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Review

Emerging roles for RNA degradation in viral replication and antiviral defense

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ABSTRACT

Viral replication significantly alters the gene expression landscape of infected cells. Many of these changes are driven by viral manipulation of host transcription or translation machinery. Several mammalian viruses encode factors that broadly dampen gene expression by directly targeting messenger RNA (mRNA). Here, we highlight how these factors promote mRNA degradation to globally regulate both host and viral gene expression. Although these viral factors are not homologous and use distinct mechanisms to target mRNA, many of them display striking parallels in their strategies for executing RNA degradation and invoke key features of cellular RNA quality control pathways. In some cases, there is a lack of selectivity for degradation of host versus viral mRNA, indicating that the purposes of virus-induced mRNA degradation extend beyond redirecting cellular resources towards viral gene expression. In addition, several antiviral pathways use RNA degradation as a viral restriction mechanism, and we will summarize new findings related to how these host-encoded ribonucleases target and destroy viral RNA.

Contents

Introduction

A recurring theme in many virus–host interactions is the attempt to restrict gene expression. For the cell, such restriction is used as an antiviral mechanism. For the virus, dampening gene expression can be used to liberate cellular resources, escape immune detection, and regulate viral transcript abundance. This review will focus on how this virus–host battle plays out at a terminal stage of the gene expression cascade – that of messenger RNA (mRNA) degradation – as research over the last several years has revealed how regulating mRNA demise plays important and unexpected roles in the lifecycles of diverse viruses. We will highlight how unrelated viruses have evolved remarkably similar strategies to promote mRNA degradation, even though the degree and nature of selectivity often differ. Also notable is the apparent viral mimicry of some cellular RNA degradation pathways, which themselves have emerging antiviral roles.

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Overview of basal and specialized mRNA degradation

Rates of individual mRNA degradation in a cell vary widely, and are regulated by a large cohort of RNA binding proteins that control translation, localization, and access to the decay machinery. However, nearly all mRNAs are protected by a 5′7-methyl-guanosine (7mG) cap and a 3′ poly(A) tail, features that physically protect the mRNA ends from exonucleolytic decay, and also serve to recruit translation initiation machinery. Circularization of mRNA during translation through interactions between cap-binding and poly(A) tail binding proteins adds additional protection from cellular decay enzymes.

Degradation of mRNAs at the end of their translational life, termed basal decay, occurs in several stages but initiates with gradual shortening of the poly(A) tail, termed deadenylation, by cellular decay factors including the Ccr4-Not complex and poly(A)-specific ribonuclease (PARN). Poly(A) tail length is a determinate of mRNA stability and translational competence, and thus is tightly controlled (Eckmann et al., 2011). Deadenylation triggers removal of the 7mG cap by the decapping complex Dcp1/2 and its activators. These events expose the mRNA to rapid exonucleolytic degradation, primarily from the 5′ end by Xrn1, but also from the 3′ end by the exosome and Dis3L2 (Fig. 1) (Gallouzi and Wilusz, 2013).

The fact that basal decay proceeds from the mRNA ends allows for tight control of mRNA degradation, as removal of the poly(A) tail and cap is regulated, rate-limiting, and in some cases may even be reversible (Schoenberg and Maquat, 2009; Weill et al., 2012). However, the subsequent exonucleolytic decay of the message body is rapid and irreversible. To maintain transcriptome fidelity cells also need to immediately destroy cytoplasmic mRNAs recognized as aberrant. In such cases, the strategy for degradation differs fundamentally from that of basal decay, in that mRNAs are usually cleaved internally by an endonuclease rather than gradually trimmed from either end.

The best-characterized cellular mRNA quality control (QC) pathway is nonsense-mediated decay (NMD), which identifies mRNAs with premature termination codons (PTC) (Fig. 1) (Popp and Maquat, 2013). Numerous cellular factors comprise the NMD machinery, but the central NMD regulator is UPF1, whose activation leads to translational repression and accelerated degradation of the PTC-containing mRNA. During NMD in mammals, this rapid mRNA degradation is triggered by endonucleolytic cleavage of the mRNA by the Smg6 endonuclease at the site of the PTC, followed by degradation of the cleaved fragments by components of the basal mRNA decay machinery such as Xrn1 (Lykke-Andersen et al., 2014; Schweingruber et al., 2013). Other RNA QC pathways similarly recognize aberrant translation events such as stalled or non-terminating ribosomes indicative of RNA errors and lead to inactivation of the mRNA in question through endonucleolytic cleavage (Inada, 2013).

Viral endonucleases and decapping enzymes bypass regulatory steps of mRNA decay

All viruses known to drive widespread mRNA degradation do so by causing internal endonucleolytic cleavages or by directly removing the mRNA 5′ cap structure (Fig. 1). Regardless of the precise mechanisms used, these strategies have in common one salient feature: they bypass the rate-limiting and regulated steps of deadenylation and cellular decapping, much like the cellular RNA QC pathways. This ensures both immediate translational inactivation and exposure of the mRNA ends to the processive cellular exonucleases. However, unlike the tightly regulated cellular QC endonucleases, during infection a large proportion of the cytoplasmic mRNA population is targeted for cleavage. This allows the viruses to broadly restrict gene expression, as mRNAs they target are degraded much more rapidly than they would be if they entered the basal decay pathway. Furthermore, akin to cellular pathways like NMD, viruses that cleave mRNAs often usurp Xrn1 to complete the degradation process (Gaglia et al., 2012).

Four classes of viruses have been shown to cause endonucleolytic cleavage of mRNAs for the purpose of restricting gene expression (Table 1). The alpha-herpesviruses, gamma-herpesviruses, and influenza A viruses encode non-homologous endonucleases that cleave mRNAs directly. SARS coronavirus (SARS CoV) does not encode an RNA cleaving enzyme, but nonetheless activates an as yet unknown cellular endonuclease to cleave mRNAs. In each examined case, viral specificity for mRNAs (as opposed to other types of RNA) is conferred by the act of translation or recognition of mRNA features associated with translational competence, similar to cellular RNA QC pathways (Covarrubias et al., 2011; Kamitani et al., 2009; Read, 2013).

DNA virus-encoded endonucleases

Alpha-herpesviruses such as herpes simplex-1 (HSV-1) express a FEN1-like nuclease termed virion host shutoff protein (vhs) that is directed to mRNAs through interactions with the translation

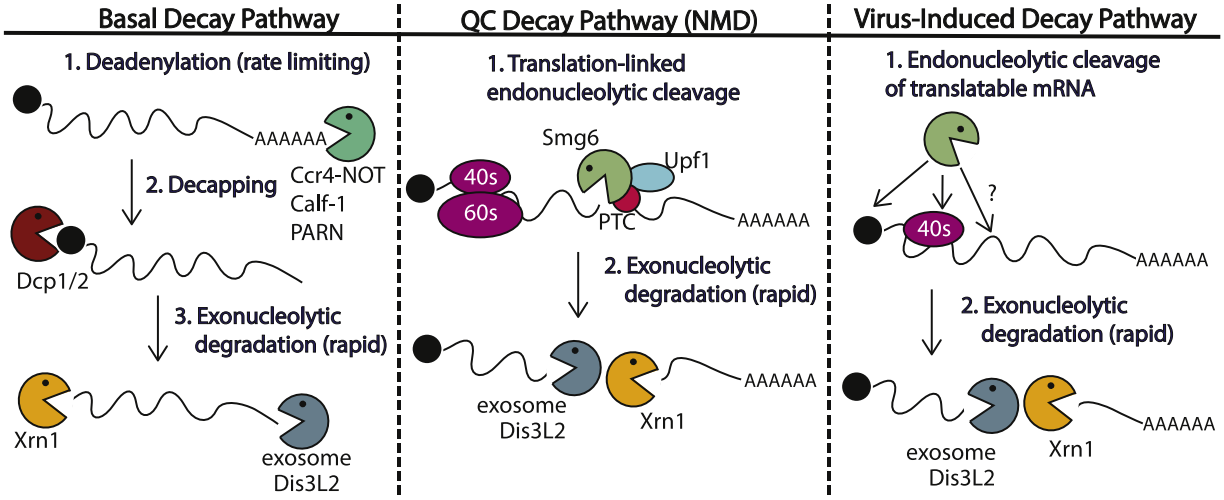

Fig. 1. Overview of cellular and viral decay pathways. Basal decay begins with the rate-limiting step of deadenylation, followed by decapping and exonucleolytic degradation of the mRNA body. Quality control decay pathways such as NMD recognize aberrant mRNAs during translation, including the presence of premature termination codons (PTC), and induce endonucleolytic cleavage, whereupon the fragments are degraded by exonucleases. Virus-induced decay also bypass early steps of the basal decay pathway and involves internal cleavage of mRNAs, usually in a translation-linked manner, which is followed by degradation by host exonucleases.

Table 1
Viral endonucleases that broadly restrict gene expression.

Virus	Host shutoff factor	Nuclease superfamily	Targeting mechanism	Cleavage location	Viral mRNAs
HSV-1	vhs	FEN-1	Binds translation factors eIF4F	5′ UTR, near cap	Susceptible (early)
KSHV, MHV68, EBV	SOX, muSOX, BGLF5	PD(D/E)XK	Unknown	At targeting sequence	Susceptible
Influenza A	PA-X	PD(D/E)XK	Unknown	Unknown	Unknown
SARS-CoV	Nsp1	Not applicable	Binds 40s ribosome	ribosome binding site	Protected by 5′ leader sequence
Vaccinia virus	D10, D9	Nudix domain decappers	Cap-binding	5′ cap	Susceptible

initiation factors eIF4H and eIF4AI/II (Feng et al., 2005; Page and Read, 2010). If this interaction is disrupted but the catalytic endonuclease activity remains intact, no host shutoff occurs, indicating that recruitment of vhs to the pool of translating mRNAs is crucial to its ability to dampen gene expression (Feng et al., 2005; Sarma et al., 2008; Shiflett and Read, 2013). In vitro, vhs lacks specificity, cleaving mRNAs and non-mRNAs indiscriminately, as well as anywhere along the RNA (Read, 2013). However, in cells or in the presence of cell extracts, vhs preferentially cuts mRNAs at unstructured sites within the 5′ UTR or near the start codon of capped mRNAs (Karr and Read, 1999; Shiflett and Read, 2013). Cut sites also cluster downstream of the encephalomyocarditis virus (EMCV) internal ribosome entry site (IRES), which recruits the vhs-targeting translation factors eIF4AI/II, but not near the more minimal Cricket Paralysis virus (CrPV) IRES that recruits the ribosome in the absence of eIF4F (Shiflett and Read, 2013). Further support for the hypothesis that vhs accesses its cleavage sites during translation initiation comes from experiments showing that specific cleavage sites can be repressed or enhanced by mutating the target mRNA start codon or enhancing its Kozak consensus context, respectively (Read, 2013; Shiflett and Read, 2013). However, the observation that an mRNA with a cap-proximal hairpin structure that prevents 40S recruitment remains fully susceptible to vhs cleavage argues against an absolute requirement for ribosomal scanning (Gaglia et al., 2012). One possibility is that assembly of the eIF4F complex on the mRNA cap induces local RNA structure remodeling that creates vhs accessible sites, but that more directed cleavages occur near the start codon during the process of 40S scanning. After vhs-induced cleavage, the resulting 3′ mRNA fragments are degraded by the cellular Xrn1 exonuclease (Gaglia et al., 2012).

Gamma-herpesviruses encode a viral endonuclease that, although not homologous to alpha-herpesvirus vhs, also broadly targets cytoplasmic mRNAs for cleavage and subsequent degradation. This protein, termed SOX in Kaposi's sarcoma-associated herpesvirus (KSHV), muSOX in murine gamma-herpesvirus 68 (MHV68), and BGLF5 in Epstein–Barr virus (EBV), is a member of the PD(D/E)XK restriction endonuclease superfamily. The SOX ortholog in HSV-1 was originally shown to have DNase activity involved in viral DNA genome replication (Wilkinson and Weller, 2003), a function it presumably retains in all herpesviruses in addition to the gamma-herpesvirus-specific mRNA degradation activity. Both the DNA and RNA cleavage activities of the protein require the same catalytic core region (Bagneris et al., 2011; Glaunsinger et al., 2005). Although SOX specifically targets translationally competent mRNAs, active translation is not a requirement for target recognition and the molecular features that direct SOX to mRNAs remain unknown. SOX-induced mRNA cleavage occurs at one or more specific, but as-yet poorly sequence defined RNA elements ($\geq$50 nt) that can be present anywhere along the length of a target (Covarrubias et al., 2011; Gaglia et al., 2012). Although a SOX targeting element can confer a new cleavage event if moved to a different location on an mRNA, it is incapable of directing cleavage by SOX if introduced into noncoding RNAs transcribed by RNA polymerase I or III (Gaglia et al., 2012). Similar to vhs, recombinant SOX and BGLF5 display relaxed RNA targeting specificity in vitro (Bagneris et al., 2011; Buisson et al., 2009), indicating that additional mRNA-specific features must be required for SOX recruitment in cells. Single function mutants of SOX and muSOX that are defective for mRNA cleavage but retain their DNase activity have mutations that map to regions outside the catalytic core on the protein surface (Bagneris et al., 2011; Covarrubias et al., 2009; Glaunsinger et al., 2005). Furthermore, the crystal structure of BGLF5 revealed the presence of a flexible "bridge" domain that crosses the active site and contains residues involved in host shutoff (Buisson et al., 2009; Horst et al., 2012). These non-catalytic regions may therefore function in targeting the gamma-herpesvirus SOX orthologs to translationally competent mRNAs, perhaps through interactions with specific mRNA binding proteins. Similar to vhs, SOX-cleaved mRNAs subsequently enter the cellular mRNA decay pathway and are degraded by Xrn1 (Covarrubias et al., 2011; Gaglia et al., 2012).

RNA virus-encoded endonucleases

The PA-X protein of influenza A virus (IAV) is a recently discovered mRNA endonuclease involved in restricting host gene expression (Jagger et al., 2012). It is expressed by a ribosome frameshifting event during translation of the PA subunit of the viral RNA-dependent RNA polymerase (RdRp), itself an endonuclease that is responsible for cap snatching in the nucleus. Like the gamma-herpesvirus SOX orthologs (and many endonucleases involved in cap snatching), PA-X is a member of the PD(D/E)XK nuclease family. PA-X retains the N-terminal PA endonuclease domain but contains a distinct C-terminus that augments the cellular mRNA degradation activity of the protein via unknown mechanisms (Desmet et al., 2013; Jagger et al., 2012). One possibility is that C-terminal sequences are involved in directing PA-X to its mRNA targets. In this regard, it would be interesting to determine whether PA-X targeting is linked to translation and feeds into the cellular Xrn1 decay pathway, as has been shown for other viral mRNA restriction factors.

SARS CoV expresses a host shutoff factor, nsp1, that binds the 40s ribosome, simultaneously inducing cleavage of mRNAs and inactivating the ribosome (Huang et al., 2011; Kamitani et al., 2009). By binding the 40s ribosome, nsp1 is recruited to all translationally competent mRNAs, allowing for broad targeting of cellular transcripts. Nsp1 itself does not possess detectable intrinsic nuclease activity, suggesting that nsp1-induced mRNA cleavage may instead occur through activation of a cellular RNA surveillance pathway (Almeida et al., 2007; Huang et al., 2011). Candidate pathways include those involved in monitoring translational efficiency, given that the nsp1–40S interaction leads to ribosome inactivation in addition to mRNA cleavage (Narayanan and Makino, 2013). For example, the no-go decay pathway degrades mRNAs with stalled ribosomes, albeit using a currently unknown endonuclease (Harigaya and Parker, 2010). As has been observed for cellular QC pathways like NMD as well as the herpesviral endonucleases, degradation of the cleaved mRNAs in nsp1-expressing cells is executed by Xrn1 (Gaglia et al., 2012).

Viral decapping enzymes

Poxviruses and African Swine Fever Virus (ASFV) are the only viruses known to encode decapping enzymes. Similar to cellular

decappers, the vaccinia virus (VACV) D9 and D10 decapping proteins contain a Nudix hydrolase domain that is essential for cleaving the 7mGpppN cap between the alpha- and beta-phosphates (Parrish et al., 2007; Shors et al., 1999; Souliere et al., 2009). The ASFV decapping enzyme g5R also contains a Nudix domain essential for decapping. Both the VACV and ASFV decapping enzymes are inhibited in the presence of excess uncapped RNAs, but only the VACV D10 enzyme is also inhibited by cap analogs (Parrish et al., 2009). This suggests that g5R recognizes its substrates by binding the RNA body rather than the cap, whereas VACV D10 binds both the methylated cap and the RNA body (Parrish et al., 2009). Extensive site-directed mutagenesis of VACV D10 identified eight amino acids in the catalytic core of D10 important for decapping activity and showed that D10 recognizes the cap in a manner distinct from other characterized cap binding proteins (Souliere et al., 2010).

It is unknown why poxviruses expresses two functional decapping enzymes, although the reason may be linked to the fact that D9 is expressed early during infection while D10 is expressed later, after DNA replication. Additionally, there are some differences between the two enzymes, including the observations that D9 requires longer RNA substrates than D10, and D9 mutants have less pronounced phenotypes than D10 mutants (Parrish and Moss, 2006, 2007). Therefore, the kinetic and functional requirements for decapping may vary as VACV infection progresses. As decapping renders the 5′ end of an mRNA unprotected, it is likely that D9 and D10 cleaved mRNAs are digested by Xrn1, similar to the cleavage products induced by vhs, SOX, and nsp1. Interestingly, a recent RNAi screen suggested a positive role for Xrn1 in VACV replication (Sivan et al., 2013), perhaps indicating that Xrn1-mediated RNA degradation plays an important role in the viral lifecycle.

Viral mRNAs do not broadly escape inactivation

It is often presumed that restriction of cellular gene expression during infection serves in part to divert resources for the selective enhancement of viral gene expression. However, in each of the above documented examples there is not a clear escape mechanism to broadly protect viral mRNAs from inactivation. Instead, these viruses may benefit from reduced transcript levels during infection, either because mRNA inactivation helps them regulate their gene expression kinetics or other aspects of the viral lifecycle.

During VACV infection, the decapping enzymes D9 and D10 fail to discriminate between viral and cellular mRNA. Targeting viral transcripts is proposed to help facilitate transitions between the classes of gene expression, as D10 mutants exhibit delayed onset of early and late viral gene expression (Liu et al., 2014; Parrish and Moss, 2006). Similarly, alpha- and gamma-herpesviral mRNAs are inherently susceptible to endonucleolytic cleavage. During HSV-1 infection, vhs plays an important role in mediating the effective transition between the expression of immediate-early (α), early (β), and late (γ) genes (Read, 2013). There are some discrepancies in the field as to exactly which viral mRNAs are susceptible to vhs-mediated degradation during infection. Some data suggest that only α mRNAs are targeted (Shu et al., 2013; Taddeo et al., 2013), while data from other groups indicate that α, β, and even some γ mRNAs are susceptible to degradation by vhs (Kwong and Frenkel, 1987; Oroskar and Read, 1987, 1989). Regardless of the extent of viral mRNA degradation, targeting of viral mRNAs by vhs helps facilitate the transition between viral gene classes as infection progresses. Furthermore, during infection with a vhs null virus, γ mRNAs are excluded from polysomes due to 'translational overload', whereby the capacity of the translation machinery becomes overwhelmed due to an excess of mRNAs produced earlier in infection (Dauber et al., 2014). This confirms the long-held hypothesis that host shutoff is a means of liberating translational machinery for viral use—with the twist that both host and viral transcripts must be degraded to ensure efficient translation of γ mRNAs. Further contributing to the robust accumulation of γ proteins is the inactivation of vhs later during infection by the virion proteins VP16, VP22, and UL47 (Read, 2013; Shu et al., 2013). All three are packaged into the viral particle along with vhs, and it has been suggested that sequestering vhs in this complex represents an early stage in virion assembly and protects mRNAs from cleavage late in infection. Thus, despite widespread viral mRNA susceptibility, vhs targeting of mRNAs appears temporally controlled.

The SOX homologs in MHV68 (muSOX) and EBV (BGLF5) have also been shown to target viral mRNAs for cleavage (Abernathy et al., 2014; Horst et al., 2012). Unlike vhs, however, there is no indication that SOX or its orthologs are inactivated as infection progresses. During MHV68 infection, muSOX broadly targets viral mRNAs from all three kinetic classes, which generally leads to corresponding decreases in viral protein levels in each class (Abernathy et al., 2014). Thus, unlike HSV-1 infection, the targeting of viral mRNAs during gamma-herpesvirus infection is not a mechanism to redirect the translation machinery towards viral genes. This also suggests that translation factors do not become limiting during MHV68 infection. Selective inactivation of the mRNA degradation activity of muSOX results in altered protein composition of progeny virions, which ultimately impacts subsequent rounds of infection by favoring lytic cycle entry over latency. The mutant also exhibits replication defects in multiple cell types (Abernathy et al., 2014; Richner et al., 2011). Deletion of BGLF5 during EBV infection also results in accumulation of several viral proteins, as well as causes nuclear egress defects (Feederle et al., 2009). However, because BGLF5 has dual roles in viral genome maturation and mRNA degradation and the BGLF5 mutant virus lacks both functions, it is not possible to ascribe the above phenotypes solely to a defect in host shutoff. Nonetheless, these data support the hypothesis that degradation of viral mRNA during gamma-herpesvirus infection plays important roles in regulating gene expression and subsequent viral particle composition.

Unlike herpesviral and poxviral mRNAs, SARS CoV transcripts are categorically resistant to nsp1-induced cleavage and degradation. This protection is due to the presence of a protective 5′ leader sequence present on all viral mRNAs, although the mechanism of protection remains unclear (Huang et al., 2011). However, while CoV mRNAs escape endonucleolytic cleavage, they do not escape nsp1-induced ribosome inactivation, raising the issue of what advantage is conferred by the protective sequence (Huang et al., 2011; Lokugamage et al., 2012). One likely possibility is that ribosome inactivation is not complete, and consequently viral gene expression is not as severely impacted as cellular gene expression. Whether this represents a mechanism to fine tune viral protein synthesis in a manner important for the viral lifecycle in vivo remains an interesting question for future investigation.

Downstream consequences of virus-induced cytoplasmic mRNA degradation

Degradation of mRNA has recently been shown to be highly interconnected with many other cellular processes including transcription, mRNA export, and translation (Braun and Young, 2014; Huch and Nissan, 2014). It is thus likely that the broad virus-induced mRNA decay described above will result in changes to other RNA processes as well. One example of this is altered mRNA 3′ end processing in the nucleus that occurs as a consequence of enhanced mRNA decay in the cytoplasm (Fig. 2). Poly(A) binding protein (PABPC) normally binds to poly(A) tails of mRNAs in the cytoplasm, where it contributes to the regulation of mRNA stability and enhances translation. However, PABPC becomes strongly relocalized to the nucleus in cells expressing

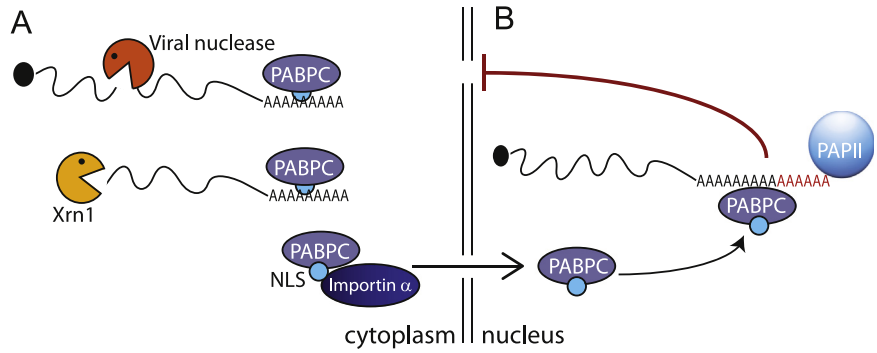

Fig. 2. Virus-induced mRNA degradation impacts RNA processing. (A) Widespread mRNA degradation in the cytoplasm leads to release of PABPC from poly(A) tails. This exposes its NLS, which is normally masked during RNA binding, leading to nuclear import via interactions with importin α. (B) Nuclear accumulation of PABPC promotes hyperadenylation of nascent transcripts via PAP II and an mRNA export block.

SOX, muSOX, BGLF5, vhs, PA-X or nsp1 (Arias et al., 2009; Khaperskyy et al., 2014; Kumar and Glaunsinger, 2010; Lee and Glaunsinger, 2009; Park et al., 2014). Nuclear import occurs because within its RNA binding domains, PABPC harbors noncanonical nuclear localization signals (NLS) that are masked when it is bound to poly(A) tails in the cytoplasm. However, during accelerated mRNA degradation by these viral proteins, PABPC is released from poly(A) tails, exposing its NLS for interaction with the nuclear import machinery (Kumar et al., 2011). Such aberrant accumulation of PABPC in the nucleus causes hyperadenylation of nascent transcripts by cellular poly(A) polymerase II (Kumar and Glaunsinger, 2010; Lee and Glaunsinger, 2009). These hyperadenylated mRNAs are retained in the nucleus, presumably because they are recognized as aberrant by the nuclear RNA QC machinery. This process thus contributes to the overall magnitude of host shutoff, as the cytoplasm cannot be efficiently repopulated with newly transcribed mRNAs.

Accelerated cytoplasmic decay may also lead to inhibition of stress granule (SG) formation. SGs are storage sites for translationally stalled mRNAs, and form in response to translational arrest that often occurs during viral infection (Valiente-Echeverria et al., 2012). Many viruses have evolved mechanisms to block their formation, presumably to ensure continued translation of viral proteins. Viral nucleases can contribute to SG dispersal, presumably through the bulk reduction of mRNAs needed to nucleate SG formation. For example, along with several other IAV-encoded proteins, the endonuclease PA-X was recently identified as a potent inhibitor of SGs (Khaperskyy et al., 2014). PA-X-mediated SG inhibition coincides with PABPC relocalization, hinting at a link between host shutoff and SG dynamics. Similarly, the vhs nuclease of HSV-2 is required for the SG disruption that occurs during HSV-2 infection (Finnen et al., 2014). However, vhs has also been implicated in translational enhancement of viral late genes (a role separable from its RNase activity) (Dauber et al., 2011, 2014), making it difficult to ascribe the SG dispersal phenotype solely to mRNA depletion. Nonetheless, viral mRNA-targeting nucleases provide a unique system to dissect the link between mRNA decay and SG assembly.

Contributions of virus-induced mRNA degradation towards immune evasion

Widespread dampening of gene expression during infection is presumed to contribute to viral immune evasion, both by inhibiting expression of cellular immune regulatory genes and by reducing the abundance of viral antigens available for detection. Indeed, viruses containing mutations in HSV-1 vhs, MHV68 muSOX, coronavirus nsp1, and VACV D10 exhibit more severe phenotypes in a mouse model of infection than in cultured cells (Liu et al., 2014; Richner et al., 2011; Smiley, 2004; Zust et al., 2007), suggesting mRNA degradation contributes to virulence. Activation of the innate immune response leads to expression of hundreds of genes involved in establishing an antiviral state. Vhs suppresses the expression of several of these genes including tetherin and viperin, which would normally act to restrict HSV-1 infection (Shen et al., 2014; Zenner et al., 2013), as well as many pro-inflammatory cytokines (Suzutani et al., 2000). Some of the differences in the *in* vivo infectivity of WT versus the vhs mutant HSV-1 are alleviated in interferon receptor defective (IFNAR KO) mice, suggesting that vhs-induced suppression of the innate immune response contributes to viral fitness (Leib et al., 1999; Smiley, 2004).

Selective inactivation of the muSOX mRNA degradation activity leads to a severe attenuation of MHV68 in B cells during the phase of peak latency establishment (Richner et al., 2011). This could be due to improper immune evasion and/or cell-type specific replication defects, as the muSOX mutant virus replicates to WT titers in the mouse lung but traffics inefficiently to B cells and displays cell type specific replication defects in cultured cells (Abernathy et al., 2014; Richner et al., 2011). Similar to the ability of vhs to degrade immune modulatory mRNAs, EBV BGLF5 also reduces expression of immune molecules, in particular HLA I and II (Rowe et al., 2007; Zuo et al., 2008). However, this activity is redundant with other EBV proteins that specifically combat HLA processing and transport and thus appears to have only a small effect on CD8+ T cell recognition (Quinn et al., 2014). Whether CD8+ T cell recognition or innate immune signaling are influenced by mRNA degradation during in vivo infection with other gamma-herpesviruses remains to be determined.

Both VACV decapping mutants and CoV nsp1 mutants also display altered virulence phenotypes, although further research is needed to determine the extent to which these are directly linked to mRNA degradation. Mice infected with VACV D10 stop and catalytic mutants show less weight loss and mortality compared to a WT infection, and these mutant viruses replicate to lower titers in all organs (Liu et al., 2014). Although there is not in vivo data for nsp1 of SARS CoV, the nsp1 protein of the coronavirus mouse hepatitis virus (MHV) retains the mRNA degradation function, as well as several additional roles in inhibiting immune signaling pathways. These activities align well with the observation that an MHV nsp1 deletion virus is severely attenuated in WT mice, but is completely rescued in IFNAR KO mice (Zust et al., 2007). Determining the extent to which nsp1-induced virulence links to its host shutoff activity will require the use of single function nsp1 mutants selectively defective for mRNA cleavage or immune pathway impairment. In this regard, the recent characterization of a panel of SARS CoV nsp1 mutants that exhibit selective functional defects should help determine the contribution of mRNA degradation to the nsp1 virulence phenotypes (Jauregui et al., 2013).

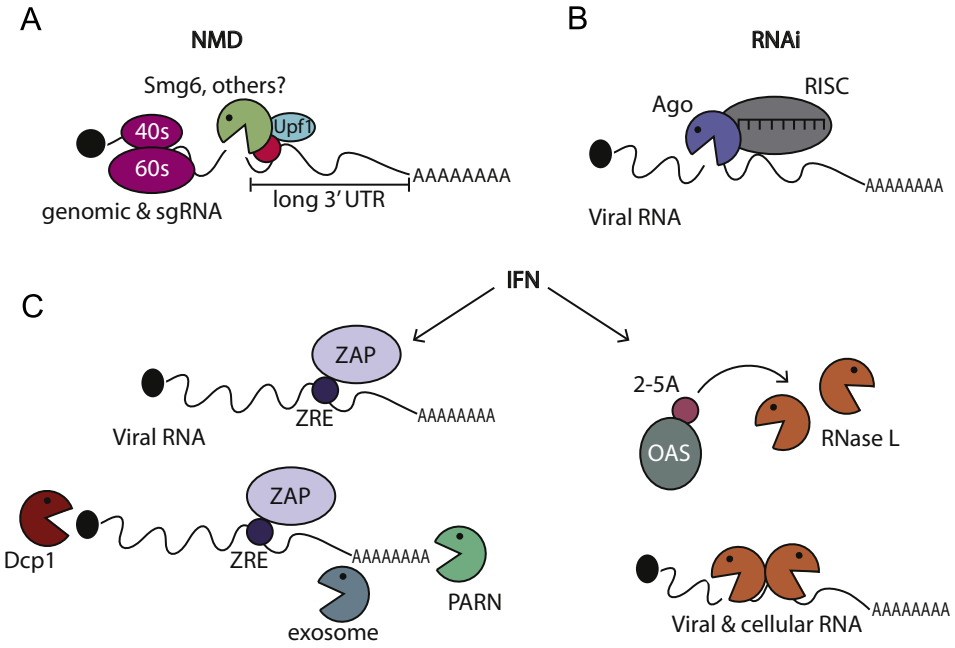

Fig. 3. Cellular nucleases with antiviral roles. (A) Viral RNA of (+) RNA viruses can be recognized by cellular QC pathways like NMD, in some cases due to long 3′ UTRs which are inherent to subgenomic RNAs (sgRNA). This leads to their degradation by Smg6 and perhaps other nucleases. (B) RNAi cleaves viral dsRNA, which is loaded into a RNA induced silencing complex (RISC) that targets viral RNA for endonucleolytic cleavage by Ago. (C) IFN-activated mRNA degradation pathways include ZAP and RNase L. ZAP binds viral RNA at specific response elements (ZRE) and recruits cellular decay factors, including deadenylase PARN, de-capping enzyme Dcp1, and the 3′–5′ exosome. IFN also induces 2–5A synthase (OAS) to synthesize the RNase L activator 2–5A, leading to RNase L dimerization and cleavage of viral and cellular RNAs.

New roles for cellular nucleases in counteracting viral infection

The use of RNA-targeting nucleases is also a component of many of the cellular antiviral defense pathways, some of which play dual roles in regulating normal cellular metabolism and viral restriction (Fig. 3). For example, in addition to its well-established role in eliminating PTC-containing mRNA, the NMD pathway has recently been shown to function in the restriction of positive strand (+) RNA viruses in plants and in mammalian cells (Balistreri et al., 2014; Garcia et al., 2014). A genetic screen uncovered the central NMD effector Upf1 as a cellular restriction factor of the plant (+) RNA viruses *Potato virus X* (PVX) and *Turnip crinkle virus* (TCV) (Garcia et al., 2014). NMD-based restriction is hypothesized to act upon the input genomic viral RNA undergoing initial rounds of translation, and thus might function before the onset of RNAi, the major antiviral pathway in plants. One of the known activators of NMD is an unusually long 3′ UTR on the target mRNA, as this can be associated with less efficient translation termination (Inada, 2013; Kervestin and Jacobson, 2012). In this regard, many (+) RNA plant viruses encode subgenomic (sg) RNAs, which creates the appearance of a long 3′ UTR on the genomic mRNA and select sgRNAs. Indeed, these long 3′ UTRs are required for degradation of PVX and TCV RNAs via NMD, confirming that intrinsic features of viral RNAs render them susceptible to cellular QC pathways (Garcia et al., 2014).

In mammalian cells, depleting NMD factors Upf1, Smg5, or Smg7 leads to increased replication of the alphaviruses Semliki Forest virus (SFV) and Sindbis virus (SINV), suggesting that NMD may target viral genomic RNA for degradation (Balistreri et al., 2014). Unexpectedly, although like PVX and TCV these viruses have long 3′ UTRs, deletion of the long 3′ UTR of SFV does not alter the restriction by Upf1 (Balistreri et al., 2014). Furthermore, viral restriction does not require the NMD endonuclease Smg6. Thus, the mechanism of decay and the viral RNA feature(s) that trigger virus-induced activation of NMD in mammalian cells remain to be elucidated. However, a broader role for NMD in controlling mammalian viruses is supported by the fact that multiple retroviruses have evolved mechanisms to restrict NMD. This can occur through inhibitory interactions with NMD components or through viral RNA sequences that protect against NMD (Mocquet et al., 2012; Withers and Beemon, 2010).

In plants and insects, RNA interference (RNAi) is the primary antiviral defense mechanism. The RNAi pathway restricts gene expression by processing the long double stranded RNAs frequently generated during viral replication into short interfering RNAs (siRNAs), which guide endonucleolytic cleavage of complementary target mRNAs. Although mammalian cells possess the RNAi machinery, in most cases RNAi does not appear to play a significant antiviral role, and has instead been supplanted by the protein-based interferon response (Cullen, 2014). However, recent data reveal that in select cell types such as ES cells, RNAi indeed functions in an antiviral capacity (Li et al., 2013; Maillard et al., 2013). One hypothesis is that an antiviral role for RNAi is retained in these cells because they lack a fully functional interferon response. Furthermore, mice express an oocyte-specific N-terminally truncated isoform of the nuclease responsible for generating mature forms of the effector small RNAs (miRNAs or siRNAs), termed Dcr° (Flemr et al., 2013). Dcr° has increased siRNA-processing activity relative to the full-length Dcr nuclease, perhaps explaining why undifferentiated cells contain RNAi-based antiviral activity (Cullen, 2014; Flemr et al., 2013). Because Dcr° is not expressed in primates, whether similar RNAi-based antiviral activity is active in human ES cells remains an open question.

The interferon (IFN) pathway is the primary effector of the mammalian innate immune response, and its activation can induce the expression of proteins that drive either selective destruction of viral RNA or more indiscriminate destruction of viral and cellular RNA. An example of the former is the zinc-finger antiviral protein (ZAP), which binds specifically to viral RNAs that contain a ZAP response element (ZRE). Upon binding to viral RNA, ZAP recruits cellular RNA decay machinery, including the deadenylase PARN, the RNA 3′–5′-directed exonuclease complex called the exosome, and the Dcp1/2 decapping enzymes via their p72 helicase co-factor (Zhu et al., 2011). Many, but not all viruses, contain ZREs and are restricted by ZAP,

including HIV, filoviruses, Sindbis virus, and MHV68 (Bick et al., 2003; Muller et al., 2007; Xuan et al., 2013; Zhu et al., 2011). Zap contains four CCCH-type zinc fingers in its N-terminal domain that specifically bind RNA and recruit decay factors (Zhu et al., 2011; Zhu and Gao, 2008). As with many other mRNA decay pathways, ZAP-induced degradation is preceded by inhibition of mRNA translation. ZAP restricts translation of its target mRNAs by interacting with the eIF4A helicase in a manner that disrupts the ability of eIF4A to associate with eIF4G (Zhu et al., 2012). Translational repression appears selective for ZRE-containing transcripts, suggesting that ZAP only binds eIF4A associated with its target mRNAs (Zhu et al., 2012).

Unlike the ZRE-specific targeting of ZAP, the IFN-activated cellular endonuclease RNase L cleaves a much broader spectrum of RNAs. RNase L is inactive as a monomer, but becomes active upon binding 2′–5′ oligoadenylates (2–5A) that are produced by another IFN-induced protein, 2–5A synthase (OAS). Binding of 2–5A allosterically activates RNase L by inducing its dimerization, whereupon it cleaves both viral and cellular RNAs, usually at a 5′-UNN-3′ consensus (Bhattacharyya, 2014; Han et al., 2014). That said, two features of RNase L might cause it to favor viral over cellular mRNAs. First, the UU/UA dinucleotides that often make up the RNaseL cleavage site are relatively rare in the coding regions of cellular mRNAs, possibly as an evolutionary trend to avoid RNase L cleavage (Al-Saif and Khabar, 2012). Second, cellular RNAs contain a variety of nucleoside modifications, some of which confer increased resistance to RNase L (Anderson et al., 2011). Not surprisingly, many viruses have evolved mechanisms to counteract the activation of RNase L, including blocking IFN induction and directly disrupting 2–5A production (Bhattacharyya, 2014; Silverman and Weiss, 2014).

Conclusions

The expanding number of viruses shown to exert control over the cytoplasmic mRNA population through the activity of virally encoded endonucleases or by activating cellular nucleases highlights the importance of this process in diverse viral lifecycles. Although we have highlighted select examples of viral endonucleases that promote mRNA decay, many other viruses impact RNA fate by inactivating mRNA degradation enzymes, hijacking or competing with the cellular decay machinery, and relocalizing cellular proteins that control mRNA stability (Moon and Wilusz, 2013).

Furthermore, as is frequently the case in virology, the study of this virus–host interplay is sure to offer new insights into the regulation of cellular RNA decay pathways. The field is now beginning to uncover how cellular RNA degradation enzymes with central roles in basal and QC-associated RNA decay are also key contributors to the antiviral response. Yet, in some cases the precise players or their regulation may differ from their previously characterized roles in the context of uninfected cells. In this regard, revealing how viral RNAs are recognized and marked for degradation by pathways such as NMD remains an important endeavor. This should simultaneously provide insight into cellular RNA features that impact QC surveillance, especially given the numerous parallels between mRNA degradation by viruses and cellular QC pathways. Furthermore, additional research is required to define the importance of RNAi in the mammalian antiviral response, including the cell context in which it operates as well as whether it plays antiviral roles in primates.

Much remains to be discovered about the mechanisms underlying mRNA targeting by viral endonucleases as well. Questions surrounding the precise roles of translation factors in recruiting or activating nucleases, what sequence elements and context confer cleavage, as well as how active translation impacts targeting all remain active areas of research. Finally, although the data all point to important roles for virus-induced mRNA degradation in replication and immune evasion in vivo, very little is known about the relative importance of regulating host versus viral mRNA abundance in these processes. Ongoing and future research should provide answers to these questions, as well as reveal the impact of virus-induced mRNA degradation on a diversity of other cellular processes.

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