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Review

Interplay between viruses and host mRNA degradation ☆

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ABSTRACT

Messenger RNA degradation is a fundamental cellular process that plays a critical role in regulating gene expression by controlling both the quality and the abundance of mRNAs in cells. Naturally, viruses must successfully interface with the robust cellular RNA degradation machinery to achieve an optimal balance between viral and cellular gene expression and establish a productive infection in the host. In the past several years, studies have discovered many elegant strategies that viruses have evolved to circumvent the cellular RNA degradation machinery, ranging from disarming the RNA decay pathways and co-opting the factors governing cellular mRNA stability to promoting host mRNA degradation that facilitates selective viral gene expression and alters the dynamics of host–pathogen interaction. This review summarizes the current knowledge of the multifaceted interaction between viruses and cellular mRNA degradation machinery to provide an insight into the regulatory mechanisms that influence gene expression in viral infections. This article is part of a Special Issue entitled: RNA Decay mechanisms.

1. Introduction

Gene expression in eukaryotic cells is the result of a series of complex and highly regulated events that include transcription, translation, decay of mRNAs and protein degradation. Among these fundamental cellular processes, mRNA turnover by the cellular RNA decay machinery plays a major role in regulating gene expression by altering the stability of mRNAs in response to developmental, physiological and environmental signals [1–4]. The surveillance arm of the cellular RNA decay machinery also controls the quality of gene expression by constantly monitoring the newly synthesized RNA transcripts for aberrant structural and sequence features and targets them for destruction [5–8]. Thus, the cellular RNA decay machinery, consisting of a multitude of enzymes, auxiliary factors and pathways, controls the fate of newly synthesized RNA transcripts and mRNAs undergoing translation in a cell [9–12]. In addition to the conventional RNA decay pathways, eukaryotic cells also have specialized RNA decay pathways that are induced in response to external stress signals like virus infection [13]. It is reasonable to expect that nascent viral RNA transcripts carrying features that are recognized as "aberrant or non-self" by host mRNA surveillance pathways would also be shunted to the cellular RNA decay machinery for degradation. Therefore, viruses must not only contend with the intrinsically antiviral host immune response pathways but also evolve strategies to elude, counter or sometimes even utilize the inherently hostile cellular mRNA degradation machinery to facilitate viral gene expression and establish a successful infection. The goal of this review is to highlight this complex interplay between viruses and cellular mRNA degradation pathways by illustrating the diverse array of mechanisms that viruses utilize to gain an advantage in this evolutionary arms race with their hosts.

2. Cellular mRNA degradation pathways

The different pathways of mRNA decay in eukaryotic cells involve the coordinated action of exoribonucleases and endoribonucleases that target an mRNA substrate for destruction depending on the presence of cis-acting instability elements, trans-acting mRNA destabilizing factors and cellular environment [9,11] (Fig. 1). A majority of eukaryotic mRNAs carry a 5′ 7-methylguanosine cap and a 3′ poly(A) tail that serve as primary determinants of mRNA stability by protecting the ends from the action of exoribonucleases, besides influencing different aspects of mRNA metabolism including splicing and nuclear export [3,14–16]. Furthermore, binding of the cytoplasmic proteins eIF4E and the poly(A)-binding protein (PABP) to the 5′ cap and the 3′ poly(A) tail, respectively, ensures efficient translation initiation [17,18]. The fate of an mRNA molecule after translation is controlled by processes that target these mRNA stability determinants at the ends of the molecule. The major pathway of cytoplasmic

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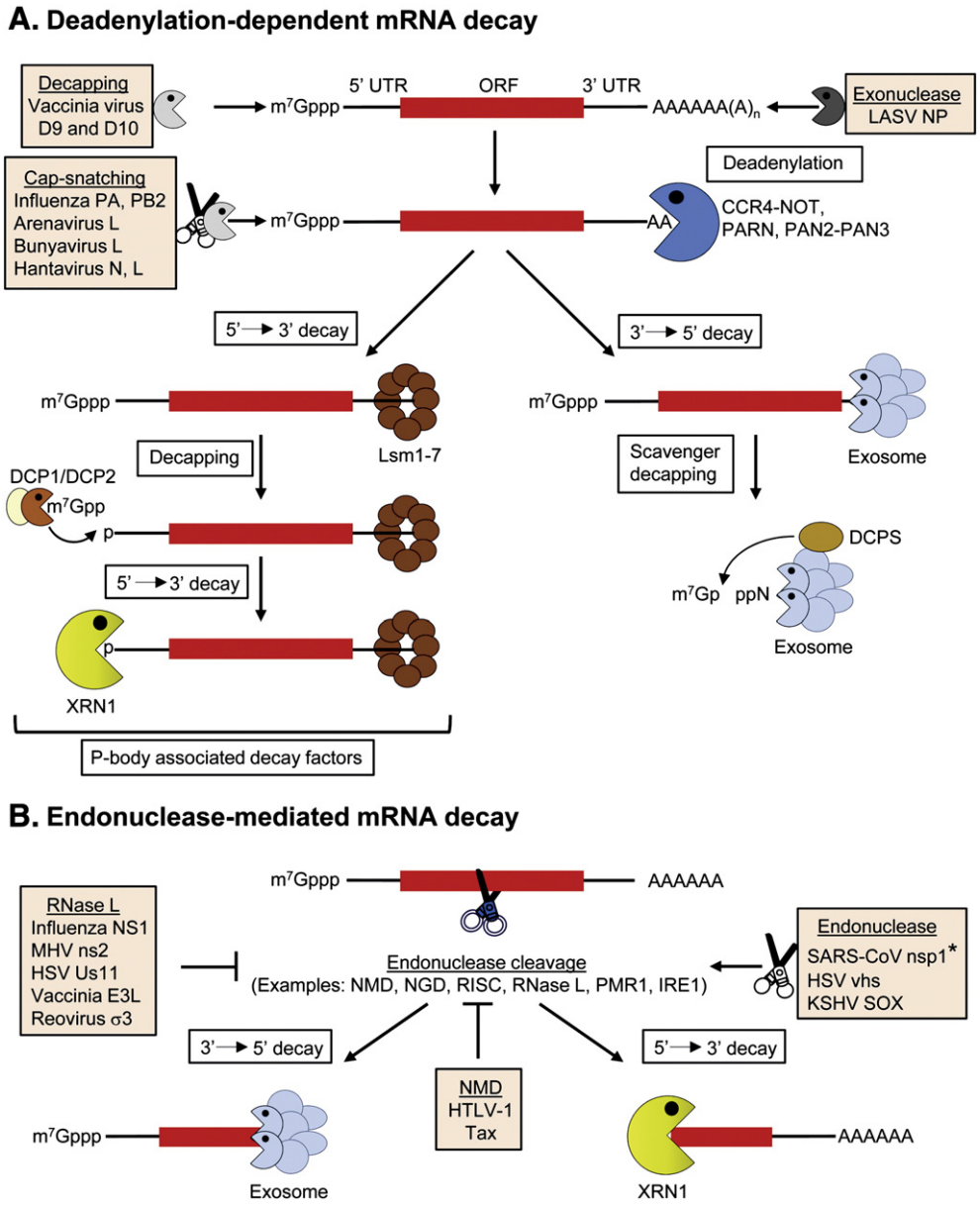

Fig. 1. Major pathways of cellular mRNA decay. A) A majority of cellular mRNAs are degraded by the deadenylation-dependent decay pathway. The cellular deadenylase complexes, CCR4-NOT, PARN or PAN2-PAN3 removes the poly(A) tail and subsequently, the body of the deadenylated mRNA is degraded by 5′-3′ or 3′-5′decay mechanisms. In the 5′-3′ decay pathway, the Lsm1-7 protein complex binds to the 3′-end of the deadenylated mRNA and stimulates decapping by the DCP1-DCP2 enzyme complex that generates a monophosphorylated 5′-end. Following decapping, the mRNA body is degraded by the action of the 5′-3′ exoribonuclease, XRN1. Most of the proteins involved in the 5′-3′ decay pathway are localized in P bodies. The 3′-5′ decay of the deadenylated mRNA is catalyzed by the 3′-5′ exoribonucleolytic activity of the exosome followed by the removal of the cap structure by the scavenger decapping enzyme, DCPS. B) The endonuclease-mediated decay pathway triggers the degradation of some mRNAs, including those recognized by cellular mRNA surveillance and stress response pathways like NMD, NGD, RNase L and IRE1. The decay is initiated by an endonuclease cleavage event followed by the digestion of the resulting unprotected fragments by exosome and XRN1. The figure is adapted from Fig. 1 in Ref. [9]. Selected examples of viral proteins that interfere with the cellular mRNA decay machinery are provided. See text for details. * denotes that the SARS-CoV nsp1-induced endonuclease activity could be host-encoded.

mRNA decay in eukaryotic cells is initiated by the removal of one of these barriers to exoribonucleases through a process known as deadenylation that results in the shortening of the poly(A) tail [19]. Deadenylation is the first and often the rate-limiting step of mRNA decay that is performed by one or more of the cellular deadenylase enzyme complexes, CCR4-NOT, PAN2-PAN3 and PARN [20,21].

Following deadenylation, the body of mRNA is degraded by two exonuclease-mediated decay pathways acting either at the 3′ or 5′ end. The 3′-5′ decay is carried out by the cytoplasmic exosome, which is a highly conserved multi-protein complex of 3′-5′ exoribonucleases, RRP44 and exosome component 10 (EXOSC10, otherwise known as RRP6 in yeast and PM/SCL-100 in humans) [22,23]. In mammalian cells, DIS3L, the cytoplasmic form of the processive exonuclease RRP44, is involved in 3′-5′ mRNA degradation [23]. The exosome activity is regulated by cofactors that include the SKI complex [22]. Subsequently, the action of the scavenger decapping enzyme DCPS on the products of exosome-mediated mRNA decay removes the cap structure [24,25].

Alternatively, the decay of the deadenylated transcript proceeds in a 5′-3′ direction through the removal of the 5′ cap structure by the cellular decapping enzyme DCP2 (or NUDT16) [26]. Decapping is a highly regulated process involving several cofactors that function as decapping enhancers, including Lsm1-7 protein complex that binds

to the 3′-end of the deadenylated mRNAs, Rck/p54 (Dhh1p in yeast), Hedls, PatL1 and DCP1a [26]. Following decapping that generates a monophosphorylated 5′-end, the mRNA body is degraded by the 5′ monophosphate-dependent 5′-3′ exoribonucleolytic activity of XRN1 [19,27].

In addition to the default pathway of deadenylation-dependent mRNA decay, eukaryotic cells also have specialized endonucleolytic RNA decay pathways that is initiated by an endonucleolytic cleavage event within the body of the mRNA or in the untranslated region (UTR) followed by exonuclease digestion of the resulting fragments by exosome and XRN1 [11,28] (Fig. 1). Several endonucleases such as PMR1, IRE1, Zc3h12a, APE1, G3BP and SMG6 have been identified that target actively translating mRNAs in response to stress and other physiological stimuli or recognize substrate mRNAs based on associated proteins and aberrant structural and sequence features [11,28]. The RNA interference pathway, catalyzed by argonaute protein (Ago) in the RNA-induced silencing complex (RISC), and the interferon (IFN)-inducible endonuclease RNase L, are also examples of endonuclease-mediated decay pathways that are elicited in response to endogenous and viral double-stranded RNA (dsRNA) molecules generated in the cytoplasm, respectively [11,13,28]. The cellular zinc finger antiviral protein (ZAP) is an IFN-induced host factor that inhibits the replication of several viruses by promoting viral mRNA decay in the cytoplasm [29]. ZAP selectively restricts the replication of retroviruses, alphaviruses and filoviruses by targeting the ZAP-responsive element (ZRE) in the genomes of these viruses [29]. ZAP also regulates the maintenance of murine gammaherpesvirus 68 (MHV-68) latency by selectively inhibiting the expression of the latency-associated M2 gene [30]. ZAP promotes the degradation of ZRE-containing viral mRNAs through the recruitment of the deadenylase PARN to remove the poly(A) tail and the exosome to degrade the body of the mRNA [29]. ZAP also requires the RNA helicase p72 for its activity [29]. In addition to promoting mRNA degradation, ZAP also inhibits the translation of target mRNAs by blocking the interaction between the translation initiation factors eIF4G and eIF4A [31]. Importantly, the ZAP-mediated translational repression precedes and is required for target mRNA degradation [31]. Furthermore, among the cellular mRNA surveillance pathways that maintain the fidelity of gene expression, the nonsense-mediated decay (NMD), which eliminates mRNAs harboring a premature termination codon (PTC) or an abnormally long 3′ UTR between the normal stop codon and the poly(A) tail, and no-go decay (NGD), which targets mRNAs with secondary structure-induced stalled ribosomes, are also initiated by an endonucleolytic cleavage event [9,32]. NMD and NGD pathways are mediated by a complex of SMG and UPF proteins and the DOM34-Hbs1 complex, respectively [9,32]. The endoribonuclease activity of SMG6 protein is responsible for the cleavage of PTC-harboring mRNAs in the NMD pathway [33]. The identity of the endonuclease that triggers mRNA decay in the NGD pathway is unknown. Nonstop decay, a specific quality control pathway that eliminates mRNAs lacking a termination codon, is catalyzed by exosome and the SKI complex [34,35].

Cellular mRNA degradation is also regulated by other cis-acting instability elements within mRNAs, like the AU-rich elements (AREs) found in 3′ UTRs of many mRNAs, which determine the fate of an mRNA depending on their interaction with mRNA-destabilizing proteins, such as TTP, BRF1, AUF1, KSRP, or mRNA-stability factors like HuR protein and poly(C)-binding protein 2 (PCBP2) [9,11]. Other mRNA-destabilizing factors include small, complementary regulatory noncoding RNAs such as microRNAs (miRNAs) that interact with 3′-UTRs in target mRNAs to repress translation or promote mRNA degradation [36]. Many of the factors involved in mRNA surveillance and degradation, including most of the proteins that function in the 5′-3′ decay pathway, are localized in discrete cytoplasmic granular compartments called processing bodies (P-bodies) [37,38]. P bodies play a fundamental role in cellular mRNA degradation and have been shown to contain several mRNA-destabilizing and decay enzymes like TTP, DCP1-DCP2 complex, XRN1, Lsm1-7 complex, Dhh1p (Rck/p54), PAN2-PAN3, CCR4-CAF1-NOT deadenylase complex along with the P-body component GW182 [38]. Strikingly, exosome and the SKI complex proteins, involved in the 3′-5′ decay pathway, have not been observed in P bodies [37,39]. Mammalian cells also have specialized cytoplasmic RNA granules called stress granules (SGs) that are formed in response to different types of cellular stress, including heat shock, oxidative stress and viral infections, which often inhibit cellular translation initiation [40,41]. P bodies and SGs are dynamically linked and share several components, including XRN1, TTP and eIF4E [42]. However, proteins such as eIF3, G3BP, eIF4G, the cytoplasmic poly(A)-binding protein-1 (PABPC1) along with 40S ribosomal subunits are exclusively found in SGs and in contrast to P bodies, the assembly of SGs requires eIF2α phosphorylation that inhibits translation initiation [42]. SGs serve as dynamic sorting centers for translationally-silenced or repressed mRNAs that can be targeted for storage, translation or delivery to the P bodies for degradation through the mRNA triage pathway [40]. We would like to urge the reader to refer to some excellent reviews on the topics discussed above for details [9,38].

Both DNA and RNA viruses, regardless of whether their life cycle includes a nuclear phase and/or their replication occurs in nuclease-resistant membranous compartments, rely on the host translation machinery in the cytoplasm for the efficient production of viral proteins. Therefore, viruses must protect their mRNAs from the panoply of cellular pathways and enzymes described above that are geared to recognize the viral transcripts as “non-self” and funnel them to the host mRNA decay machinery for degradation. The following sections will summarize the arsenal of specific strategies that many viruses have developed during the course of virus-host co-evolution to ensure both the escape of viral-specific transcripts from detection by the host mRNA decay pathways and the efficient translation of viral mRNAs in infected cells (Figs. 2 and 3).

3. Viral evasion of cellular mRNA decay pathways

3.1. Cis-acting RNA stability elements and trans-acting RNA stabilization factors

Viruses have evolved several mechanisms to protect their nascent RNA transcripts produced in an infected cell from the mRNA decay machinery and these strategies include mimicking the inherent elements that confer stability to cellular mRNAs, carrying cis-acting RNA stability sequence or structural elements and masking the instability elements in their mRNAs by co-opting the cellular RNA stabilization factors.

Viral RNA transcripts with unprotected ends lacking the cellular cis-acting determinants of mRNA stability, namely the 5′ cap structure and the 3′ poly(A) tail, are susceptible to degradation by the major pathway of cellular mRNA decay. Moreover, the uncapped 5′-triphosphate RNA produced by viral polymerases in infected cells is also recognized as non-self by the host, triggering an antiviral immune response in mammalian cells resulting in the production of interferons [43–45]. Therefore, many viruses have evolved to protect the 5′-ends of their mRNAs by either acquiring or synthesizing a cap structure that resembles the 5′ cap structure of cellular mRNAs, including the 2′-O-methylated cap-1 and cap-2 structures present in mRNAs of higher eukaryotes that facilitates the escape of viral mRNAs from detection by the host innate antiviral response [46,47]. The various RNA capping strategies employed by viruses in eukaryotic cells include the synthesis of the cap structure, using either the cellular capping machinery or virus-encoded capping enzymes, and acquiring the cap structure from cellular mRNAs by a process called

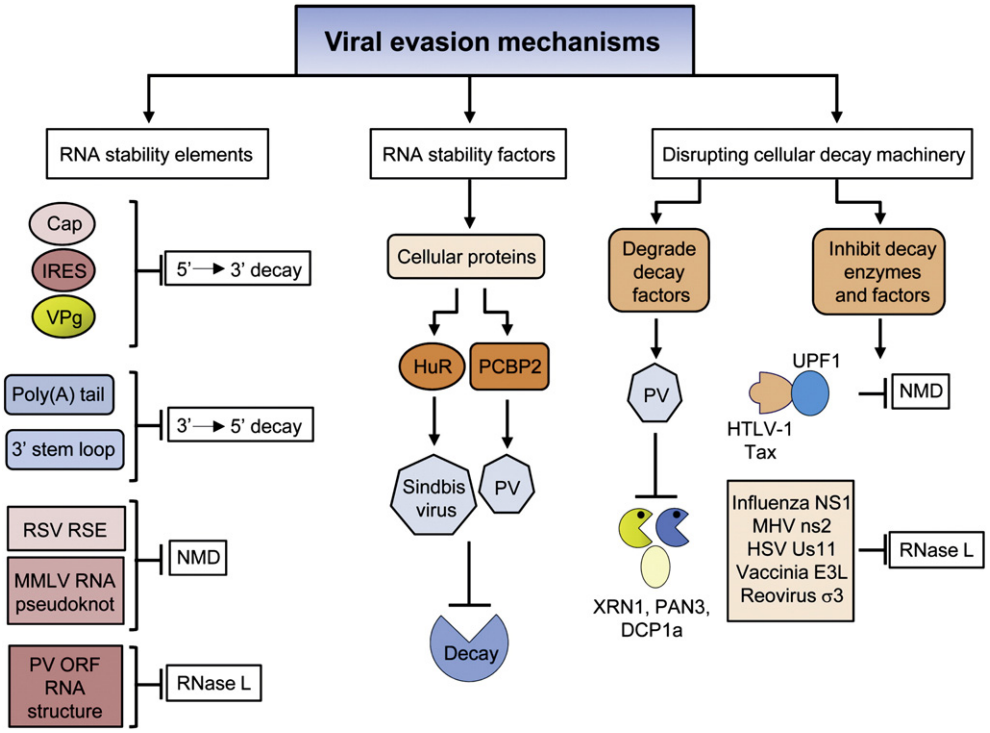

Fig. 2. Schematic representation of the viral evasion mechanisms. Examples of the various strategies of viral evasion of the cellular mRNA decay pathways. A description of these examples is provided in the text. PV, poliovirus.

"cap snatching" [48]. Most DNA viruses and RNA viruses of the family Retroviridae and Bornaviridae, which replicate in the nucleus and rely on cellular RNA polymerase II for their RNA transcription, utilize the cellular capping machinery to synthesize their cap structure [48,49]. Among the viruses that encode their own capping enzymes include the double-stranded DNA virus, vaccinia virus, of the Poxviridae family and RNA viruses of the families Reoviridae, Flaviviridae, Coronaviridae, Arteriviridae, Togaviridae, Rhabdoviridae, Filoviridae and Paramyxoviridae [48]. RNA viruses of the families Orthomyxoviridae, Arenaviridae and Bunyaviridae utilize a strategy called "cap snatching" to steal the cap structure, along with additional downstream sequences, from host mRNAs through endonucleolytic cleavage and prime the synthesis of viral RNAs [48,49]. This strategy not only results in the stabilization of the viral RNA transcript but also shifts the balance towards the selective expression of viral genes by removing cellular mRNAs through the targeting of the decapped cellular mRNAs to the RNA degradation machinery [50,51]. The cap snatching activity in influenza viruses that belong to the family Orthomyxoviridae resides in the polymerase subunits, PA and PB2, which carry the endonuclease and cap-binding domains, respectively [52–54]. In arenaviruses and

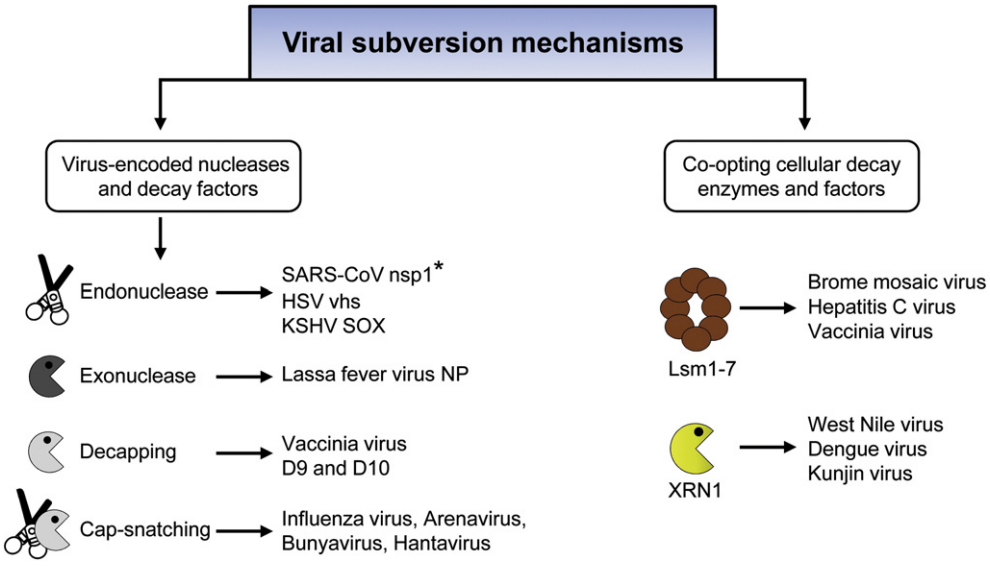

Fig. 3. Schematic representation of the viral subversion mechanisms. Selected examples of the viral mechanisms to subvert and exploit the cellular mRNA decay machinery. Mechanistic details are provided in the text. * denotes that the SARS-CoV nsp1-induced endonuclease activity could be host-encoded.

bunyaviruses, the N-terminus of the RNA polymerase, L protein, has been shown to possess an endonuclease activity that is essential for the cap-dependent viral mRNA transcription [55,56]. In hantaviruses, which belong to the family Bunyaviridae, the viral nucleocapsid protein, N, has been shown to cooperate with L protein in the cap snatching process by binding to the 5′ caps of cellular transcripts and rescuing them from degradation by the cellular decapping machinery in P bodies [57]. These 5′ capped cellular transcripts, stored in P bodies by N protein, are utilized by L protein for cap snatching and transcription initiation [57]. In contrast to the examples describe above, the yeast L-A double-stranded RNA virus from the family Totiviridae utilizes a novel cap snatching mechanism through a decapping enzymatic activity in the viral capsid protein Gag to generate capped viral transcripts [50]. Interestingly, the viral capping reaction involves the transfer of only the m^7Gp moiety from the cellular mRNA to the diphosphorylated 5′ end of the viral transcript and also requires the viral polymerase actively engaged in transcription [50]. The cooperation between the cap snatching and transcription reactions could ensure the efficient production of capsid protein from the newly synthesized viral RNA transcripts [58].

Some positive-strand RNA virus families like Picornaviridae, Caliciviridae and Astroviridae protect the 5′-end of their RNAs with a covalently attached viral genome-linked protein (VPg), which in the case of caliciviruses also facilitates the translation of viral mRNAs by directly interacting with the cap-binding protein eIF4E [59]. Picornaviruses and viruses belonging to the genera Hepacivirus and Pestivirus in the family Flaviviridae carry a structured element called the internal ribosome entry site (IRES) in the 5′ UTR that facilitates viral mRNA translation in a cap-independent manner and the presence of this highly structured IRES at the 5′-end could pose a barrier to the action of nucleases [59,60].

Many viruses protect the 3′-ends of their mRNAs by either carrying a poly(A) tail to mimic the cellular mRNAs or a stable 3′ stem loop structure, which stabilizes the transcript by inhibiting the action of exosome-associated 3′-5′ exonucleases [61]. The genomes and viral mRNAs of alphaviruses, picornaviruses and coronaviruses have a poly(A) tail at the 3′-end whereas flaviviruses, arenaviruses and bunyaviruses possess a stem loop structure in the 3′ UTR [62–64].

In addition to the cis-acting viral elements that counter the default pathway of mRNA turnover and facilitate viral mRNA translation, some viruses carry RNA elements that allow the viral mRNAs to escape detection and destruction by the specialized endonuclease-mediated decay pathways like NMD and RNase L. The substrates of the NMD surveillance pathway include mRNAs bearing a PTC or a long 3′ UTR between the termination codon and the poly(A) tail [32,65]. The RNA helicase UPF1 has been shown to be a critical and essential factor in sensing the 3′ UTR length on mRNAs by binding to the eukaryotic release factors eRF1 and eRF3 at the terminating ribosome followed by the phosphorylation of UPF1 by SMG-1 kinase resulting in routing of the mRNA to the NMD pathway for degradation [66]. The multiple open reading frames and a long 3′ UTR in retroviral mRNAs makes them a target of the NMD pathway and several retroviruses have evolved mechanisms to avoid detection and decay by this pathway. The RNA pseudoknot, downstream of the Gag translation termination codon, in the unspliced mRNA of Moloney murine leukemia virus (MMLV) promotes translational readthrough of the stop codon that disrupts the association of UPF1 with the mRNA, thereby preventing mRNA recognition and decay by the NMD pathway [66]. Rous sarcoma virus (RSV), another retrovirus, carries a cis-acting RNA sequence, called the RNA stability element (RSE), downstream of the gag termination codon, which allows the unspliced viral mRNA with an abnormally long 3′ UTR to be immune to degradation by the NMD pathway [67].

Viruses also carry elements in their mRNAs that facilitate their escape from cleavage by RNase L. Poliovirus mRNA is resistant to cleavage by RNase L due to the presence of an RNA structural element in the $3C^{pro}$ open reading frame (ORF) that inhibits the endonuclease domain of RNase L [68,69]. As RNase L cleaves RNAs predominantly after single-stranded UA and UU dinucleotides, the variably reduced frequencies of these dinucleotides within the ORFs of Hepatitis C virus (HCV) RNAs could be a viral evasion mechanism that results in reduced recognition and cleavage of viral mRNAs by RNase L [70]. An interesting observation is the presence of fewer UA and UU dinucleotides in HCV mRNAs from the interferon-resistant HCV genotypes, 1a and 1b, as compared to mRNAs from the interferon-sensitive genotypes, 2a, 2b, 3a and 3b [71]. The correlation between sensitivity to RNase L cleavage and interferon therapy in human patients suggests the role of the selection pressure imposed by the interferon-regulated RNase L pathway in HCV infection [70].

Some viruses utilize the cellular RNA stability factors to mask the instability elements in their mRNAs and promote viral transcript stability. One of these cellular RNA stability factors, HuR protein, binds to AU-rich and U-rich RNA instability elements on both cellular and viral mRNAs to regulate transcript stability [11,72–74]. HCV and alphaviruses, such as Sindbis virus, Semliki forest virus, Venezuelan equine encephalitis virus and Western equine encephalitis virus, have been shown to recruit HuR protein to the 3′ UTR of their RNAs to stabilize their transcripts and also activate translation [74–76]. In Sindbis virus, the binding of HuR to the U-rich sequences in the 3′ UTR of its mRNAs prevents the decay of viral RNAs by deadenylases and promotes a productive infection in mammalian and mosquito cells [74,77]. PCBP2 is another multifunctional cellular RNA-binding protein that plays an important role in regulating mRNA stability and translation [78]. HCV and picornaviruses, such as poliovirus and coxsackievirus, use the interaction of PCBP2 with the 5′ UTR of their RNAs to promote RNA stability, translation and RNA replication [79–82]. PCBP2 also interacts selectively with the 3′ UTR of rabies virus glycoprotein mRNA to promote its stability [83].

3.2. Interfering with cellular mRNA decay pathways

Besides ensuring the stability of their own transcripts through the acquisition of RNA stability elements and factors, viruses have also evolved mechanisms to disrupt or disarm the cellular decay machinery by inactivating the enzymes and co-factors involved in both the constitutive and virus-induced mRNA surveillance and degradation pathways. The cellular factors involved in deadenylation, decapping and 5′-3′ mRNA decay are either directly or indirectly targeted by polioviruses for degradation. Poliovirus infection induces the degradation of PAN3, a component of the deadenylase enzyme complex, DCP1a, a major decapping co-factor that has been shown to be a direct substrate of the poliovirus 3C proteinase as it contains a putative 3C protease recognition site, and XRN1, the major cellular 5′-3′ exonuclease [84]. Furthermore, PABPC1 and G3BP, which are components of SGs, are also cleaved by poliovirus 3C proteinase [85,86]. Thus, polioviruses, in addition to inhibiting deadenylation, also disrupt P bodies, possibly through the degradation of P-body proteins, DCP1a and PAN3, and prevent the assembly of SGs through the 3C-proteinase-mediated cleavage of G3BP. Flaviviruses, such as West Nile virus (WNV) and Dengue virus, also inhibit SG formation through the relocalization and interaction of the cellular SG components, T cell intracellular antigen-1 (TIA-1) and TIA-1-related protein (TIAR), with the viral replication complexes that facilitates flavivirus genomic RNA synthesis and also prevents the shutoff of host translation [87]. Both TIA-1 and TIAR bind to the WNV minus-strand 3′ terminal stem loop (SL) RNA and also colocalize with WNV and Dengue virus NS3 protein and viral dsRNA in infected mammalian cells [87]. Moreover, WNV infection also results in a reduction in the number of P bodies, although the mechanism of interference with P body assembly is not yet known [87].

Some viruses encode proteins that inhibit the NMD pathway in infected cells. The global downregulation of the NMD pathway by the virus-encoded Tax protein in human T-lymphotropic virus type 1 (HTLV-1)-infected cells is an example of such an interference mechanism [88]. Tax protein interacts with both the core NMD effector protein UPF1 as well as INT6, also called EIF3E, a subunit of the translation initiation factor eIF3 shown to be important for efficient degradation of mRNAs by NMD pathway [88]. This interaction along with the accumulation of phosphorylated UPF1-Tax complexes in P bodies, observed in HTLV-1-infected cells, disrupts the UPF1-INT6 association and presumably prevents the recycling of UPF1 leading to the inhibition of the NMD pathway [88]. Importantly, the consequence of the NMD inhibition in HTLV-1 infection is the stabilization of the viral transcript, encoding HTLV-1 basic leucine zipper factor (HBZ), and cellular mRNAs, encoding proteins that are involved in transactivation of HTLV-1 long terminal repeat (LTR) sequence-mediated gene expression [88].

Viruses have also evolved to counteract the interferon-induced RNase L pathway that is triggered in response to dsRNAs produced as replicative intermediates or annealed complementary viral RNAs of opposite polarities in virus-infected cells [13]. The dsRNA stimulates the 2′, 5′-oligoadenylate synthetase enzyme (OAS) that generates the RNase L activator, 2′, 5′-oligoadenylate (2-5A) from ATP and this activation results in the RNase L-mediated cleavage of viral RNAs as well as cellular RNAs, including ribosomal RNAs [13]. Several viruses overcome this obstacle by encoding proteins that bind to viral dsRNAs and physically shield the dsRNAs from recognition by OAS, which requires this ligand for activation [13]. Examples of viral dsRNA-binding proteins that utilize this strategy to inhibit the activation of OAS include vaccinia virus E3L, influenza virus NS1, reovirus σ3, human cytomegalovirus (HCMV) proteins TRS1 and IRS1 and herpes simplex virus (HSV) type 1 Us11 protein [13,89,90]. In the case of human immunodeficiency virus (HIV), the transactivation responsive region (TAR) at the 5′ termini of HIV-1 mRNAs activates OAS and the HIV Tat protein prevents this activation by binding to TAR [91–93]. In mouse hepatitis virus (MHV), a murine coronavirus, the 2, 5′-phosphodiesterase activity of the viral accessory protein nonstructural protein 2 (ns2), expressed by the hepatotropic and neurotropic MHV A59 strain, cleaves the RNase L activator, 2-5A, to block the activation of the RNase L pathway and this activity is essential for the development of virus-induced hepatitis in mice [94,95].

4. Viral exploitation and subversion of cellular mRNA decay pathways

Viruses have also evolved the ability to exploit the cellular mRNA decay machinery to their own advantage and promote mRNA turnover through virally-encoded factors and enzymes that serves to modulate both viral and host gene expression in infected cells. The following section will outline some of these subversion mechanisms in viruses.

4.1. Virus-encoded mRNA decay-promoting factors and nucleases

Many viruses adopt a seemingly self-destructive strategy of promoting accelerated mRNA turnover in infected cells by encoding nucleases and mRNA decay factors that can also potentially target viral mRNAs. Poxviruses, such as vaccinia virus, encode the Nudix hydrolase motif-containing mRNA decapping enzymes D9 and D10 that mediate the increased turnover of host mRNAs resulting in the removal of competing cellular mRNAs and shutdown of host protein synthesis [96–98]. Interestingly, D10 seems to have a preference for m^7GpppGm-capped cellular and early-phase viral transcripts rather than m^7GpppAm-capped intermediate and late-phase viral transcripts [96,98]. Thus, the differential decay of both cellular and early stage viral mRNAs combined with the expression of D10 in the late phase of infection suggests the role of D10 in the temporal regulation of viral gene expression in vaccinia virus-infected cells [96,98]. Both herpes simplex virus (HSV) and kaposi's sarcoma-associated herpesvirus (KSHV), in the α- and γ-herpesvirus subfamilies, respectively, encode proteins that induce host shutoff by promoting the global degradation of cellular mRNAs [99]. The virion host shutoff (vhs) protein of HSV possesses a potent mRNA-specific endonuclease activity that triggers the accelerated decay of cellular mRNAs and also destabilizes viral mRNAs [100–102]. Studies have reported that the nuclease activity of vhs is stimulated by the eukaryotic translation initiation factors eIF4B and eIF4H, a property that directs vhs to the translating mRNAs [103]. Furthermore, vhs associates with eIF4F cap-binding complex, probably through its interaction with eIF4AI and eIF4AII, which allows it to endonucleolytically cleave substrate mRNAs at preferred sites during translation initiation [104,105]. The ability of vhs to degrade viral mRNAs could facilitate the stage-specific expression of viral genes in HSV infection [99]. Similarly, the shutoff and exonuclease (SOX) protein of KSHV and the BGLF5 protein of the related Epstein–Barr virus (EBV), in addition to possessing DNA alkaline exonuclease (DNase) activity, also induce the degradation of cellular mRNAs [106–108]. KSHV SOX protein functions as a site-specific endonuclease that specifically degrades actively translating RNA polymerase II-transcribed mRNAs [109]. Although SOX protein co-sediments with the 40S ribosomal subunit-containing translation initiation complex, the recruitment of SOX to mRNAs does not require its association with the 40S ribosomal subunit and can occur in a ribosome-independent manner [109,110]. The SOX-induced cellular mRNA turnover is facilitated by the XRN1-mediated exonucleolytic decay of the SOX-generated cleavage intermediate [109]. Moreover, the inhibitory effect of SOX-induced depletion of cytoplasmic mRNAs on host gene expression is further amplified by the relocalization of PABPC1 to the nucleus, which results in hyperadenylation and the nuclear retention of RNA transcripts due to a nuclear mRNA export block [111,112]. It is unclear how the viral transcripts are able to overcome the effects of SOX protein in KSHV infection.

The severe acute respiratory syndrome coronavirus (SARS-CoV) nonstructural protein 1 (nsp1) uses a novel mechanism to induce the accelerated degradation of cellular mRNAs in SARS-CoV-infected cells [113,114]. Nsp1 inhibits the translation of host mRNAs at the initiation step and induces an endonucleolytic RNA cleavage in the 5′ UTR of capped host mRNAs [115–117]. These functions require the binding of nsp1 to the 40S ribosomal subunit that allows nsp1 to inactivate the translation function of the ribosome and also gain access to actively translating host mRNAs [116,117]. Notably, viral mRNAs are immune to nsp1-mediated RNA cleavage and the leader sequence, which is present in the 5′-end of all SARS-CoV mRNAs, protected the viral mRNAs from nsp1-induced endonucleolytic RNA cleavage [115]. Unlike the herpesvirus vhs and SOX proteins, SARS-CoV nsp1 does not possess any intrinsic nuclease activity and possibly, recruits a cellular endonuclease, the identity of which is still unknown. Furthermore, nsp1 does not target any specific sequence in the mRNA substrate for cleavage [115]. Like KSHV SOX protein, the nsp1-induced mRNA endonuclease activity liberates the cellular mRNAs from the rate-limiting steps of the default deadenylation-dependent decay pathway and the internally cleaved mRNA substrate is degraded by XRN1-mediated exonucleolytic decay [110]. Importantly, the outcome of the selective degradation of host mRNAs induced by SARS-CoV nsp1 along with the escape of viral mRNAs from nsp1-induced endonucleolytic RNA cleavage is the inhibition of cellular protein synthesis, including antiviral proteins, and the efficient accumulation of viral proteins in SARS-CoV-infected cells [114]. The nucleoprotein (NP) of Lassa fever virus (LASV), in the family Arenaviridae, possesses a 3′-5′ exoribonuclease activity with specificity for dsRNA substrates [118,119]. The exonuclease activity in LASV NP has been mapped to the C-terminal half of the protein, which also contains residues that are critical for its suppressive effect on

the innate IFN response [118,119]. In line with the overlap of these functional domains in NP, studies have demonstrated that the exonuclease activity of LASV NP is essential for its ability to suppress the innate immune system [118,119].

In addition to the direct action of the virally-encoded nucleases on cellular mRNAs, the cap-snatching mechanism in Bunyaviruses, Orthomyxoviruses and Arenaviruses could also indirectly destabilize cellular mRNAs by generating substrates for XRN1-mediated exonucleolytic decay. Similarly, in yeast L-A virus, the cap snatching activity of Gag protein also facilitates the expression of viral mRNAs, probably through an indirect mechanism by generating decapped cellular mRNA substrates as decoys for yeast XRN1-mediated decay that deflects the attention away from viral RNAs [51,120].

Besides eluding and attacking the cellular mRNA decay machinery, viruses have also evolved ways to adeptly exploit the cellular mRNA decay factors and pathways for their replication and gene expression. Several viruses, such as brome mosaic virus (BMV), HCV and vaccinia virus, have been shown to use the cellular decapping activator Lsm1-7 complex to promote viral RNA replication, translation and mRNA stability [121–125]. Studies of BMV replication in yeast have shown that Lsm1-7 complex directly binds to an internal A-rich region and the tRNA-like structure at the 3′ UTR of BMV genome and along with the yeast decapping activators, Pat1p and Dhh1p, is required for viral RNA translation and efficient recruitment of BMV RNA to the replication complex [122–124]. In poxviruses, such as vaccinia virus and cowpox virus, some early phase and a majority of immediate and late phase viral mRNAs have an unusual 5′ poly(A) leader of variable length located upstream of the translation initiation codon [126,127]. Surprisingly, recombinant Lsm 1-7 complex specifically binds to these 5′ poly(A) tracts and stabilizes the mRNAs by inhibiting 3′-5′ exonucleases as well as decapping [121]. It has been proposed that the Lsm1-7 complex could mediate the stabilization of immediate and late phase mRNAs of vaccinia virus by binding to these 5′ poly(A) tracts and inhibiting both decapping and 3′-5′ decay [121]. Perhaps, this could also be the escape mechanism of vaccinia virus late phase mRNAs from the decapping activity of the virus-encoded decapping enzyme D10. Similarly, recombinant Lsm1-7 complex specifically interacted with the UTRs of HCV RNA and siRNA-mediated downregulation of Lsm1, Rck/p54 and PatL1 inhibited HCV RNA translation and replication suggesting the positive role of these proteins in regulating HCV RNA replication and gene expression [125,128]. HCV also utilizes an unconventional strategy to stabilize its RNA by recruiting a RISC-like complex of Ago2 protein and the liver-specific miRNA, miR-122, to the 5′ UTR that protects the viral genome from 5′ exonucleases like XRN1 [129,130]. A somewhat similar counterintuitive finding is the induction of SGs by HCV through the phosphorylation of dsRNA-activated protein kinase R (PKR) to downregulate the translation of antiviral proteins [131]. Interestingly, HCV also exploits the SG machinery directly for its own purpose by usurping the SG proteins TIA-1, TIAR and G3BP to promote RNA replication as well as the production of infectious particles [131]. The cellular 3′-5′ exonuclease XRN1 is utilized by many arthropod-borne flaviviruses, including WNV, Dengue virus, Kunjin virus, Japanese encephalitis virus and yellow fever virus, to produce a short noncoding RNA (sfRNA) during infection [132]. The sfRNA, derived from the 3′ UTR of the viral genome is generated by the stalling of XRN1 on the viral genome due to the presence of RNA pseudoknot structures resulting in the incomplete degradation of viral genomic RNA [133]. A secondary effect of the stalled XRN1 is the inhibition of its activity in flavivirus-infected cells that could profoundly alter the regulation of cellular mRNA decay pathways and the profile of cellular proteins, including those involved in antiviral immune response [134]. In fact, a WNV mutant, deficient in sfRNA production, replicates poorly in wild-type mice and its replication and virulence is rescued in type I IFN receptor knockout mice [135]. This observation underscores the functional role of sfRNA in the evasion of type I IFN response by WNV and also suggests the importance of sfRNA in flavivirus pathogenesis, although the mechanism of sfRNA-mediated evasion is still unclear [135]. Finally, the yeast P-body-associated proteins DCP1, DCP2, XRN1, Dhh1p, Pat1p and Lsm1 are used by the retrovirus-like retrotransposons Ty1 and Ty3 to promote efficient retrotransposition and packaging of RNA into virus-like particles (VLPs) [136,137].

5. Concluding remarks

A broader view of the cellular mRNA decay machinery, as not just an obstacle that viruses overcome but also as the host machinery that viruses harness for their own benefit, has now emerged from the knowledge gained through numerous studies exploring the different adaptation strategies of viruses. Viruses have played a vital role in the discovery of cellular mRNA stability and decay components, like the mRNA cap structure and the SKI proteins, which highlights the importance of viruses as valuable tools for understanding the regulation of fundamental cellular processes [138–142]. The large repertoire of viral strategies that facilitate a successful and productive interaction with the cellular mRNA decay apparatus has also revealed some potential viral targets that can be exploited for the development of novel therapeutic antiviral drugs. The RNA capping machinery of viruses represents one such attractive target and designing specific inhibitors of viral methyltransferases (MTases), especially the 2′-O methyltransferase (2′-O MTAse) activity that promotes the escape of viruses from the host innate immune response, and cap-snatching endonucleases can be a promising antiviral strategy. Several studies have described the inhibitors of these enzymes, including the broad-spectrum antiviral Ribavirin, which, in addition to its other pleiotropic effects on viral replication, has also been shown to inhibit the dengue virus 2′-O MTase activity [143].

There are still gaps in our knowledge of the role of mRNA turnover pathways in viral infections and several fundamental and important questions remain to be answered. How do cytoplasmic RNA viruses with genomes carrying multiple open reading frames and long 3′ UTRs avoid detection by the alternative surveillance pathway of NMD that senses the 3′ UTR length? Is it simply due to the cytoplasmically-generated viral mRNPs lacking the nucleus-derived mRNA quality control proteins that mediate recognition or are there unidentified viral mechanisms that shield the viral mRNAs from the cellular surveillance machinery? Does SARS-CoV nsp1 recruit a novel eukaryotic endoribonuclease that targets translating mRNAs at the initiation stage as all the known eukaryotic endoribonucleases that cleave mRNAs in association with ribosomes act during the elongation stage of translation [115,116]? How do viral mRNAs carrying the stability determinants of cellular mRNAs escape degradation in the case of viruses that encode or induce cellular mRNA decay enzymes? Future investigations exploring the intricate dynamics of the interaction between viruses and host mRNA decay pathways could provide important insights into viral adaptation strategies and also lead to the discovery of previously unknown mRNA surveillance pathways and regulatory mechanisms.

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References

[1] S. Komili, P.A. Silver, Coupling and coordination in gene expression processes: a systems biology view, Nat. Rev. Genet. 9 (2008) 38–48.
[2] S.E. Munchel, R.K. Shultzaberger, N. Takizawa, K. Weis, Dynamic profiling of mRNA turnover reveals gene-specific and system-wide regulation of mRNA decay, Mol. Biol. Cell 22 (2011) 2787–2795.
[3] A.B. Sachs, Messenger RNA degradation in eukaryotes, Cell 74 (1993) 413–421.

[4] B. Schwanhausser, D. Busse, N. Li, G. Dittmar, J. Schuchhardt, J. Wolf, W. Chen, M. Selbach, Global quantification of mammalian gene expression control, Nature 473 (2011) 337–342.
[5] I. Behm-Ansmant, I. Kashima, J. Rehwinkel, J. Sauliere, N. Wittkopp, E. Izaurralde, mRNA quality control: an ancient machinery recognizes and degrades mRNAs with nonsense codons, FEBS Lett. 581 (2007) 2845–2853.
[6] M.K. Doma, R. Parker, RNA quality control in eukaryotes, Cell 131 (2007) 660–668.
[7] M.B. Fasken, A.H. Corbett, Process or perish: quality control in mRNA biogenesis, Nat. Struct. Mol. Biol. 12 (2005) 482–488.
[8] J. Rehwinkel, J. Raes, E. Izaurralde, Nonsense-mediated mRNA decay: target genes and functional diversification of effectors, Trends Biochem. Sci. 31 (2006) 639–646.
[9] N.L. Garneau, J. Wilusz, C.J. Wilusz, The highways and byways of mRNA decay, Nat. Rev. Mol. Cell Biol. 8 (2007) 113–126.
[10] R. Parker, H. Song, The enzymes and control of eukaryotic mRNA turnover, Nat. Struct. Mol. Biol. 11 (2004) 121–127.
[11] D.R. Schoenberg, L.E. Maquat, Regulation of cytoplasmic mRNA decay, Nat. Rev. Genet. 13 (2012) 246–259.
[12] X. Wu, G. Brewer, The regulation of mRNA stability in mammalian cells: 2.0, Gene 500 (2012) 10–21.
[13] R.H. Silverman, Viral encounters with 2′, 5′-oligoadenylate synthetase and RNase L during the interferon antiviral response, J. Virol. 81 (2007) 12720–12729.
[14] J.E. Darnell Jr., Transcription units for mRNA production in eukaryotic cells and their DNA viruses, Prog. Nucleic Acid Res. Mol. Biol. 22 (1979) 327–353.
[15] M.J. Moore, N.J. Proudfoot, Pre-mRNA processing reaches back to transcription and ahead to translation, Cell 136 (2009) 688–700.
[16] A.J. Shatkin, Capping of eucaryotic mRNAs, Cell 9 (1976) 645–653.
[17] P. Bernstein, S.W. Peltz, J. Ross, The poly(A)-poly(A)-binding protein complex is a major determinant of mRNA stability in vitro, Mol. Cell. Biol. 9 (1989) 659–670.
[18] W. Filipowicz, Y. Furuichi, J.M. Sierra, S. Muthukrishnan, A.J. Shatkin, S. Ochoa, A protein binding the methylated 5′-terminal sequence, m7GpppN, of eukaryotic messenger RNA, Proc. Natl. Acad. Sci. U. S. A. 73 (1976) 1559–1563.
[19] C.J. Decker, R. Parker, A turnover pathway for both stable and unstable mRNAs in yeast: evidence for a requirement for deadenylation, Genes Dev. 7 (1993) 1632–1643.
[20] C.Y. Chen, A.B. Shyu, Mechanisms of deadenylation-dependent decay, Wiley Interdiscip. Rev. RNA 2 (2010) 167–183.
[21] A.C. Goldstrohm, M. Wickens, Multifunctional deadenylase complexes diversify mRNA control, Nat. Rev. Mol. Cell Biol. 9 (2008) 337–344.
[22] J. Houseley, J. LaCava, D. Tollervey, RNA-quality control by the exosome, Nat. Rev. Mol. Cell Biol. 7 (2006) 529–539.
[23] S. Lykke-Andersen, R. Tomecki, T.H. Jensen, A. Dziembowski, The eukaryotic RNA exosome: same scaffold but variable catalytic subunits, RNA Biol. 8 (2011) 61–66.
[24] H. Liu, N.D. Rodgers, X. Jiao, M. Kiledjian, The scavenger mRNA decapping enzyme DcpS is a member of the HIT family of pyrophosphatases, EMBO J. 21 (2002) 4699–4708.
[25] Z. Wang, M. Kiledjian, Functional link between the mammalian exosome and mRNA decapping, Cell 107 (2001) 751–762.
[26] M.G. Song, Y. Li, M. Kiledjian, Multiple mRNA decapping enzymes in mammalian cells, Mol. Cell 40 (2010) 423–432.
[27] C.L. Hsu, A. Stevens, Yeast cells lacking 5′→3′ exoribonuclease 1 contain mRNA species that are poly(A) deficient and partially lack the 5′ cap structure, Mol. Cell. Biol. 13 (1993) 4826–4835.
[28] R. Tomecki, A. Dziembowski, Novel endoribonucleases as central players in various pathways of eukaryotic RNA metabolism, RNA 16 (2010) 1692–1724.
[29] Y. Zhu, G. Gao, ZAP-mediated mRNA degradation, RNA Biol. 5 (2008) 65–67.
[30] Y. Xuan, L. Liu, S. Shen, H. Deng, G. Gao, Zinc finger antiviral protein inhibits murine gammaherpesvirus 68 m2 expression and regulates viral latency in cultured cells, J. Virol. 86 (2012) 12431–12434.
[31] Y. Zhu, X. Wang, S.P. Goff, G. Gao, Translational repression precedes and is required for ZAP-mediated mRNA decay, EMBO J. 31 (2012) 4236–4246.
[32] Y.F. Chang, J.S. Imam, M.F. Wilkinson, The nonsense-mediated decay RNA surveillance pathway, Annu. Rev. Biochem. 76 (2007) 51–74.
[33] E. Huntzinger, I. Kashima, M. Fauser, J. Sauliere, E. Izaurralde, SMG6 is the catalytic endonuclease that cleaves mRNAs containing nonsense codons in metazoan, RNA 14 (2008) 2609–2617.
[34] P.A. Frischmeyer, A. van Hoof, K. O'Donnell, A.L. Guerrerio, R. Parker, H.C. Dietz, An mRNA surveillance mechanism that eliminates transcripts lacking termination codons, Science 295 (2002) 2258–2261.
[35] A. van Hoof, P.A. Frischmeyer, H.C. Dietz, R. Parker, Exosome-mediated recognition and degradation of mRNAs lacking a termination codon, Science 295 (2002) 2262–2264.
[36] E. Huntzinger, E. Izaurralde, Gene silencing by microRNAs: contributions of translational repression and mRNA decay, Nat. Rev. Genet. 12 (2011) 99–110.
[37] U. Sheth, R. Parker, Decapping and decay of messenger RNA occur in cytoplasmic processing bodies, Science 300 (2003) 805–808.
[38] A. Eulalio, I. Behm-Ansmant, E. Izaurralde, P bodies: at the crossroads of post-transcriptional pathways, Nat. Rev. Mol. Cell Biol. 8 (2007) 9–22.
[39] M. Brengues, D. Teixeira, R. Parker, Movement of eukaryotic mRNAs between polysomes and cytoplasmic processing bodies, Science 310 (2005) 486–489.
[40] P. Anderson, N. Kedersha, Stress granules: the Tao of RNA triage, Trends Biochem. Sci. 33 (2008) 141–150.
[41] J.R. Buchan, R. Parker, Eukaryotic stress granules: the ins and outs of translation, Mol. Cell 36 (2009) 932–941.
[42] N. Kedersha, G. Stoecklin, M. Ayodele, P. Yacono, J. Lykke-Andersen, M.J. Fritzler, D. Scheuner, R.J. Kaufman, D.E. Golan, P. Anderson, Stress granules and processing bodies are dynamically linked sites of mRNP remodeling, J. Cell Biol. 169 (2005) 871–884.
[43] S.R. Nallagatla, R. Toroney, P.C. Bevilacqua, A brilliant disguise for self RNA: 5′-end and internal modifications of primary transcripts suppress elements of innate immunity, RNA Biol. 5 (2008) 140–144.
[44] A. Pichlmair, O. Schulz, C.P. Tan, T.I. Naslund, P. Liljestrom, F. Weber, C. Reis e Sousa, RIG-I-mediated antiviral responses to single-stranded RNA bearing 5′-phosphates, Science 314 (2006) 997–1001.
[45] J. Rehwinkel, C.P. Tan, D. Goubau, O. Schulz, A. Pichlmair, K. Bier, N. Robb, F. Vreede, W. Barclay, E. Fodor, C. Reis e Sousa, RIG-I detects viral genomic RNA during negative-strand RNA virus infection, Cell 140 (2010) 397–408.
[46] S. Daffis, K.J. Szretter, J. Schriewer, J. Li, S. Youn, J. Errett, T.Y. Lin, S. Schneller, R. Zust, H. Dong, V. Thiel, G.C. Sen, V. Fensterl, W.B. Klimstra, T.C. Pierson, R.M. Buller, M. Gale Jr., P.Y. Shi, M.S. Diamond, 2′-O methylation of the viral mRNA cap evades host restriction by IFIT family members, Nature 468 (2010) 452–456.
[47] R. Zust, L. Cervantes-Barragan, M. Habjan, R. Maier, B.W. Neuman, J. Ziebuhr, K.J. Szretter, S.C. Baker, W. Barchet, M.S. Diamond, S.G. Siddell, B. Ludewig, V. Thiel, Ribose 2′-O-methylation provides a molecular signature for the distinction of self and non-self mRNA dependent on the RNA sensor Mda5, Nat. Immunol. 12 (2011) 137–143.
[48] E. Decroly, F. Ferron, J. Lescar, B. Canard, Conventional and unconventional mechanisms for capping viral mRNA, Nat. Rev. Microbiol. 10 (2012) 51–65.
[49] E.V. Koonin, B. Moss, Viruses know more than one way to don a cap, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 3283–3284.
[50] T. Fujimura, R. Esteban, Cap-snatching mechanism in yeast L-A double-stranded RNA virus, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 17667–17671.
[51] H. Naitow, J. Tang, M. Canady, R.B. Wickner, J.E. Johnson, L-A virus at 3.4 A resolution reveals particle architecture and mRNA decapping mechanism, Nat. Struct. Biol. 9 (2002) 725–728.
[52] A. Dias, D. Bouvier, T. Crepin, A.A. McCarthy, D.J. Hart, F. Baudin, S. Cusack, R.W. Ruigrok, The cap-snatching endonuclease of influenza virus polymerase resides in the PA subunit, Nature 458 (2009) 914–918.
[53] D. Guilligay, F. Tarendeau, P. Resa-Infante, R. Coloma, T. Crepin, P. Sehr, J. Lewis, R.W. Ruigrok, J. Ortin, D.J. Hart, S. Cusack, The structural basis for cap binding by influenza virus polymerase subunit PB2, Nat. Struct. Mol. Biol. 15 (2008) 500–506.
[54] P. Yuan, M. Bartlam, Z. Lou, S. Chen, J. Zhou, X. He, Z. Lv, R. Ge, X. Li, T. Deng, E. Fodor, Z. Rao, Y. Liu, Crystal structure of an avian influenza polymerase PA(N) reveals an endonuclease active site, Nature 458 (2009) 909–913.
[55] B. Morin, B. Coutard, M. Lelke, F. Ferron, R. Kerber, S. Jamal, A. Frangeul, C. Baronti, R. Charrel, X. de Lamballerie, C. Vonrhein, J. Lescar, G. Bricogne, S. Gunther, B. Canard, The N-terminal domain of the arenavirus L protein is an RNA endonuclease essential in mRNA transcription, PLoS Pathog. 6 (2010) e1001038.
[56] J. Reguera, F. Weber, S. Cusack, Bunyaviridae RNA polymerases (L-protein) have an N-terminal, influenza-like endonuclease domain, essential for viral cap-dependent transcription, PLoS Pathog. 6 (2010) e1001101.
[57] M.A. Mir, W.A. Duran, B.L. Hjelle, C. Ye, A.T. Panganiban, Storage of cellular 5′ mRNA caps in P bodies for viral cap-snatching, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 19294–19299.
[58] T. Fujimura, R. Esteban, Cap snatching of yeast L-A double-stranded RNA virus can operate in trans and requires viral polymerase actively engaging in transcription, J. Biol. Chem. 287 (2012) 12797–12804.
[59] E. Martinez-Salas, A. Pacheco, P. Serrano, N. Fernandez, New insights into internal ribosome entry site elements relevant for viral gene expression, J. Gen. Virol. 89 (2008) 611–626.
[60] L. Balvay, R. Soto Rifo, E.P. Ricci, D. Decimo, T. Ohlmann, Structural and functional diversity of viral IRESes, Biochim. Biophys. Acta 1789 (2009) 542–557.
[61] L.P. Ford, J. Wilusz, 3′-Terminal RNA structures and poly(U) tracts inhibit initiation by a 3′→5′ exonuclease in vitro, Nucleic Acids Res. 27 (1999) 1159–1167.
[62] M.A. Brinton, A.V. Fernandez, J.H. Dispoto, The 3′-nucleotides of flavivirus genomic RNA form a conserved secondary structure, Virology 153 (1986) 113–121.
[63] C. Geerts-Dimitriadou, Y.Y. Lu, C. Geertsema, R. Goldbach, R. Kormelink, Analysis of the Tomato spotted wilt virus ambisense S RNA-encoded hairpin structure in translation, PLoS One 7 (2012) e31013.
[64] B.J. Meyer, P.J. Southern, Concurrent sequence analysis of 5′ and 3′ RNA termini by intramolecular circularization reveals 5′ nontemplated bases and 3′ terminal heterogeneity for lymphocytic choriomeningitis virus mRNAs, J. Virol. 67 (1993) 2621–2627.
[65] A.B. Eberle, L. Stalder, H. Mathys, R.Z. Orozco, O. Muhlemann, Posttranscriptional gene regulation by spatial rearrangement of the 3′ untranslated region, PLoS Biol. 6 (2008) e92.
[66] J.R. Hogg, S.P. Goff, Upf1 senses 3′UTR length to potentiate mRNA decay, Cell 143 (2010) 379–389.
[67] J.E. Weil, M. Hadjithomas, K.L. Beemon, Structural characterization of the Rous sarcoma virus RNA stability element, J. Virol. 83 (2009) 2119–2129.
[68] J.Q. Han, H.L. Townsend, B.K. Jha, J.M. Paranjape, R.H. Silverman, D.J. Barton, A phylogenetically conserved RNA structure in the poliovirus open reading frame inhibits the antiviral endoribonuclease RNase L, J. Virol. 81 (2007) 5561–5572.
[69] H.L. Townsend, B.K. Jha, J.Q. Han, N.K. Maluf, R.H. Silverman, D.J. Barton, A viral RNA competitively inhibits the antiviral endoribonuclease domain of RNase L, RNA 14 (2008) 1026–1036.
[70] C.L. Washenberger, J.Q. Han, K.J. Kechris, B.K. Jha, R.H. Silverman, D.J. Barton, Hepatitis C virus RNA: dinucleotide frequencies and cleavage by RNase L, Virus Res. 130 (2007) 85–95.

[71] J.Q. Han, D.J. Barton, Activation and evasion of the antiviral 2′-5′ oligoadenylate synthetase/ribonuclease L pathway by hepatitis C virus mRNA, RNA 8 (2002) 512–525.
[72] K. Abdelmohsen, M. Gorospe, Posttranscriptional regulation of cancer traits by HuR, Wiley Interdiscip. Rev. RNA 1 (2010) 214–229.
[73] D. Harris, Z. Zhang, B. Chaubey, V.N. Pandey, Identification of cellular factors associated with the 3′-nontranslated region of the hepatitis C virus genome, Mol. Cell. Proteomics 5 (2006) 1006–1018.
[74] K.J. Sokoloski, A.M. Dickson, E.L. Chaskey, N.L. Garneau, C.J. Wilusz, J. Wilusz, Sindbis virus usurps the cellular HuR protein to stabilize its transcripts and promote productive infections in mammalian and mosquito cells, Cell Host Microbe 8 (2010) 196–207.
[75] M. Korf, D. Jarczak, C. Beger, M.P. Manns, M. Kruger, Inhibition of hepatitis C virus translation and subgenomic replication by siRNAs directed against highly conserved HCV sequence and cellular HCV cofactors, J. Hepatol. 43 (2005) 225–234.
[76] A. Rivas-Aravena, P. Ramdohr, M. Vallejos, F. Valiente-Echeverria, V. Dormoy-Raclet, F. Rodriguez, K. Pino, C. Holzmann, J.P. Huidobro-Toro, I.E. Gallouzi, M. Lopez-Lastra, The Elav-like protein HuR exerts translational control of viral internal ribosome entry sites, Virology 392 (2009) 178–185.
[77] N.L. Garneau, K.J. Sokoloski, M. Opyrchal, C.P. Neff, C.J. Wilusz, J. Wilusz, The 3′ untranslated region of sindbis virus represses deadenylation of viral transcripts in mosquito and Mammalian cells, J. Virol. 82 (2008) 880–892.
[78] A.V. Makeyev, S.A. Liebhaber, The poly(C)-binding proteins: a multiplicity of functions and a search for mechanisms, RNA 8 (2002) 265–278.
[79] S. Fukushi, M. Okada, T. Kageyama, F.B. Hoshino, K. Nagai, K. Katayama, Interaction of poly(rC)-binding protein 2 with the 5′-terminal stem loop of the hepatitis C-virus genome, Virus Res. 73 (2001) 67–79.
[80] S.A. Ogram, A. Spear, N. Sharma, J.B. Flanegan, The 5′CL-PCBP RNP complex, 3′ poly(A) tail and 2A(pro) are required for optimal translation of poliovirus RNA, Virology 397 (2010) 14–22.
[81] A. Spear, N. Sharma, J.B. Flanegan, Protein-RNA tethering: the role of poly(C) binding protein 2 in poliovirus RNA replication, Virology 374 (2008) 280–291.
[82] L. Wang, K.S. Jeng, M.M. Lai, Poly(C)-binding protein 2 interacts with sequences required for viral replication in the hepatitis C virus (HCV) 5′ untranslated region and directs HCV RNA replication through circularizing the viral genome, J. Virol. 85 (2011) 7954–7964.
[83] S. Palusa, C. Ndaluka, R.A. Bowen, C.J. Wilusz, J. Wilusz, The 3′ untranslated region of the rabies virus glycoprotein mRNA specifically interacts with cellular PCBP2 protein and promotes transcript stability, PLoS One 7 (2012) e33561.
[84] J.D. Dougherty, J.P. White, R.E. Lloyd, Poliovirus-mediated disruption of cytoplasmic processing bodies, J. Virol. 85 (2011) 64–75.
[85] N.M. Kuyumcu-Martinez, M. Joachims, R.E. Lloyd, Efficient cleavage of ribosome-associated poly(A)-binding protein by enterovirus 3C protease, J. Virol. 76 (2002) 2062–2074.
[86] J.P. White, A.M. Cardenas, W.E. Marissen, R.E. Lloyd, Inhibition of cytoplasmic mRNA stress granule formation by a viral proteinase, Cell Host Microbe 2 (2007) 295–305.
[87] M.M. Emara, M.A. Brinton, Interaction of TIA-1/TIAR with West Nile and dengue virus products in infected cells interferes with stress granule formation and processing body assembly, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 9041–9046.
[88] V. Mocquet, J. Neusiedler, F. Rende, D. Cluet, J.P. Robin, J.M. Terme, M. Duc Dodon, J. Wittmann, C. Morris, H. Le Hir, V. Ciminale, P. Jalinot, The human T-lymphotropic virus type 1 tax protein inhibits nonsense-mediated mRNA decay by interacting with INT6/EIF3E and UPF1, J. Virol. 86 (2012) 7530–7543.
[89] E.E. Marshall, C.J. Bierle, W. Brune, A.P. Geballe, Essential role for either TRS1 or IRS1 in human cytomegalovirus replication, J. Virol. 83 (2009) 4112–4120.
[90] R. Sanchez, I. Mohr, Inhibition of cellular 2′-5′ oligoadenylate synthetase by the herpes simplex virus type 1 Us11 protein, J. Virol. 81 (2007) 3455–3464.
[91] R.K. Maitra, N.A. McMillan, S. Desai, J. McSwiggen, A.G. Hovanessian, G. Sen, B.R. Williams, R.H. Silverman, HIV-1 TAR RNA has an intrinsic ability to activate interferon-inducible enzymes, Virology 204 (1994) 823–827.
[92] H.C. Schroder, D. Ugarkovic, R. Wenger, P. Reuter, T. Okamoto, W.E. Muller, Binding of Tat protein to TAR region of human immunodeficiency virus type 1 blocks TAR-mediated activation of (2′-5′)oligoadenylate synthetase, AIDS Res. Hum. Retroviruses 6 (1990) 659–672.
[93] D.N. SenGupta, R.H. Silverman, Activation of interferon-regulated, dsRNA-dependent enzymes by human immunodeficiency virus-1 leader RNA, Nucleic Acids Res. 17 (1989) 969–978.
[94] L. Zhao, B.K. Jha, A. Wu, R. Elliott, J. Ziebuhr, A.E. Gorbalenya, R.H. Silverman, S.R. Weiss, Antagonism of the interferon-induced OAS-RNase L pathway by murine coronavirus ns2 protein is required for virus replication and liver pathology, Cell Host Microbe 11 (2012) 607–616.
[95] L. Zhao, K.M. Rose, R. Elliott, N. Van Rooijen, S.R. Weiss, Cell-type-specific type I interferon antagonism influences organ tropism of murine coronavirus, J. Virol. 85 (2011) 10058–10068.
[96] A.G. McLennan, Decapitation: poxvirus makes RNA lose its head, Trends Biochem. Sci. 32 (2007) 297–299.
[97] S. Parrish, B. Moss, Characterization of a second vaccinia virus mRNA-decapping enzyme conserved in poxviruses, J. Virol. 81 (2007) 12973–12978.
[98] S. Parrish, W. Resch, B. Moss, Vaccinia virus D10 protein has mRNA decapping activity, providing a mechanism for control of host and viral gene expression, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 2139–2144.
[99] B.A. Glaunsinger, D.E. Ganem, Messenger RNA turnover and its regulation in herpesviral infection, Adv. Virus Res. 66 (2006) 337–394.
[100] M.M. Elgadi, C.E. Hayes, J.R. Smiley, The herpes simplex virus vhs protein induces endoribonucleolytic cleavage of target RNAs in cell extracts, J. Virol. 73 (1999) 7153–7164.
[101] A.D. Kwong, N. Frenkel, Herpes simplex virus-infected cells contain a function(s) that destabilizes both host and viral mRNAs, Proc. Natl. Acad. Sci. U. S. A. 84 (1987) 1926–1930.
[102] A.A. Oroskar, G.S. Read, Control of mRNA stability by the virion host shutoff function of herpes simplex virus, J. Virol. 63 (1989) 1897–1906.
[103] R.C. Doepker, W.L. Hsu, H.A. Saffran, J.R. Smiley, Herpes simplex virus virion host shutoff protein is stimulated by translation initiation factors eIF4B and eIF4H, J. Virol. 78 (2004) 4684–4699.
[104] H.G. Page, G.S. Read, The virion host shutoff endonuclease (UL41) of herpes simplex virus interacts with the cellular cap-binding complex eIF4F, J. Virol. 84 (2010) 6886–6890.
[105] L.A. Shiflett, G.S. Read, mRNA decay during herpes simplex virus (HSV) infections: mutations that affect translation of an mRNA influence the sites at which it is cleaved by the HSV virion host shutoff (Vhs) protein, J. Virol. 87 (2013) 94–109.
[106] M. Buisson, T. Geoui, D. Flot, N. Tarbouriech, M.E. Ressing, E.J. Wiertz, W.P. Burmeister, A bridge crosses the active-site canyon of the Epstein–Barr virus nuclease with DNase and RNase activities, J. Mol. Biol. 391 (2009) 717–728.
[107] B. Glaunsinger, L. Chavez, D. Ganem, The exonuclease and host shutoff functions of the SOX protein of Kaposi's sarcoma-associated herpesvirus are genetically separable, J. Virol. 79 (2005) 7396–7401.
[108] M. Rowe, B. Glaunsinger, D. van Leeuwen, J. Zuo, D. Sweetman, D. Ganem, J. Middeldorp, E.J. Wiertz, M.E. Ressing, Host shutoff during productive Epstein–Barr virus infection is mediated by BGLF5 and may contribute to immune evasion, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 3366–3371.
[109] S. Covarrubias, M.M. Gaglia, G.R. Kumar, W. Wong, A.O. Jackson, B.A. Glaunsinger, Coordinated destruction of cellular messages in translation complexes by the gammaherpesvirus host shutoff factor and the mammalian exonuclease Xrn1, PLoS Pathog. 7 (2011) e1002339.
[110] M.M. Gaglia, S. Covarrubias, W. Wong, B.A. Glaunsinger, A common strategy for host RNA degradation by divergent viruses, J. Virol. 86 (2012) 9527–9530.
[111] G.R. Kumar, B.A. Glaunsinger, Nuclear import of cytoplasmic poly(A) binding protein restricts gene expression via hyperadenylation and nuclear retention of mRNA, Mol. Cell. Biol. 30 (2010) 4996–5008.
[112] Y.J. Lee, B.A. Glaunsinger, Aberrant herpesvirus-induced polyadenylation correlates with cellular messenger RNA destruction, PLoS Biol. 7 (2009) e1000107.
[113] W. Kamitani, K. Narayanan, C. Huang, K. Lokugamage, T. Ikegami, N. Ito, H. Kubo, S. Makino, Severe acute respiratory syndrome coronavirus nsp1 protein suppresses host gene expression by promoting host mRNA degradation, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 12885–12890.
[114] K. Narayanan, C. Huang, K. Lokugamage, W. Kamitani, T. Ikegami, C.T. Tseng, S. Makino, Severe acute respiratory syndrome coronavirus nsp1 suppresses host gene expression, including that of type I interferon, in infected cells, J. Virol. 82 (2008) 4471–4479.
[115] C. Huang, K.G. Lokugamage, J.M. Rozovics, K. Narayanan, B.L. Semler, S. Makino, SARS coronavirus nsp1 protein induces template-dependent endonucleolytic cleavage of mRNAs: viral mRNAs are resistant to nsp1-induced RNA cleavage, PLoS Pathog. 7 (2011) e1002433.
[116] W. Kamitani, C. Huang, K. Narayanan, K.G. Lokugamage, S. Makino, A two-pronged strategy to suppress host protein synthesis by SARS coronavirus Nsp1 protein, Nat. Struct. Mol. Biol. 16 (2009) 1134–1140.
[117] K.G. Lokugamage, K. Narayanan, C. Huang, S. Makino, SARS coronavirus nsp1 protein is a novel eukaryotic translation inhibitor that represses multiple steps of translation initiation, J. Virol. 86 (2012) 13598–13608.
[118] K.M. Hastie, C.R. Kimberlin, M.A. Zandonatti, I.J. MacRae, E.O. Saphire, Structure of the Lassa virus nucleoprotein reveals a dsRNA-specific 3′ to 5′ exonuclease activity essential for immune suppression, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 2396–2401.
[119] X. Qi, S. Lan, W. Wang, L.M. Schelde, H. Dong, G.D. Wallat, H. Ly, Y. Liang, C. Dong, Cap binding and immune evasion revealed by Lassa nucleoprotein structure, Nature 468 (2010) 779–783.
[120] J. Tang, H. Naitow, N.A. Gardner, A. Kolesar, L. Tang, R.B. Wickner, J.E. Johnson, The structural basis of recognition and removal of cellular mRNA 7-methyl G 'caps' by a viral capsid protein: a unique viral response to host defense, J. Mol. Recognit. 18 (2005) 158–168.
[121] N. Bergman, K.C. Moraes, J.R. Anderson, B. Zaric, C. Kambach, R.J. Schneider, C.J. Wilusz, J. Wilusz, Lsm proteins bind and stabilize RNAs containing 5′ poly(A) tracts, Nat. Struct. Mol. Biol. 14 (2007) 824–831.
[122] R.P. Galao, A. Chari, I. Alves-Rodrigues, D. Lobao, A. Mas, C. Kambach, U. Fischer, J. Diez, LSm1-7 complexes bind to specific sites in viral RNA genomes and regulate their translation and replication, RNA 16 (2010) 817–827.
[123] A. Mas, I. Alves-Rodrigues, A. Noueiry, P. Ahlquist, J. Diez, Host deadenylation-dependent mRNA decapping factors are required for a key step in brome mosaic virus RNA replication, J. Virol. 80 (2006) 246–251.
[124] A.O. Noueiry, J. Diez, S.P. Falk, J. Chen, P. Ahlquist, Yeast Lsm1p-7p/Pat1p deadenylation-dependent mRNA-decapping factors are required for brome mosaic virus genomic RNA translation, Mol. Cell. Biol. 23 (2003) 4094–4106.
[125] N. Scheller, L.B. Mina, R.P. Galao, A. Chari, M. Gimenez-Barcons, A. Noueiry, U. Fischer, A. Meyerhans, J. Diez, Translation and replication of hepatitis C virus genomic RNA depends on ancient cellular proteins that control mRNA fates, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 13517–13522.
[126] B.Y. Ahn, E.V. Jones, B. Moss, Identification of the vaccinia virus gene encoding an 18-kilodalton subunit of RNA polymerase and demonstration of a 5′ poly(A) leader on its early transcript, J. Virol. 64 (1990) 3019–3024.
[127] B.Y. Ahn, B. Moss, Capped poly(A) leaders of variable lengths at the 5′ ends of vaccinia virus late mRNAs, J. Virol. 63 (1989) 226–232.

[128] R.K. Jangra, M. Yi, S.M. Lemon, DDX6 (Rck/p54) is required for efficient hepatitis C virus replication but not for internal ribosome entry site-directed translation, J. Virol. 84 (2010) 6810–6824.
[129] E.S. Machlin, P. Sarnow, S.M. Sagan, Masking the 5′ terminal nucleotides of the hepatitis C virus genome by an unconventional microRNA-target RNA complex, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 3193–3198.
[130] T. Shimakami, D. Yamane, R.K. Jangra, B.J. Kempf, C. Spaniel, D.J. Barton, S.M. Lemon, Stabilization of hepatitis C virus RNA by an Ago2-miR-122 complex, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 941–946.
[131] U. Garaigorta, M.H. Heim, B. Boyd, S. Wieland, F.V. Chisari, Hepatitis C virus (HCV) induces formation of stress granules whose proteins regulate HCV RNA replication and virus assembly and egress, J. Virol. 86 (2012) 11043–11056.
[132] G.P. Pijlman, A. Funk, N. Kondratieva, J. Leung, S. Torres, L. van der Aa, W.J. Liu, A.C. Palmenberg, P.Y. Shi, R.A. Hall, A.A. Khromykh, A highly structured, nuclease-resistant, noncoding RNA produced by flaviviruses is required for pathogenicity, Cell Host Microbe 4 (2008) 579–591.
[133] P.A. Silva, C.F. Pereira, T.J. Dalebout, W.J. Spaan, P.J. Bredenbeek, An RNA pseudoknot is required for production of yellow fever virus subgenomic RNA by the host nuclease XRN1, J. Virol. 84 (2010) 11395–11406.
[134] S.L. Moon, J.R. Anderson, Y. Kumagai, C.J. Wilusz, S. Akira, A.A. Khromykh, J. Wilusz, A noncoding RNA produced by arthropod-borne flaviviruses inhibits the cellular exoribonuclease XRN1 and alters host mRNA stability, RNA 18 (2012) 2029–2040.
[135] A. Schuessler, A. Funk, H.M. Lazear, D.A. Cooper, S. Torres, S. Daffis, B.K. Jha, Y. Kumagai, O. Takeuchi, P. Hertzog, R. Silverman, S. Akira, D.J. Barton, M.S. Diamond, A.A. Khromykh, West Nile virus noncoding subgenomic RNA contributes to viral evasion of the type I interferon-mediated antiviral response, J. Virol. 86 (2012) 5708–5718.
[136] N. Beliakova-Bethell, C. Beckham, T.H. Giddings Jr., M. Winey, R. Parker, S. Sandmeyer, Virus-like particles of the Ty3 retrotransposon assemble in association with P-body components, RNA 12 (2006) 94–101.
[137] J.A. Dutko, A.E. Kenny, E.R. Gamache, M.J. Curcio, 5′ to 3′ mRNA decay factors colocalize with Ty1 gag and human APOBEC3G and promote Ty1 retrotransposition, J. Virol. 84 (2010) 5052–5066.
[138] Y. Furuichi, M. Morgan, S. Muthukrishnan, A.J. Shatkin, Reovirus messenger RNA contains a methylated, blocked 5′-terminal structure: m-7G(5′)ppp(5′)G-MpCp, Proc. Natl. Acad. Sci. U. S. A. 72 (1975) 362–366.
[139] Y. Furuichi, S. Muthukrishnan, A.J. Shatkin, 5′-Terminal m-7G(5′)ppp(5′)G-m-p in vivo: identification in reovirus genome RNA, Proc. Natl. Acad. Sci. U. S. A. 72 (1975) 742–745.
[140] Y. Furuichi, A.J. Shatkin, Viral and cellular mRNA capping: past and prospects, Adv. Virus Res. 55 (2000) 135–184.
[141] E.A. Toh, P. Guerry, R.B. Wickner, Chromosomal superkiller mutants of Saccharomyces cerevisiae, J. Bacteriol. 136 (1978) 1002–1007.
[142] C.M. Wei, B. Moss, Methylated nucleotides block 5′-terminus of vaccinia virus messenger RNA, Proc. Natl. Acad. Sci. U. S. A. 72 (1975) 318–322.
[143] D. Benarroch, M.P. Egloff, L. Mulard, C. Guerreiro, J.L. Romette, B. Canard, A structural basis for the inhibition of the NS5 dengue virus mRNA 2′-O-methyltransferase domain by ribavirin 5′-triphosphate, J. Biol. Chem. 279 (2004) 35638–35643.