virus mRNA synthesis. *Journal of Virology*, 83(4), 1930–1940.
- Li, J., Wang, J. T., & Whelan, S. P. J. (2006). A unique strategy for mRNA cap methylation used by vesicular stomatitis virus. *Proceedings of the National Academy of Sciences of the United States of America*, 103(22), 8493–8498.
- Li, M. L., Weng, K. F., Shih, S. R., & Brewer, G. (2016). The evolving world of small RNAs from RNA viruses. *WIREs RNA*, 7(5), 575–588.
- Li, S., Dong, H., Li, X., Xie, X., Zhao, H., Deng, Y. Q., ... Shi, P. Y. (2013). Rational design of a flavivirus vaccine by abolishing viral RNA 2'—O methylation. *Journal of Virology*, 87(10), 5812–5819.
- Li, Y., Basavappa, M., Lu, J., Dong, S., Cronkite, D. A., Prior, J. T., ... Jeffrey, K. L. (2016). Induction and suppression of antiviral RNA interference by influenza A virus in mammalian cells. *Nature Microbiology*, 2, 16250. <https://doi.org/10.1038/nmicrobiol.2016.250>
- Lichinchi, G., Zhao, B. S., Wu, Y., Lu, Z., Qin, Y., He, C., & Rana, T. M. (2016). Dynamics of human and viral RNA methylation during Zika virus infection. *Cell Host and Microbe*, 20(5), 666–673.
- Lim, S. P., Sonntag, L. S., Noble, C., Nilar, S. H., Ng, R. H., Zou, G., ... Shi, P. Y. (2011). Small molecule inhibitors that selectively block dengue virus methyltransferase. *The Journal of Biological Chemistry*, 286(8), 6233–6240.
- Lin, S., Choe, J., Du, P., Triboulet, R., & Gregory, R. I. (2016). The m6A methyltransferase METTL3 promotes translation in human cancer cells. *Molecular Cell*, 62(3), 335–345.
- Lin, Z., Ge, J., Wang, Z., Ren, J., Wang, X., Xiong, H., ... Zhang, Q. (2017). Let-7e modulates the inflammatory response in vascular endothelial cells through ceRNA crosstalk. *Scientific Reports*, 7, 42498. <https://doi.org/10.1038/srep42498>

- Lindow, M., Silahatoglu, A., Bak, M., Christensen, M., Hansen, J. B., Lind-Thomsen, A., ... Kauppinen, S. (2008). Antagonism of microRNA-122 in mice by systemically administered LNA-antimiR leads to up-regulation of a large set of predicted target mRNAs in the liver. *Nucleic Acids Research*, *36*(4), 1153–1162.
- Liu, G. Q., Ni, Z., Yun, T., Yu, B., Zhu, J. M., Hua, J. G., & Chen, J. P. (2008). Rabbit hemorrhagic disease virus poly(A) tail is not essential for the infectivity of the virus and can be restored in vivo. *Archives of Virology*, *153*(5), 939–944.
- Liu, N., Zhang, J., Jiao, T., Li, Z., Peng, J., Cui, Z., & Ye, X. (2013). Hepatitis B virus inhibits apoptosis of hepatoma cells by sponging the microRNA 15a/16 cluster. *Journal of Virology*, *87*(24), 13370–13378.
- Liu, Y., Ma, T., Liu, J., Zhao, X., Cheng, Z., Guo, H., ... Wang, S. (2015). Circulating type 1 vaccine-derived poliovirus may evolve under the pressure of adenosine deaminases acting on RNA. *The Journal of Maternal-Fetal & Neonatal Medicine*, *28*(17), 2096–2099.
- Lopez, A. J. (1998). Alternative splicing of pre-mRNA: Developmental consequences and mechanisms of regulation. *Annual Review of Genetics*, *32*(1), 279–305.
- Luna, J. M., Scheel, T. K., Danino, T., Shaw, K. S., Mele, A., Fak, J. J., ... Darnell, R. B. (2015). Hepatitis C virus RNA functionally sequesters miR-122. *Cell*, *160*(6), 1099–1110.
- Manokaran, G., Finol, E., Wang, C., Gunaratne, J., Bahl, J., Ong, E. Z., ... Ooi, E. E. (2016). Dengue subgenomic RNA binds TRIM25 to inhibit interferon expression for epidemiological fitness. *Science*, *350*(6257), 217–221.
- Masaki, T., Arend, K. C., Moorman, N. J., Lemon, S. M., Masaki, T., Kato, T., ... Lemon, S. M. (2015). miR-122 stimulates hepatitis C virus RNA synthesis by altering the balance of viral RNAs engaged in replication versus translation. *Cell Host and Microbe*, *17*(2), 217–228.
- Mbisa, J. L., Becker, M. M., Zou, S., Dermody, T. S., & Brown, E. G. (2000). Reovirus mu2 protein determines strain-specific differences in the rate of viral inclusion formation in L929 cells. *Virology*, *272*(1), 16–26.
- Mengardi, C., Limousin, T., Ricci, E. P., Soto-Rifo, R., Decimo, D., & Ohlmann, T. (2017). microRNAs stimulate translation initiation mediated by HCV-like IRESes. *Nucleic Acid Research*, *45*(8), 4810–4824. <https://doi.org/10.1093/nar/gkw1345>
- Milani, M., Mastrangelo, E., Bollati, M., Selisko, B., Decroly, E., Bouvet, M., ... Bolognesi, M. (2009). Flaviviral methyltransferase/RNA interaction: Structural basis for enzyme inhibition. *Antiviral Research*, *83*(1), 28–34.
- Mok, B. W.-Y., Song, W., Wang, P., Tai, H., Chen, Y., Zheng, M., ... Chen, H. (2012). The NS1 protein of influenza A virus interacts with cellular processing bodies and stress granules through RNA-associated protein 55 (RAP55) during virus infection. *Journal of Virology*, *86*(23), 12695–12707.
- Molleston, J. M., Sabin, L. R., Moy, R. H., Menghani, S. V., Rausch, K., Gordesky-Gold, B., ... Cherry, S. (2016). A conserved virus-induced cytoplasmic TRAMP-like complex recruits the exosome to target viral RNA for degradation. *Genes and Development*, *30*(14), 1658–1670.
- Moon, J., Lee, S., Kim, E., Cho, H., & Lee, W. (2016). Inhibition of hepatitis C virus in mice by a small interfering RNA targeting a highly conserved sequence in viral IRES pseudoknot. *PLoS One*, *11*(1), e0146710. <https://doi.org/10.1371/journal.pone.0146710>
- Moon, S. L., Anderson, J. R., Kumagai, Y., Wilusz, C. J., Akira, S., Khromykh, A. A., & Wilusz, J. (2012). A noncoding RNA produced by arthropod-borne flaviviruses inhibits the cellular exoribonuclease XRN1 and alters host mRNA stability. *RNA*, *18*(11), 2029–2040.
- Moon, S. L., Blackinton, J. G., Anderson, J. R., Dozier, M. K., Dodd, B. J., Keene, J. D., ... Wilusz, J. (2015). XRN1 stalling in the 5' UTR of Hepatitis C virus and Bovine Viral Diarrhea virus is associated with dysregulated host mRNA stability. *PLoS Pathogens*, *11*(3), e1004708. <https://doi.org/10.1371/journal.ppat.1004708>
- Moon, S. L., Dodd, B. J. T., Brackney, D. E., Wilusz, C. J., Ebel, G. D., & Wilusz, J. (2015). Flavivirus sRNA suppresses antiviral RNA interference in cultured cells and mosquitoes and directly interacts with the RNAi machinery. *Virology*, *485*, 322–329.
- Moteki, S., & Price, D. (2002). Functional coupling of capping and transcription of mRNA. *Cell*, *10*, 599–609.
- Mühlbauer, D., Dzieciolowski, J., Hardt, M., Hocke, A., Schierhorn, K. L., Mostafa, A., ... Pleschka, S. (2015). Influenza virus-induced caspase-dependent enlargement of nuclear pores promotes nuclear export of viral ribonucleoprotein complexes. *Journal of Virology*, *89*(11), 6009–6021.
- Nelson, E. V., Schmidt, K. M., Deflubé, L. R., Doğanay, S., Banadyga, L., Olejnik, J., ... Mühlberger, E. (2016). Ebola virus does not induce stress granule formation during infection and sequesters stress granule proteins within viral inclusions. *Journal of Virology*, *90*(16), 7268–7284.
- Nishitsuji, H., Ujino, S., Yoshio, S., Sugiyama, M., Mizokami, M., Kanto, T., & Shimotohno, K. (2016). Long noncoding RNA #32 contributes to antiviral responses by controlling interferon-stimulated gene expression. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(37), 10388–10393.
- Ogino, M., & Ogino, T. (2017). 5' -Phospho-RNA acceptor specificity of GDP polyribonucleotidyltransferase of vesicular stomatitis virus in mRNA capping. *Journal of Virology*, *91*(6), e02322-16. <https://doi.org/10.1128/JVI.02322-16>
- Ogino, T., Yadav, S. P., & Banerjee, A. K. (2010). Histidine-mediated RNA transfer to GDP for unique mRNA capping by vesicular stomatitis virus RNA polymerase. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(8), 3463–3468.
- Ottosen, S., Parsley, T. B., Yang, L., Zeh, K., van Doorn, L. J., van der Veer, E., ... Patick, A. K. (2015). In vitro antiviral activity and preclinical and clinical resistance profile of miravirsen, a novel anti-hepatitis C virus therapeutic targeting the human factor miR-122. *Antimicrobial Agents and Chemotherapy*, *59*(1), 599–608.
- Pacheco, A., Serrano, P., & Fernandez, N. (2008). New insights into internal ribosome entry site elements relevant for viral gene expression. *Journal of General Virology*, *89*(3), 611–626.
- Pager, C. T., Schütz, S., Abraham, T. M., Luo, G., & Sarnow, P. (2013). Modulation of hepatitis C virus RNA abundance and virus release by dispersion of processing bodies and enrichment of stress granules. *Virology*, *435*(2), 472–484.
- Pan, Q., Shai, O., Lee, L. J., Frey, B. J., & Blencowe, B. J. (2008). Deep surveying of alternative splicing complexity in the human transcriptome by high-throughput sequencing. *Nature Genetics*, *40*(12), 1413–1415.

- Panas, M. D., Varjak, M., Lulla, A., Er Eng, K., Merits, A., Karlsson Hedestam, G. B., & McInerney, G. M. (2012). Sequestration of G3BP coupled with efficient translation inhibits stress granules in Semliki Forest virus infection. *Molecular Biology of the Cell*, *23*(24), 4701–4712.
- Park, N., Schweers, N. J., & Gustin, K. E. (2015). Selective removal of FG repeat domains from the nuclear pore complex by enterovirus 2A(pro). *Journal of Virology*, *89*(21), 11069–11079.
- Parker, J. S. L., Broering, T. J., Kim, J., Higgins, D. E., & Nibert, M. L. (2002). Reovirus core protein mu2 determines the filamentous morphology of viral inclusion bodies by interacting with and stabilizing microtubules. *Journal of Virology*, *76*(9), 4483–4496.
- Pelletier, J., & Sonenberg, N. (1988). Internal initiation of translation of eukaryotic mRNA directed by a sequence derived from poliovirus RNA. *Nature*, *334*(6180), 320–325.
- Peng, X., Gralinski, L., Armour, C. D., Ferris, M. T., Thomas, M. J., Proll, S., ... Katze, M. G. (2010). Unique signatures of long noncoding RNA expression in response to virus infection and altered innate immune signaling. *mBio*, *1*(5), e00206–e00210. <https://doi.org/10.1128/mBio.00206-10>
- Pérez-Vilaró, G., Scheller, N., Saludes, V., & Díez, J. (2012). Hepatitis C virus infection alters P-body composition but is independent of P-body granules. *Journal of Virology*, *86*(16), 8740–8749.
- Pestova, T. V., Shatsky, I. N., Fletcher, S. P., Jackson, R. J., & Hellen, C. U. T. (1998). A prokaryotic-like mode of cytoplasmic eukaryotic ribosome binding to the initiation codon during internal translation initiation of hepatitis C and classical swine fever virus RNAs. *Genes and Development*, *12*(1), 67–83.
- Pijlman, G. P., Funk, A., Kondratieva, N., Leung, J., Torres, S., van der Aa, L., ... Khromykh, A. A. (2008). A highly structured, nuclease-resistant, noncoding RNA produced by flaviviruses is required for pathogenicity. *Cell Host & Microbe*, *4*(6), 579–591.
- Pleet, M. L., DeMarino, C., Lepene, B., Aman, M. J., & Kashanchi, F. (2017). The role of exosomal VP40 in Ebola virus disease. *DNA and Cell Biology*, *36*(4), 243–248.
- Polacek, C., Friebe, P., & Harries, E. (2009). Poly(A)-binding protein binds to the non-polyadenylated 3' untranslated region of dengue virus and modulates translation efficiency. *The Journal of General Virology*, *90*, 698–692.
- Poon, L. L. M., Pritlove, D. C., Fodor, E., & Brownlee, G. G. (1999). Direct evidence that the poly(A) tail of influenza A virus mRNA is synthesized by reiterative copying of a U track in the virion RNA template. *Journal of Virology*, *73*(4), 3473–3476.
- Protter, D. S., & Parker, R. (2016). Principles and properties of stress granules. *Trends in Cell Biology*, *26*(9), 668–679.
- Rabouw, H. H., Langereis, M. A., Knaap, R. C. M., Dalebout, T. J., Canton, J., Sola, I., ... van Kuppeveld, F. J. M. (2016). Middle East respiratory coronavirus accessory protein 4a inhibits PKR-mediated antiviral stress responses. *PLoS Pathogens*, *12*(10), e1005982. <https://doi.org/10.1371/journal.ppat.1005982>
- Rawlinson, S. M., Pryor, M. J., Wright, P. J., & Jans, D. A. (2009). CRM1-mediated nuclear export of dengue virus RNA polymerase NS5 modulates interleukin-8 induction and virus production. *The Journal of Biological Chemistry*, *284*(23), 15589–15597.
- Reguera, J., Gerlach, P., Rosenthal, M., Gaudon, S., Coscia, F., Gunther, S., & Cusack, S. (2016). Comparative structural and functional analysis of bunyavirus and arenavirus cap-snatching endonucleases. *PLoS Pathogens*, *12*(6), e1005636. <https://doi.org/10.1371/journal.ppat.1005636>
- Reguera, J., Weber, F., & Cusack, S. (2010). Bunyaviridae RNA polymerases (L-protein) have an N-terminal, influenza-like endonuclease domain, essential for viral cap-dependent transcription. *PLoS Pathogens*, *6*(9), e1001101. <https://doi.org/10.1371/journal.ppat.1001101>
- Rivera-Serrano, E. E., Fritch, E. J., Scholl, E. H., & Sherry, B. (2017). A cytoplasmic RNA virus alters the function of the cell splicing protein SRSF2. *Journal of Virology*, *91*(7), e02488-16. <https://doi.org/10.1128/JVI.02488-16>
- Roby, J. A., Pijlman, G. P., Wilusz, J., & Khromykh, A. A. (2014). Noncoding subgenomic flavivirus RNA: Multiple functions in West Nile virus pathogenesis and modulation of host responses. *Viruses*, *6*(2), 404–427.
- Romeo, V., & Schümperli, D. (2016). Cycling in the nucleus: Regulation of RNA 3' processing and nuclear organization of replication-dependent histone genes. *Current Opinion in Cell Biology*, *40*, 23–31.
- Rosenthal, M., Gogrefe, N., Vogel, D., Reguera, J., Rauschenberger, B., Cusack, S., ... Reindl, S. (2017). Structural insights into reptarenavirus cap-snatching machinery. *PLoS Pathogens*, *13*(5), e1006400. <https://doi.org/10.1371/journal.ppat.1006400>
- Sage, V., Cint, A., McCarty, S., Amorim, R., Rao, S., Danio, G., ... Mouland, A. (2016). Ebola virus VP35 blocks stress granule assembly. *Virology*, *502*, 73–83.
- Scheel, T. K. H., Luna, J. M., Liniger, M., Darnell, R. B., Ruggli, N., Shlomai, A., ... Rice, C. M. (2016). A broad RNA virus survey reveals both miRNA dependence and functional sequestration. *Cell Host and Microbe*, *19*(3), 409–423.
- Schlee, M., Roth, A., Hornung, V., Hagmann, C. A., Wimmenauer, V., Barchet, W., ... Hartmann, G. (2009). Recognition of 5' triphosphate by RIG-I helicase requires short blunt double-stranded RNA as contained in panhandle of negative-strand virus. *Immunity*, *31*, 25–34.
- Schnettler, E., Sterken, M. G., Leung, J. Y., Metz, S. W., Geertsema, C., Goldbach, R. W., ... Pijlman, G. P. (2012). Noncoding flavivirus RNA displays RNA interference suppressor activity in insect and mammalian cells. *Journal of Virology*, *86*(24), 13486–13500.
- Schoenberg, D. R., & Maquat, L. E. (2012). Regulation of cytoplasmic mRNA decay. *Nature Reviews Genetics*, *13*(4), 246–259.
- Scholte, F. E. M., Tas, A., Albulescu, I. C., Žusinaite, E., Merits, A., Snijder, E. J., & van Hemert, M. J. (2015). Stress granule components G3BP1 and G3BP2 play a proviral role early in chikungunya virus replication. *Journal of Virology*, *89*(8), 4457–4469.
- Schwartz, S., Mumbach, M. R., Jovanovic, M., Wang, T., Maciag, K., Bushkin, G. G., ... Regev, A. (2012). Perturbation of m6A writers reveals two distinct classes of mRNA methylation at internal and 5' sites. *Cell Reports*, *8*(1), 284–296.
- Selman, M., Dankar, S. K., Forbes, N. E., Jia, J.-J., & Brown, E. G. (2012). Adaptive mutation in influenza A virus non-structural gene is linked to host switching and induces a novel protein by alternative splicing. *Emerging Microbes Infections*, *1*(11), e42. <https://doi.org/10.1038/emi.2012.38>

- Shah, K., Zhang, B., Ramachandran, V., & Herman, P. (2013). Processing body and stress granule assembly occur by independent and differentially regulated pathways in *Saccharomyces cerevisiae*. *Genetics*, *193*, 109–123.
- Shi, Y., & Manley, J. L. (2015). The end of the message: multiple protein-RNA interactions define the mRNA polyadenylation site. *Genes & Development*, *29*(9), 889–897.
- Shih, S. R., Suen, P. C., Chen, Y. S., & Chang, S. C. (1998). A novel spliced transcript of influenza A/WSN/33 virus. *Virus Genes*, *17*(2), 179–183.
- Shimizu, K., Iguchi, A., Gomyou, R., & Ono, Y. (1998). Influenza virus inhibits cleavage of the HSP70 pre-mRNAs at the Polyadenylation site. *Virology*, *254*(2), 213–219.
- Sikora, D., Rocheleau, L., Brown, E. G., & Pelchat, M. (2017). Influenza A virus cap-snatches host RNAs based on their abundance early after infection. *Virology*, *509*, 167–177.
- Silva, P. A. G. C., Pereira, C. F., Dalebout, T. J., Spaan, W. J. M., & Bredenbeek, P. J. (2010). An RNA pseudoknot is required for production of yellow fever virus subgenomic RNA by the host nuclease XRN1. *Journal of Virology*, *84*(21), 11395–11406.
- Siu, R. W. C., Fragkoudis, R., Simmonds, P., Donald, C. L., Chase-Topping, M. E., Barry, G., ... Kohl, A. (2011). Antiviral RNA interference responses induced by Semliki Forest virus infection of mosquito cells: Characterization, origin, and frequency-dependent functions of virus-derived small interfering RNAs. *Journal of Virology*, *85*(6), 2907–2917.
- Sokoloski, K. J., Dickson, A. M., Chaskey, E. L., Garneau, N. L., Wilusz, C. J., & Wilusz, J. (2010). Sindbis virus usurps the cellular HuR protein to stabilize its transcripts and promote productive infections in mammalian and mosquito cells. *Cell Host and Microbe*, *8*(2), 196–207.
- Staals, R. H. J., Bronkhorst, A. W., Schilders, G., Slomovic, S., Schuster, G., Heck, A. J. R., ... Pruijn, G. J. M. (2010). Dis3-like 1: A novel exoribonuclease associated with the human exosome. *The EMBO Journal*, *29*(14), 2358–2367.
- Steil, B., Kempf, B., & Barton, D. (2010). Poly(A) at the 3' end of positive-strand RNA and VPg-linked poly(U) at the 5' end of negative-strand RNA are reciprocal templates during replication of poliovirus RNA. *Journal of Virology*, *84*(6), 2843–2858.
- Szittyá, G., & Burgyán, J. (2013). RNA interference-mediated intrinsic antiviral immunity in plants. *Current Topics in Microbiology and Immunology*, *371*, 153–181.
- Terrier, O., Carron, C., De Chasse, B., Dubois, J., Traversier, A., Julien, T., ... Rosa-Calatrava, M. (2016). Nucleolin interacts with influenza A nucleoprotein and contributes to viral ribonucleoprotein complexes nuclear trafficking and efficient influenza viral replication. *Scientific Reports*, *6*, 29006. <https://doi.org/10.1038/srep29006>
- Tian, B., & Manley, J. L. (2017). Alternative polyadenylation of mRNA precursors. *Nature Reviews Molecular Cell Biology*, *18*(1), 18–30.
- Tsai, P. L., Chiou, N. T., Kuss, S., García-Sastre, A., Lynch, K. W., & Fontoura, B. M. (2013). Cellular RNA binding proteins NS1-BP and hnRNP K regulate influenza A virus RNA splicing. *PLoS Pathogens*, *9*(6), e1003460. <https://doi.org/10.1371/journal.ppat.1003460>
- Ullmer, W., & Semler, B. L. (2016). Diverse strategies used by picornaviruses to escape host RNA decay pathways. *Viruses*, *8*(12), E335. <https://doi.org/10.3390/v8120335>
- van den Hoogen, B. G., van Boheemen, S., de Rijck, J., van Nieuwkoop, S., Smith, D. J., Laksono, B., ... Fouchier, R. A. M. (2014). Excessive production and extreme editing of human metapneumovirus defective interfering RNA is associated with type I IFN induction. *The Journal of General Virology*, *95*(8), 1625–1633.
- Vasudevan, S. (2012). Posttranscriptional upregulation by microRNAs. *WIREs RNA*, *3*(3), 311–330.
- Volchkova, V. A., Vorac, J., Repiquet-Paire, L., Lawrence, P., & Volchkov, V. E. (2015). Ebola virus GP gene polyadenylation versus RNA editing. *The Journal of Infectious Diseases*, *212*(Suppl 2), S191–S198.
- Wang, Y., Ludwig, J., Schuberth, C., Goldeck, M., Schlee, M., Li, H., ... Patel, D. J. (2010). Structural and functional insights into 5' -ppp RNA pattern recognition by the innate immune receptor RIG-I. *Nature Structural & Molecular Biology*, *17*(7), 781–787.
- Wang, Y., Zhou, J., & Du, Y. (2014). hnRNP A2/B1 interacts with influenza A viral protein NS1 and inhibits virus replication potentially through suppressing NS1 RNA/protein levels and NS1 mRNA nuclear export. *Virology*, *449*, 53–61.
- Ward, A. M., Bidet, K., Yinglin, A., Ler, S. G., Hogue, K., Blackstock, W., ... Garcia-Blanco, M. A. (2011). Quantitative mass spectrometry of DENV-2 RNA-interacting proteins reveals that the DEAD-box RNA helicase DDX6 binds the DB1 and DB2 3' UTR structures. *RNA Biology*, *8*(6), 1173–1186.
- Weaver, S. C., Costa, F., Garcia-Blanco, M. A., Ko, A. I., Ribeiro, G. S., Saade, G., ... Vasilakis, N. (2016). Zika virus: History, emergence, biology, and prospects for control. *Antiviral Research*, *130*, 69–80.
- Weinheimer, I., Jiu, Y., Rajamäki, M.-L., Matilainen, O., Kallijärvi, J., Cuellar, W. J., ... Valkonen, J. P. T. (2015). Suppression of RNAi by dsRNA-degrading RNase III enzymes of viruses in animals and plants. *PLoS Pathogens*, *11*(3), e1004711. <https://doi.org/10.1371/journal.ppat.1004711>
- Wells, M. L., Perera, L., & Blackshear, P. J. (2017). An ancient family of RNA-binding proteins: Still important! *Trends Biochemical Sciences*, *42*(4), 285–296.
- White, E. J., Matsangos, A. E., & Wilson, G. M. (2017). AUF1 regulation of coding and noncoding RNA. *WIREs RNA*, *8*(2), e1393. <https://doi.org/10.1002/wrna.1393>
- Wilson, J. A., & Huys, A. (2013). miR-122 promotion of the hepatitis C virus life cycle: Sound in the silence. *WIREs RNA*, *4*(6), 665–676.
- Winterling, C., Koch, M., Koeppl, M., Garcia-Alcalde, F., Karlas, A., & Meyer, T. F. (2014). Evidence for a crucial role of a host non-coding RNA in influenza A virus replication. *RNA Biology*, *11*(1), 66–75.
- Wise, H. M., Hutchinson, E. C., Jagger, B. W., Stuart, A. D., Kang, Z. H., Robb, N., ... Digard, P. (2012). Identification of a novel splice variant form of the influenza A virus M2 ion channel with an antigenically distinct ectodomain. *PLoS Pathogens*, *8*(11), e1002998. <https://doi.org/10.1371/journal.ppat.1002998>

- Wu, H., Ke, T., Liao, W., & Chang, N. (2013). Regulation of coronaviral poly(A) tail length during infections. *PLoS One*, *8*(7), e70548. <https://doi.org/10.1371/journal.pone.0070548>
- Xia, J., Chen, X., Xu, F., Wang, Y., Shi, Y., Li, Y., ... Zhang, P. (2015). Dengue virus infection induces formation of G3BP1 granules in human lung epithelial cells. *Archives of Virology*, *160*, 2991–2999. <https://doi.org/10.1007/s00705-015-2578-9>
- Xiong, Y., Zhang, C., Yuan, J., Zhu, Y. A. N., Tan, Z., ... X. (2015). Hepatitis C virus represses the cellular antiviral response by upregulating the expression of signal transducer and activator of transcription 3 through sponging microRNA—122. *Molecular Medicine Reports*, *11*(3), 1733–1737.
- Yang, W.-H., Yu, J. H., Gulick, T., Bloch, K. D., & Bloch, D. B. (2006). RNA-associated protein 55 (RAP55) localizes to mRNA processing bodies and stress granules. *RNA*, *12*(4), 547–554.
- Zeng, C., Wu, A., Wang, Y., Xu, S., Tang, Y., Jin, X., ... Guo, D. (2016). Identification and characterization of a ribose 2' -O-methyltransferase encoded by the ronivirus branch of Nidovirales. *Journal of Virology*, *90*(15), 6675–6685.
- Zhang, R., Guo, Y., Ma, Z., Ma, G., & Xue, Q. (2017). Long non-coding RNA PTENP1 functions as a ceRNA to modulate PTEN level by decoying miR-106b and miR-93 in gastric cancer. *Oncotarget*, *8*(16), 26079–26089.
- Zhang, Y., Wei, Y., Zhang, X., Cai, H., & Niewiesk, S. (2014). Rational design of human metapneumovirus live attenuated vaccine candidates by inhibiting viral mRNA cap methyltransferase. *Journal of Virology*, *88*(19), 11411–11429.
- Zheng, Z., Ke, X., Wang, M., He, S., Li, Q., Zheng, C., ... Wang, H. (2013). Human microRNA hsa-miR-296-5p suppresses enterovirus 71 replication by targeting the viral genome. *Journal of Virology*, *87*(10), 5645–5656.
- Zhou, Y., Fang, L., Wang, D., Cai, K., Chen, H., & Xiao, S. (2017). Porcine reproductive and respiratory syndrome virus infection induces stress granule formation depending on protein kinase R-like endoplasmic reticulum kinase (PERK) in MARC-145 cells. *Frontiers in Cellular and Infection Microbiology*, *7*, 111. <https://doi.org/10.3389/fcimb.2017.00111>
- Zurney, J., Kobayashi, T., Holm, G. H., Dermody, T. S., & Sherry, B. (2009). Reovirus mu2 protein inhibits interferon signaling through a novel mechanism involving nuclear accumulation of interferon regulatory factor 9. *Journal of Virology*, *83*(5), 2178–2187.
- Züst, R., Cervantes-Barragan, L., Habjan, M., Maier, R., Neuman, B. W., Ziebuhr, J., ... Thiel, V. (2011). Ribose 2'-O-methylation provides a molecular signature for the distinction of self and non-self mRNA dependent on the RNA sensor Mda5. *Nature Immunology*, *12*(2), 137–143.

How to cite this article: Cross ST, Michalski D, Miller MR, Wilusz J. RNA regulatory processes in RNA virus biology. *WIREs RNA*. 2019;10:e1536. <https://doi.org/10.1002/wrna.1536>