Virus Meets Host MicroRNA: the Destroyer, the Booster, the Hijacker

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Virus-host interactions highlight key regulatory steps in the control of gene expression. MicroRNAs (miRNAs) are small noncoding RNAs that regulate protein production via base pairing with mRNAs. Both DNA and RNA viruses have evolved mechanisms to degrade, boost, or hijack cellular miRNAs to benefit the viral life cycle. This minireview focuses on recent discoveries in virus-host miRNA interactions.

Viruses are masters of gene regulation. Their parasitic life style employs host machinery to carry out basic biological processes, from transcription to protein synthesis. Thus, viruses can dramatically downsize their genomes to the minimum number of genes essential for successful infection (1). Even though some viruses, such as pandoravirus (2) and mimivirus (3, 4), encode as many as several thousand proteins—more than some free-living bacteria—they are exceptions to the rule. Typical mammalian herpesviruses possess from 70 to 200 genes in 120,000 to 250,000 base pairs of viral genomic DNA (5). These viral genomes are remarkably compacted compared to those of the host. For example, of the 3.2 billion base pairs in the human genome, more than 98% do not encode proteins (6). In contrast, only ~10 to 20% of a herpesviral genome is noncoding (Fig. 1). With miniature genomes that are several orders of magnitude smaller than those of their hosts, viruses produce proteins and noncoding RNAs (ncRNAs) to regulate key components in host gene networks to ensure successful infection. Therefore, a deeper understanding of virus-host interactions often reveals important mechanisms of host gene regulation.

MicroRNAs (miRNAs) are ~22-nucleotide ncRNAs that play important roles in posttranscriptional regulation of gene expression. The specificity of target mRNA recognition is mostly determined by the seed region (nucleotides 2 to 8) at the 5′ end of a miRNA (7), although there are multiple experimentally validated mRNA targets that lack perfect base-pairing interactions with the miRNA seed region (8, 9). The relatively short seed sequence confers on a single miRNA the ability to regulate hundreds of mRNAs. One current hypothesis argues that miRNAs, like transcription factors, are master regulators of gene networks or pathways (10, 11). Given the importance and versatility of miRNAs, many viruses exploit this host pathway by destroying, boosting, or hijacking miRNAs to benefit the viral life cycle.

THE DESTROYER

miR-27 degradation by herpesvirus saimiri and murine cytomegalovirus. Herpesvirus saimiri (HVS) is an oncogenic gammaherpesvirus that transforms primate and human T cells (12). The most abundant viral transcripts in latently infected marmoset T cells are seven small U-rich Sm-class ncRNAs called HSURs (13–15). In these cells, HSUR 1 base pairs with the host miRNA 27 (miR-27), leading to miRNA degradation in a sequence-specific and binding-dependent manner (16) (Fig. 2), although the mechanism of miR-27 degradation is unknown. Recent high-throughput sequencing of RNA after cross-linking immunoprecipitation

(HITS-CLIP) (17) analysis revealed that miR-27 interacts with mRNAs encoding components of the T-cell receptor (TCR) signaling pathway and downstream effectors in HVS-infected T cells (18). Specifically, miR-27 robustly decreases the levels of the cell surface signaling protein semaphorin 7A (SEMA7A), the adaptor protein growth factor receptor-bound protein 2 (GRB2), and the effector cytokine gamma interferon (IFN-γ) (18). This repressive role of miR-27 in T-cell activation explains the link between HSUR 1-induced miR-27 degradation (16) and activation of infected T cells conferred by expression of HSUR 1 and/or 2 (19). Unexpectedly, gammaherpesviruses distantly related to HVS, alcelaphine herpesvirus 1 (AlHV-1) and ovine herpesvirus 2 (OvHV-2), which cause similar T-lymphoproliferative disease, do not produce homologs of HSUR 1. Instead, AlHV-1 and OvHV-2 encode—in the syntenic regions of their genomes—viral homologs of miR-27 target proteins involved in T-cell activation (18) (Fig. 3).

Murine cytomegalovirus (MCMV), a betaherpesvirus, also degrades host miR-27 using an antisense mechanism similar to that of HVS (20–22). Here the viral agent is not an ncRNA but a MCMV mRNA called m169, which contains a miR-27 target site in its 3′ untranslated region (3′ UTR). Interaction between m169 and miR-27 leads to 3′ tailing, trimming, and degradation of miR-27 (21, 22). In addition to rapid miRNA degradation, the level of the m169 transcript is reciprocally regulated by miR-27 (22). Like HSUR 1, m169 forms extensive base-pairing interactions not just with the seed sequence at the 5′ end but also with the 3′ end of miR-27. This interaction mode is different from the usual complementarity between cellular mRNAs and miR-27, which involves strong interaction only with the seed sequence (Fig. 2B). Presumably these more extensive base-pairing interactions lead to uridylation and degradation of miR-27 (23).
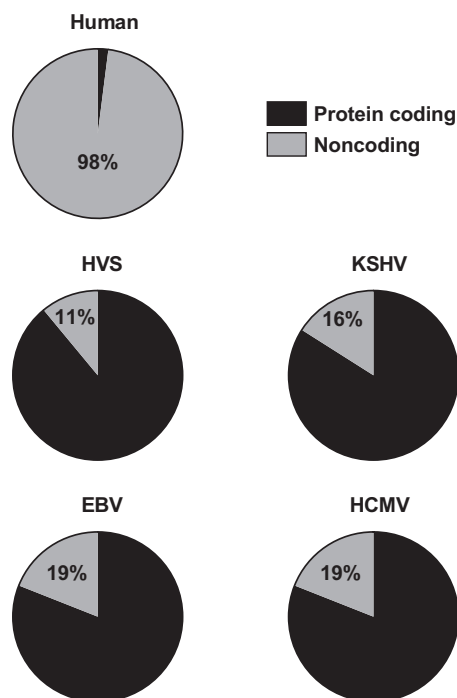
Why MCMV degrades miR-27 is still a mystery, even though it was reported that miR-27 degradation is important for efficient MCMV replication in mice (22). Because MCMV has a different cell tropism (such as macrophages, dendritic cells, fibroblasts, and hepatocytes [24]) than the T-lymphotropic gammaherpesvirus HVS, it is unlikely that MCMV degrades miR-27 to promote T-

FIG 1 Protein coding potential of human and herpesviral genomes. HVS, herpesvirus saimiri; KSHV, Kaposi's sarcoma-associated herpesvirus; EBV, Epstein-Barr virus; HCMV, human cytomegalovirus.

cell activation. One miR-27 target that might be important for both beta- and gammaherpesviruses is interleukin 10 (IL-10) (18). Many herpesviruses encode viral homologs of IL-10 that function similarly to cellular IL-10; these viral homologs modulate the host immune response and are thus important for the viral life cycle (25).

In contrast to MCMV, human cytomegalovirus (HCMV) does not regulate miR-27 levels. It instead encodes a IL-10 homolog in its genome. This approach may be functionally equivalent to upregulation of cellular IL-10 via degradation of miR-27 by MCMV. Together, these observations suggest that herpesviruses employ two alternative mechanisms—antisense-RNA-mediated miRNA degradation and acquisition of host protein-coding gene targets of miRNAs—to modify the host cell expression program to the benefit of the virus.

Since miRNAs usually target hundreds of mRNAs, one question regarding the biological function of miRNAs is whether the repression of the entire target network (with only moderate effects on individual targets) is important or whether only a few targets are dominant (7). The degradation of miR-27 by HVS versus the acquisition of the miR-27 target gene homologs by AlHV-1 and OvHV-2 sheds light on this critical question. Even though cellular miR-27 targets many mRNAs in the TCR signaling network, one target, SEMA7A, seems to be most important for T-lymphotropic gammaherpesviruses. Indeed, cellular SEMA7A mRNA contains two highly conserved target sites among the most robust miR-27–Argonaute binding sites revealed by HITS-CLIP, and the magnitude of SEMA7A protein repression by miR-27 is the largest for all validated targets (18).

miR-17~92 degradation by human cytomegalovirus. HCMV clinical strains contain a 15-kilobase region in the viral genome that is required for host cell tropism, latency, host cyto-
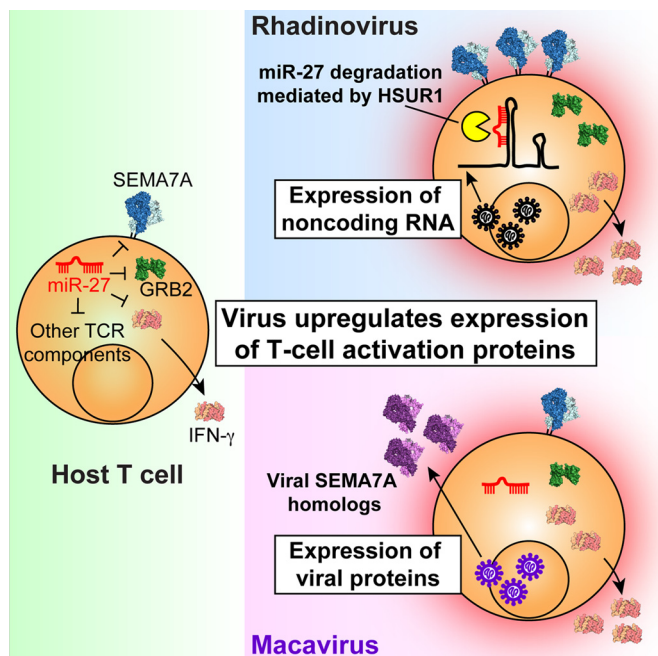
kine regulation, and immune response (26). This region, which is absent in attenuated HCMV laboratory strains (26), produces a bicistronic mRNA UL144-145 that mediates degradation of cellular miR-17/miR-20a family miRNAs in a base-pairing-dependent and sequence-specific manner, similar to miR-27 degradation by HVS and MCMV (26). The host miR-17 ~92 cluster generates six mature miRNAs: miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1. This cluster and its paralogs (mir-106a~363 and mir-106b~25 clusters) act as oncogenes by promoting cell proliferation and tumor angiogenesis, while suppressing apoptosis (27). However, because HCMV is not a cancer-causing virus, degradation of these host miRNAs is likely beneficial to the virus for reasons other than oncogenesis. HCMV degrades only two of the miRNAs in the cluster, miR-17 and miR-20a, which differ by only two nucleotides and share the same seed sequence (26). Among the few direct mRNA targets that are currently known for miR-17 and miR-20a are the E2F-family transcription factors E2F1, E2F2, and E2F3 (28). HCMV strains carrying mutations in the single miR-17/miR-20a binding site show reduced synthesis of viral DNA and delayed viral production during lytic infection (26). It is currently unclear how miR-17 and miR-20a degradation affects HCMV DNA synthesis.

Degradation of host microRNAs by poxviruses. Poxviruses are complex DNA viruses that replicate in the cytosol of infected cells, causing human diseases such as smallpox (5). Insect and mammalian poxviruses, *Amsacta moorei* entomopoxvirus (AMEV) and vaccinia virus (VACV), respectively, use viral poly(A) polymerase (VP55) to add A tails to all host miRNAs, which induces miRNA degradation (29). There are two possible explanations for why the virus-induced global degradation of host miRNAs might be beneficial to the viral life cycle. First, host miRNAs may target the long 3′ UTRs of viral mRNAs. Therefore, degradation of host miRNAs could reduce possible host miRNA-mediated downregulation of viral proteins—a mechanism that poxviruses may have evolved to evade the host miRNA defense system (29). Second, global downregulation of miRNAs is a common feature of many tumor and cancer cells, providing a growth advantage to these cells (30). Perhaps poxviruses reduce host miRNA levels globally (~30-fold) to enhance proliferation of infected cells.

THE BOOSTER

miR-155 upregulation by Epstein-Barr virus. Epstein-Barr virus (EBV) is a gammaherpesvirus associated with several human cancers, such as Hodgkin's disease, Burkitt's lymphoma, and nasopharyngeal carcinoma (5). In latently infected human B cells, EBV induces the expression of many host miRNAs; miR-155, which is induced ~1,000-fold, is the most highly expressed miRNA (31–33). The miR-155 host gene is located in the B-cell integration cluster (BIC), which is transcriptionally activated by insertion of retroviruses in virally induced B-cell lymphomas (34). miR-155 plays important immunomodulatory roles in B cells, T cells, macrophages, and dendritic cells (35–37). Importantly, miR-155 is an oncogenic miRNA. Transgenic mice constitutively expressing high levels of mouse miR-155 (about 10-fold compared to wild-type animals) develop B-cell leukemia and lymphoma (38); transient miR-155 induction in the bone marrow leads to pathology similar to acute myeloid leukemia (39). miR-155 target mRNAs are implicated in hematopoietic development and disease (39), transcription regulation (31), the NK-κB signaling pathway (32),

A

miR-27

HSUR 1

Sm

²,²,⁷M3GPPPACACUACAUAUUUAUUUAUUUAUUUCUUA UUGCUGACCAAUUUUUGUAGCA 3′

B

```
miR-27: 3' CGCCUUGAAUCGGUGACACUUU 5'
           .||||||||   ||||||
HSUR 1: 5' CUGGAACUUA-AAUCUGUGAU 3'
```

```
miR-27: 3' CGCCUUGAAUCGGUGACACUUU 5'
           ||||||.  |  .||||||
m169:   5' GCGGAAU-AAUAAGCUGUGAA 3'
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```
miR-27: 3' CGCCUUGAAUCGGUGACACUUU 5'
           ||.   |  | ||||||||
SEMA7A: 5' CAUGAGGGCACCGACUGUGAA 3'
Site #1
```

```
miR-27: 3' CGCCUUGAAUCGG---UGACACUUU 5'
           |||||||  |   |||||||||
SEMA7A: 5' UUAUAACUUAGGCUAAACUGUGAA 3'
Stie #2
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```
miR-27: 3' CGCCUUGAAUCGGUGACACUU 5'
           || | | |  . |||||||||
GRB2:  5'  UAGGUAGUGAUUAACUGUGAA 3'
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miR-27: 3' CGCCUUGAAUCGGUGACACUUU 5'
           ||.  |  |||||||
IFNG:  5'  AAUAUUGUUGACAACUGUGAC 3'
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FIG 2 Base-pairing interactions between miR-27 and other RNAs. miR-27 seed nucleotides 2 to 8 are highlighted in red. (A) An HVS ncRNA, HSUR 1, base pairs with host miR-27, leading to its degradation. Nucleotides conserved between HVS strains and the related virus HVA (herpesvirus ateles) are in bold. The Sm protein binding site is boxed. (B) Complementarity of miR-27 with HSUR 1 is compared to that with various viral and host mRNAs, as discussed in the text.

B-cell proliferation, and lymphocyte homeostasis (40). Recent genome-wide high-throughput studies, such as mRNA sequencing (mRNA-seq) analyses, stable isotope labeling by amino acids in cell culture (SILAC) proteomics, and HITS-CLIP, have confirmed some of these targets, as well as identified additional ones (40–42). In EBV-positive lymphoblastoid cell lines (LCLs) and diffuse large B-cell lymphomas (DLBCLs), inhibition or deletion of miR-155 reduces growth and promotes apoptosis (33). Therefore, EBV-induced upregulation of host miR-155 may be key to virus-induced oncogenesis.

miR-155 mimicry by Kaposi's sarcoma-associated herpesvirus, Marek's disease virus type 1, and simian foamy virus. Kaposi's sarcoma-associated herpesvirus (KSHV) is a gammaherpesvirus that is the causative agent of several human B-cell cancers, including Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease (5). KSHV encodes 12 precursor miRNAs (pre-miRNAs), which produce 25 mature miRNAs (one miRNA is edited) (43, 44). Among them, mature miR-K12-11 (also known as miR-K11) shares its seed sequence (nucleotides 1 to 8) with host miR-155 (45). Two groups independently showed that miR-K12-11 and miR-155 regulate a common set of host mRNA targets, including transcription factors (e.g., BACH-1, FOS,

and HIVEP2), a B-cell regulator (i.e., SLA), innate immunity modulators (e.g., PIK2CA and IKBKE), and proapoptotic proteins (e.g., LDOC-1, BIRC4BP, and XAF1) (46, 47). More recently, genome-wide Argonaute photoactivatable-ribonucleoside-enhanced cross-linking and immunoprecipitation (PAR-CLIP) and HITS-CLIP studies confirmed that ~20 to 40% of miR-155 targets (121 and 151, respectively) are also targeted by miR-K12-11 (48, 49). This interesting observation suggests that KSHV produces a miRNA that mimics a miRNA master regulator to hijack an existing host gene network. Furthermore, host miR-155 is not expressed at detectible levels in KSHV-infected BC1 cells and primary effusion lymphoma (PEL) cells; both cell types instead express high levels of miR-K12-11 (46, 47, 49). Moreover, KSHV appears to use a similar miRNA mimicry strategy on other host miRNAs. For instance, KSHV miRNA miR-K12-10a shares seed nucleotides 2 to 8 with the abundant hematopoietic-cell-specific host miR-142-3p (48); similarly, miR-K12-3 and its isoform miR-K12-3+1 share a seed sequence identical to that of cellular miR-23 (50).

One of the limitations in studies of KSHV mimicry of host miR-155 is that no direct experimental evidence shows that miR-K12-11 is functionally equivalent to miR-155 in the context of the

FIG 3 miR-27 is a pleiotropic repressor of T-cell activation that targets TCR signaling pathway components and downstream effector cytokines. In rhadinovirus (i.e., HVS)-infected cells, HSUR 1 upregulates expression of T-cell activation proteins by mediating degradation of miR-27. Distantly related macaviruses (i.e., AlHV-1 and OvHV-2) instead encode homologs of miR-27 target genes. Adapted from *Molecular Cell* (18) with permission of the publisher.

virus. However, several studies of another oncogenic herpesvirus, Marek's disease virus type 1 (MDV-1), shed light on this important question. MDV-1 is an alphaherpesvirus that causes aggressive T-cell lymphomas in chickens, known as Marek's disease (51). Interestingly, MDV-1 encodes a viral homolog of miR-155, called miR-M4, that shares seed nucleotides 1 to 8 with the host miRNA (52). Deletion of miR-M4 from MDV-1 or a 2-nucleotide mutation in the miR-M4 seed sequence abolishes MDV-1-induced oncogenicity and inhibits induction of lymphomas. This oncogenic phenotype can be rescued by revertant viruses expressing either miR-M4 or host miR-155 (53). Such studies provide direct evidence that the viral homolog and host miR-155 function similarly and argue that different viruses express miR-155 homologs to regulate the oncogenic gene network targeted by miR-155.

In addition to herpesviruses, retroviruses, such as simian foamy virus (SFV) and bovine leukemia virus (BLV), use similar mimicry strategies to boost levels of certain host miRNAs. SFV of African green monkeys (SFVagm) produces at least 6 mature miRNAs from its long terminal repeat (LTR) regions by RNA polymerase III transcription (54). Two of these viral miRNAs—SFVagm-miR-S4-3p and SFVagm-miR-S6-3p—exhibit seed sequence homology with host lymphoproliferative miR-155 and immunosuppressive miR-132, respectively (54). Similarly, one viral miRNA produced by B-lymphotropic BLV, BLV-miR-B4, shares its seed sequence with host B-cell tumorigenic miR-29a (55). All of these viral miRNA mimics target the same set of genes as their host counterparts (54, 55).

THE HIJACKER

miR-122 positively regulates hepatitis C virus replication. Hepatitis C virus (HCV) is a positive-strand RNA virus associated with many liver diseases (5). miR-122 is a very abundant liver-specific miRNA (56) which regulates fatty acid and cholesterol biosynthesis (57, 58). miR-122 facilitates the replication, but not the translation or stability, of the HCV genomic RNA via base-pairing interactions with two conserved binding sites in the internal ribosome entry site (IRES) near the 5′ terminus of the genomic RNA (59, 60). Insertion of the HCV miR-122 binding site sequences into the 3′ UTR of a reporter gene instead causes downregulation, suggesting that the context of the miR-122 sites, as well as other virus and host factors, is important for miR-122-facilitated replication of viral RNA (60). The molecular mechanism by which miR-122 facilitates replication is still unknown, but it is critical for the HCV life cycle. miR-122 expression is sufficient to convert nonhepatic cells to become HCV permissive (61, 62). On the other hand, silencing of miR-122 with an antisense locked nucleic acid oligonucleotide leads to long-lasting suppression of HCV in infected primate models (63).

miR-138 and miR-200 promote latency of herpes simplex virus type 1 and human cytomegalovirus, respectively. Herpes simplex virus type 1 (HSV-1) is an alphaherpesvirus that replicates in epithelial cells but establishes latency in sensory neurons (5). HSV-1 expresses several immediate early proteins, including ICP0, which plays important roles in both latent and lytic infection (64). Host miR-138 is abundant in the brain (65), where it regulates dendritic spine morphogenesis by downregulation of APT1 (66). The ICP0 mRNA contains two miR-138 target sites (confirmed by PAR-CLIP analysis [67]); consequently, the production of ICP0 proteins is repressed by miR-138. The biological significance of this regulation was tested *in vivo*: mice infected with HSV-1 containing three point mutations in each of the two miR-138 seed binding sites had higher levels of ICP0 and lytic gene expression during establishment of latency (67). However, no difference in virus replication was detected between wild-type and miR-138 target site-mutated HSV-1 either in culture or in mice (67). Similarly, host miR-200 family miRNAs repress HCMV immediate early protein UL122 (IE2) via a miR-200 seed binding site in the IE2 3′ UTR, and recombinant virus carrying mutations in the miR-200 binding site produces lytic rather than latent infection in primary cells (68). Because UL122 is a key transcription factor regulating HCMV lytic genes (5), miR-200 plays a critical role in viral latency. Furthermore, the host miR-17 family miRNAs regulate EBV latent transcripts LMP1 and BHRF1 (69). Therefore, critical roles for host miRNAs in controlling the lytic-to-latent switch are not uncommon in herpesvirus-infected cells.

miR-142 restricts cell type specificity of North American eastern equine encephalitis virus. North American eastern equine encephalitis virus (EEEV) has a single-stranded sense RNA genome and can cause fatal infections in humans (5). miR-142-3p is a hematopoietic-cell-specific miRNA (65) which is involved in specification, formation, and differentiation of hematopoietic stem cells (70, 71), macrophage differentiation (72), proliferation and differentiation of mesenchymal cells in lungs (73), proliferation of CD25$^+$ CD4 T cells (74), and the migration of CD4 T cells (75). miR-142-3p binds three highly conserved target sites in the 3′ UTR of the EEEV genomic RNA, thereby potently restricting EEEV in myeloid-lineage cells by blocking viral translation and

TABLE 1 Summary of virus-host miRNA interactions

Virus	Host miRNA	Mechanism	Function	Reference(s)
Herpesvirus saimiri	miR-27	Antisense-RNA-mediated degradation	Promotes T-cell activation	16, 18
Mouse cytomegalovirus	miR-27	Antisense-RNA-mediated degradation	Important for efficient viral replication	20–22
Human cytomegalovirus	miR-17/20	Antisense-RNA-mediated degradation	Accelerates viral production	26
Vaccinia virus	All miRNAs	Tailing and degradation initiated by viral poly(A) polymerase	Counteracts host antiviral defense	29
Epstein-Barr virus	miR-155	Expression increased by virus	Oncogenesis	31–33
Kaposi's sarcoma-associated herpesvirus	miR-155, miR-142-3p, miR-23	Mimicry by viral miR-K12-11, miR-K12-10a, miR-K12-3	Oncogenesis	46–48, 50
Marek's disease virus type 1 virus	miR-155	Mimicry by miR-M4	Oncogenesis	52, 53
Simian foamy virus	miR-155, miR-132	Mimicry by SFVagm-miR-S4–3p, SFVagm-miR-S6–3p	Lymphoproliferation and innate immune suppression	54
Bovine leukemia virus	miR-29a	Mimicry by BLV miR-B4	Oncogenesis	55
Hepatitis C virus	miR-122	Binds 5′ UTR of viral RNA genome	Facilitates viral genome replication	59, 60
Herpes simplex virus 1	miR-138	Represses ICP0 expression	Promotes latency	67
Human cytomegalovirus	miR-200	Represses UL122 expression	Promotes latency	68
Eastern equine encephalitis virus	miR-142-3p	Binds 3′ UTR of viral RNA genome	Restricts host tropism and suppresses innate immunity	76

subsequent replication (76). This miRNA-mediated restriction is important for efficient infection because it suppresses host cell type I interferon-induced antiviral immunity (76). miR-142-3p-mediation of innate immune suppression was reported in an earlier study where miR-142-3p binding sites were introduced into the influenza virus genome, leading to a reduced type I interferon response (77). Perhaps other viruses also hijack miR-142-3p to suppress innate immunity.

OTHER VIRUS-HOST miRNA INTERACTIONS

In addition to the examples discussed above, some host miRNAs carry out antiviral functions by suppressing viral infection in host cells. For example, miR-32 base pairs with mRNA of primate foamy virus type 1 (PFV-1, a retrovirus) and thereby restricts the accumulation of viral RNAs in human cells (78). Similarly, miR-24 and miR-93 mediate antiviral defense against vesicular stomatitis virus (VSV, a negative-sense RNA virus) infection in mice by targeting the viral large protein (L protein) and phosphoprotein (P protein) genes, respectively (79). In human T lymphocytes, miR-29a sequence-specifically targets the 3′ UTR of human immunodeficiency virus type 1 (HIV-1, a retrovirus) mRNA, reducing HIV-1 production and infectivity (80). miR-145 directly targets human papillomavirus (HPV, a DNA virus) E1 and E2 open reading frames to reduce HPV genome amplification and late gene expression (81). However, it is still debatable whether host miRNAs play antiviral roles in the physiological context of infection (43). For example, by global depletion or downregulation of host miRNAs, two recent studies show that the miRNA pathway does not counteract infection by a wide range of viruses in mammalian cells (82, 83).

FINAL REMARKS

In the past few years, there has been an explosion in discovery of novel virus-host miRNA interactions (Table 1). In most cases, the biological significance and the underlying mechanisms remain to be elucidated. More such interactions are likely to be discovered. Therefore, future work in this area will provide molecular insights

not only into viral infection but also into host gene regulation mechanisms and viral evolution.

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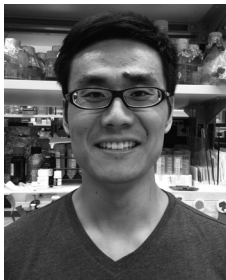
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