Chapter 12

Noncoding RNAs in Retrovirus Replication

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Chapter Outline

INTRODUCTION

Prior to the Human Genome Project, it was estimated that human genomes contained roughly 100,000 genes encoding proteins (Taft et al., 2007). In actuality, humans possess only ~20,000 protein-coding genes, which is 10,000 more than the fruit fly, *Drosophila melanogaster*, and 15,000 fewer than rice, negating the hypothesis that the number of genes correlated with complexity of the organism (Mattick, 2001). It is now apparent that only 2% of the human genome codes for proteins, whereas the remaining 98% is composed of endogenous retroviruses (ERVs) and noncoding RNA (ncRNA) (Frias-Lasserre, 2012).

Although a limited percentage of the genome produces proteins, approximately 90% is transcribed, indicating important roles for ncRNA (Veneziano et al., 2016; Birney et al., 2007; Elgar and Vavouri, 2008). The term "ncRNA" applies to any RNA that is not translated into protein (Mattick and Makunin, 2006). Generally, ncRNAs are divided into groups based on their size and activity, although other classification systems are sometimes used (Mattick and Makunin, 2006; Geisler and Coller, 2013; St Laurent et al., 2015). Ribosomal RNA (rRNA) and transfer RNA (tRNA) are the most well-characterized species of ncRNA, which are both integral components of mRNA translation (Mattick and Makunin, 2006). The untranslated regions (UTRs) of mRNAs can also be classified as ncRNA, and play critical roles in the regulation of mRNA translation, as well as viral life cycles (Mattick and Makunin, 2006). Small ncRNAs (generally <200 nt) include small nuclear RNA (snRNA), microRNA (miRNA), tRNA-derived fragments (tRFs), piwi-interacting RNA (piRNA), repeat-associated small interfering RNA, and Y RNAs (Veneziano et al., 2016; Mattick and Makunin, 2006; Berkhout and Jeang, 2007). Long ncRNAs (lncRNAs) are longer than 200 nts, more loosely classified, and less well understood (Geisler and Coller, 2013; Mercer et al., 2009; Rinn and Chang, 2012). For more in-depth analysis of small ncRNA and lncRNA nomenclature and functions see reviews by Mattick and Makunin (2006) and St Laurent et al. (2015).

Because viral genomes are compact, the evolutionary conservation of proteins and ncRNA underscores their importance in the viral life cycle (Tycowski et al., 2015). The first viral ncRNAs were identified in 1966 and were isolated from the adenovirus (Reich et al., 1966). These RNAs were found to counteract protein kinase R (PKR) through competitive binding with viral dsRNA transcripts, blocking the host's ability to sense infection (de Haro et al., 1996). ncRNAs have been found to have functions at nearly every step of viral replication cycles (Cullen, 2009). For example, many viruses use internal ribosomal entry sites (IRESs) to preferentially translate viral mRNA over host mRNA (Pelletier and Sonenberg, 1988; Jang et al., 1988). Some retroviruses and all coronaviruses exploit RNA structures to cause ribosomal frameshifting resulting in the Gag-Pol and 1a/1b polyproteins, respectively (Brierley and Dos Ramos, 2006). Specific RNA structures within viral RNA can also enhance transcription and exportation of viral RNA from the nucleus (Fisher et al., 1986; Kao et al., 1987; Feng and Holland, 1988; Malim et al., 1989). RNA interference (RNAi), thought to be an early version of the innate immune response to viral infection, can still be observed in plants and invertebrates today, as discussed in more detail later in this chapter (Cullen, 2009; Voinnet, 2001). Many viruses produce miRNAs to counteract host responses and defenses (Tycowski et al., 2015), and retroviruses and long terminal repeat (LTR) retrotransposons use host tRNAs to prime reverse transcription (Waters and Mullin, 1977; Mak and Kleiman, 1997). This chapter will focus on ncRNAs of both host and viral origin and their roles in retroviral replication cycles.

HOST RNAs PACKAGED INTO VIRIONS

It is estimated that RNA constitutes approximately 50% of the mass of retroviral particles; roughly half of retroviral RNA by weight is cellular RNA (Bonar et al., 1967; Berkowitz et al., 1996; Bonar and Beard, 1959; Eckwahl et al., 2016b). The most commonly found RNAs packaged into retrovirus virions, excluding viral RNA and tRNAs, are host mRNA, 7SL RNA, U snRNA, Y RNA, and vault RNA (typically abbreviated vtRNA or vRNA, but here it is represented by vltRNA to avoid confusion with viral tRNAs and viral RNA), a majority of which are ncRNA (Bonar et al., 1967; Telesnitsky and Wolin, 2016; Onafuwa-Nuga et al., 2005, 2006; Eckwahl et al., 2015; Bishop et al., 1970; Giles et al., 2004; Garcia et al., 2009; Ali et al., 2016). Host mRNAs are a minority species of RNA packaged into retrovirus virions (Onafuwa-Nuga et al., 2006; Harris et al., 2003; Muckenfuss et al., 2006). Generally, the amount of packaged mRNA is proportional to the concentration within the host cell in the absence of viral genomic RNA (Kiss, 2004). In addition, mRNAs packaged in place of genomic RNA tend to have longer 3′ UTRs, a common feature of retroviral genomic RNA, suggesting the length of the 3′UTRs may be a determinant for packaging (Kiss, 2004; Matera et al., 2007). Initially, it was hypothesized that packaging of cellular RNAs was either random or a contamination of the purified virions, and that these RNAs did not play a significant role in the retrovirus life cycle (Bonar et al., 1967; Wollmann and Kirsten, 1968; Harel et al., 1965). However, as more roles for ncRNA in the cell began to emerge it became clear that these RNAs may indeed participate in the viral life cycle. Below, the most common RNAs packaged into virions will be described and potential packaging mechanisms will be briefly discussed.

Transfer RNAs

During reverse transcription, retroviruses, retrotransposons, and plant viruses known as pararetroviruses, which replicate through an RNA intermediate and are also reverse transcribed, use host tRNAs as primers for cDNA synthesis (Mak and Kleiman, 1997; Guilley et al., 1983; Medberry et al., 1990; Hay et al., 1991; Marquet et al., 1995). Each virus contains a primer-binding site (PBS) in their 5′ UTR that is complementary to 8–18 nucleotides (nt) of a host tRNA (Mak and Kleiman, 1997; Marquet et al., 1995) (Table 12.1). Generally, the 3′ acceptor stem of the tRNA is unwound and annealed to the PBS (Marquet et al., 1995). However, for some members of the retrotransposon Ty1/copia and Ty5 groups, priming begins at an internal site of the tRNA overlapping the anticodon stem loop (Voytas and Boeke, 1993). Interestingly, T1 retrotransposons found in *D. melanogaster* were directly shown to be primed by a fragment of tRNA$_i^{Met}$ instead of the full-length tRNA that is thought to be the primer in most other cases (Marquet et al., 1995; Voytas and Boeke, 1993; Sandmeyer and Menees, 1996). It has been suggested that a fragment of tRNA^{Pro} (tRF-3019) could also be substituted for the primer tRNA in human T-cell leukemia virus (HTLV) (Ruggero et al., 2014; Seiki et al., 1982). tRF-3019 produced from the

TABLE 12.1 Proposed Host Transfer RNAs (tRNAs) Used as Primers for Retroviral Reverse Transcription

Genera	Virus	Host Species	Primer	References
Alpharetrovirus	ALV/RSV	Avian	tRNA[Trp]	Sawyer and Dahlberg (1973)
Betaretrovirus	MMTV	Murine	tRNA[Lys3a]	Majors and Varmus (1983)
	Mason–Pfizer monkey virus	Macaca	tRNA[Lys1,2]	Leis (1993)
Gammaretrovirus	MLV	Murine	tRNA[Pro, Glu]	Taylor (1977) and Colicelli and Goff (1986)
	GALV	Primate	tRNA[Pro]	Delassus et al. (1989)
	FLV	Feline	tRNA[Pro]	Laprevotte et al. (1984)
Deltaretrovirus	BLV	Bovine	tRNA[Pro]	Couez et al. (1984)
	HTLV	*H. sapiens*	tRNA[Pro]	Seiki et al. (1983)
Epsilonretrovirus	Walleye dermal sarcoma	*Sander vitreus*	tRNA[His]	Holzschu et al. (1995)
Lentivirus	HIV-1, HIV-2	*H. sapiens*	tRNA[Lys3]	Wain-Hobson et al. (1985)
	SIV	Primate	tRNA[Lys3]	Berkhout (1997)
	EIAV	Equine	tRNA[Lys3]	Kawakami et al. (1987)
	FIV	Feline	tRNA[Lys3]	Miller et al. (2001)
Spumavirus	SFV	Primate	tRNA[Lys1,2]	Rabin et al. (1976) and Schnitzer (1981)
	PFV	Primate	tRNA[Lys1]	Maurer et al. (1988)
	EFV	Equine	tRNA[Lys1]	Tobaly-Tapiero et al. (2000)
	FFV	Feline	tRNA[Lys1]	Riggs et al. (1969)
	BFV	Bovine	tRNA[Lys1]	Malmquist et al. (1969)

Genera	Virus	Host Species	Primer	References
Endogenous	CHIA34	Chinese Hamster	tRNA^{Phe}	Lie et al. (1994)
	PERV	Porcine	tRNA$^{Gly, Pro}$	Akiyoshi et al. (1998) and Bartosch et al. (2002)
	Squirrel Monkey	Saimirinae	tRNA^{Lys1,2}	Chiu and Skuntz (1986)
	Jaagsiekte sheep	*Ovis aries*	tRNA^{Lys1,2}	Cann (2001)
	HERV	*H. sapiens*	tRNA^{Lysb}	Tristem (2000)
	AKV	AKR mice	tRNA^{Glu}	Nikbakht et al. (1985)
	KoRV	Phascolarctos	tRNA^{Pro}	Hanger et al. (2000)
	MINERVa	Miniopteridae	tRNA$_{Pro}$	Farkasova et al. (2017)
	Rhinolophus ferrumequinum retrovirus (RfRV)	*R. ferrumequinum*	tRNA^{Pro}	Cui et al. (2012)

Continued

TABLE 12.1 Proposed Host Transfer RNAs (tRNAs) Used as Primers for Retroviral Reverse Transcription—cont'd

Genera	Virus	Host Species	Primer	References
Retrotransposons	Ty1, Ty2	*Saccharomyces cerevisiae*	$tRNA_i^{Met}$	Friant et al. (1997)
	tom	*Drosophila*	$tRNA^{Ser}$	Stefanov et al. (2012)
	Ty4	*S. cerevisiae*	$tRNA^{Asn}$	Voytas and Boeke (1993)
	Ty5	*S. cerevisiae*	$tRNA_i^{Met}$-fragment	Voytas and Boeke (1993)
	Copia	*Drosophila*	$tRNA_i^{Met}$-fragment	Kikuchi et al. (1986)
	Gypsy	*Drosophila*	$tRNA^{Lys}$	Sandmeyer and Menees (1996) and Springer and Britten (1993)
	mdg1 and 412	*Drosophila*	$tRNA^{Arg}$	Tubio et al. (2004)
	Elements 297 and 17.6	*Drosophila*	$tRNA^{Ser}$	Marquet et al. (1995)
	mdg.3	*Drosophila*	$tRNA^{Leu}$	Marquet et al. (1995)
	Ty3	*S. cerevisiae*	$tRNA_i^{Met}$	Pochart et al. (1993)

ALV, avian leukosis virus; *BFV*, bovine foamy virus; *BLV*, bovine leukemia virus; *EFV*, equine foamy virus; *EIAV*, equine infectious anemia virus; *FFV*, feline foamy virus; *FIV*, feline immunodeficiency virus; *FLV*, feline leukemia virus; *GALV*, gibbon ape leukemia virus; *HERV*, human endogenous retrovirus; *HTLV*, human T-cell leukemia lymphoma virus; *KoRV*, Koala retrovirus; *MLV*, murine leukemia virus; *RSV*, Rous sarcoma virus; *SIV*, simian immunodeficiency virus; *SFV*, simian foamy virus; *PFV*, prototype foamy virus.

[a]*Mammalian $tRNA^{Lys}$ has two isoacceptors, CUU and UUU. The human genome encodes at least 44 putative $tRNA^{Lys}$ species (Lowe and Eddy, 1997-http://gtrnadb.ucsc.edu) that have slight variation outside of the anticodon, i.e., isodecoders. Therefore, $tRNA^{Lys1,2}$ represents $tRNA^{Lys,CUU}$ with 24 different isodecoders and $tRNA^{Lys3}$ represents $tRNA^{Lys,UUU}$ with 20 different isodecoders. Whether all of these are expressed and function as tRNAs in translation or as primers is unknown.*

[b]*tRNA primer varies depending on specific HERV species, however, many use $tRNA^{Lys}$ isoacceptors.*

3′ acceptor stem was found to prime RT in vitro and was detected in viral particles collected from HTLV-infected cells (Ruggero et al., 2014).

Low levels of tRFs are present under homeostatic conditions, however specific cleavage of tRNAs occurs under stress conditions (oxidative stress, heat shock, UV radiation, and viral infection) (Anderson and Ivanov, 2014; Sobala and Hutvagner, 2011). The biological function of at least some tRFs is thought to involve the RNA silencing pathway, and exogenous expression of the 5′ acceptor stem fragments results in a 10%–15% reduction in global translation (Anderson and Ivanov, 2014; Emara et al., 2010). Production of tRFs is also found in human cancers and may play a role in neurodegenerative diseases (Anderson and Ivanov, 2014). Recently, two tRFs were characterized across several mouse stem cell lines (Schorn et al., 2017). tRFs (18-nt) derived from the 3′ terminus of tRNA^{Lys3} were found to interfere with reverse transcription of ERVs, maintaining viral expression but limiting the mobility of the retroelements (Schorn et al., 2017). Additionally, 22-nt tRFs also derived from the 3′ end of tRNA^{Lys3} resulted in posttranscriptional silencing of viral RNA and proteins (Schorn et al., 2017). These tRFs allow for fine tuning of ERV expression, many of which are thought to have gained regulatory roles in the host cells as described below.

tRNA maturation is highly regulated and involves processing 3′ and 5′ leader sequences, excision of introns, if present, and extensive nucleotide modification (Phizicky and Hopper, 2010). The process of tRNA maturation is further complicated by several nuclear export and import steps to proofread some tRNA species (Hopper, 2013). Intriguingly, some pre-tRNAs are packaged into MLV and HIV-1 virions, although the function of these RNAs is not known (Eckwahl et al., 2015). Limiting the expression of a transport protein known to export pre-tRNAs, exportin-5, blocked packaging of pre-tRNAs into MLV and HIV-1 virions (Eckwahl et al., 2015). This finding suggests that pre-tRNAs, and potentially other RNAs packaged into retroviral virions, are recruited shortly after transcription.

The evolutionary selection of one primer tRNA over another is not well understood (Marquet et al., 1995). In some cases, a subpopulation of cellular tRNAs is packaged into virions or virus-like particles (VLPs) at ratios that differ from the host pool, suggesting that these tRNA species are selectively packaged (Waters and Mullin, 1977; Marquet et al., 1995; Keith and Heyman, 1990; Mak et al., 1994). For example, tRNA^{Trp}, the primer for avian leucosis virus (ALV), accounts for 32% of the tRNA packaged into virions, in contrast to 1.4% of the tRNA found in cells (Waters and Mullin, 1977). Additionally, human tRNA^{Lys3} serves as the primer in HIV-1, and tRNA^{Lys} isoacceptors represent approximately 50%–60% of the low-molecular weight RNA within the HIV-1 virion, but only 5%–6% within the cell (Mak et al., 1994). A similar trend, albeit less striking, is observed for Moloney murine leukemia virus (MLV), where primer tRNA^{Pro} constitutes 5%–6% of cellular low-molecular weight RNA and 12%–24% of low-molecular weight vRNA (Waters and Mullin, 1977). Retrotransposons also

package their primer tRNAs into VLPs; the relative concentration of tRNA$_i^{Met}$ increases 10- to 40-fold in Ty1 VLPs (Voytas and Boeke, 1993; Prats et al., 1988).

The mechanism by which tRNA primer enrichment occurs is not known. However, in some instances the cognate aminoacyl-tRNA synthetase is also packaged (Cen et al., 2001, 2002). In the case of HIV-1, human lysyl-tRNA synthetase (LysRS) is packaged into HIV-1 virions (Cen et al., 2001). Knockdown of LysRS, which interacts with the CA domain of HIV-1 Gag, reduces the levels of tRNA^{Lys} packaged into virions, as well as viral infectivity, suggesting that primer tRNA^{Lys3} packaging is facilitated through LysRS (Cen et al., 2001, 2004; Halwani et al., 2004; Dewan et al., 2012; Guo et al., 2003; Javanbakht et al., 2003). Intriguingly, upstream of the PBS in the NL4-3 (subtype B) HIV-1 gRNA there is a stem loop that mimics both the secondary and tertiary structure of the anticodon stem loop of tRNA^{Lys3} and contains exposed uridine residues critical to LysRS binding (Jones et al., 2013, 2014; Liu et al., 2016). Mutation of the uridine residues in the tRNA-like element (TLE) to adenines reduced LysRS binding, as well as primer placement of tRNA^{Lys3} on the PBS, inhibiting reverse transcription and viral infection (Jones et al., 2013). This tRNA mimicry is also found in the MAL isolate (subtype A-like) of HIV-1, suggesting conservation of TLEs across distinct HIV subtypes (Comandur et al., 2017). Overall, HIV-1 Gag is proposed to bind tRNA^{Lys}-bound LysRS and recruit the complex to sites of virion assembly where the TLE effectively competes for LysRS binding, causing the release of the primer and facilitating efficient annealing (Jones et al., 2013; Kleiman et al., 2010).

Mutagenesis studies have been carried out to determine the importance of the specific PBS sequence in retroviral replication (Whitcomb et al., 1995; Das et al., 1995; Lund et al., 1993; Rhim et al., 1991; Wakefield et al., 1996). The PBS of HIV-1 is the best characterized of any retrovirus. Deletions of the entire PBS or nt 1–9 did not produce infectious virus (Rhim et al., 1991). However, deletion of nt 10–18, 7–18, or replacement of nt 7–18 with random nt resulted in delayed production of functionally active virus. Upon sequencing, these virions were found to contain an 18-nt region that was once again fully complementary to tRNA^{Lys3}. Nucleotide insertions and deletions were found 3′ to the PBS suggesting that tRNA^{Lys3} did in fact anneal to the PBS resulting in the reversion to the wild-type (WT), tRNA^{Lys3} specific, PBS (Rhim et al., 1991). Multiple studies mutating the PBS region of HIV-1 to become complementary to different tRNAs produced infectious virions utilizing the substituted tRNA (Das et al., 1995; Wakefield et al., 1995). However, every virus reverted back to a PBS specific for tRNA^{Lys3}, indicating a selective advantage in the use of this particular tRNA. Interestingly, an HIV-1 virus with a PBS complementary to tRNA^{His} was maintained by mutating residues within the HIV-1 genome that are thought to further stabilize interactions with the tRNA outside of the 3′ 18-nt, indicating that residues outside of the PBS may play a role in tRNA use (Wakefield et al., 1996; Berkhout, 1997). Furthermore, packaging of tRNA^{Lys}

occurs independently of HIV-1 genomic RNA packaging, which could contribute to the selective pressure in maintaining a WT PBS (Huang et al., 1994).

Similarly to HIV-1, mutations to the PBS of ALV allowing for the use of tRNA^{Pro}, tRNA^{Lys}, tRNA^{Met}, tRNA^{Ile}, tRNA^{Phe}, and tRNA^{Ser} resulted in short-term maintenance of the mutated PBS and delayed infection followed by reversion to the WT PBS-Trp, suggesting that although other tRNAs can be used, there is a distinct infectivity advantage for the WT PBS (Whitcomb et al., 1995). Interestingly, MLV appears to be more permissive to PBS mutations. Mutation of the PBS matching tRNA^{Pro} to sequences accommodating tRNA^{Glu} or tRNA^{Lys} produced infectious single-cycle replication-competent virus, suggesting that the PBS did not require perfect nt base pairing for efficient priming (Lund et al., 1993). Additionally, using a randomized PBS it was found that MLV replicated efficiently with tRNA$^{Arg(CUC)}$, tRNA$^{Phe(GAA)}$, and tRNA$^{Ser(CGA)}$ (Lund et al., 2000); however, it is possible, based on studies with HIV-1 and ALV, that after a longer period, the sequence would revert back to WT, which was not tested.

Another function of host tRNAs in the retroviral lifecycle is Gag membrane targeting. Phosphatidylinositol (4,5) bisphosphate (PI(4,5)P$_2$)is associated with the cytosolic inner leaflet of the plasma membrane (PM) and acts as a targeting mechanism for PM-localized proteins (Veneziano et al., 2016; Birney et al., 2007; van Meer et al., 2008; Ono et al., 2004). In some retroviruses, including HIV-1, the matrix (MA) domain of Gag binds to PI(4,5)P$_2$, targeting Gag to the plasma membrane (Ono et al., 2004; Olety et al., 2015; Inlora et al., 2011, 2014; Chukkapalli et al., 2008). Plasma membrane targeting of HIV-1 Gag is mediated through a bipartite signal consisting of a myristic acid moiety added to the second amino acid of MA, which inserts into the plasma membrane-anchoring Gag (Waheed and Freed, 2009), in addition to a group of positively charged residues within MA (Zhou et al., 1994). HIV-1 MA contains a highly basic patch that sequesters the myristate prior to membrane binding and is also capable of binding RNA (Waheed and Freed, 2009). Interestingly, cellular RNAs block binding to nonspecific liposomes but are not able to compete for binding to specific PI(4,5)P2-containing membranes, thus enhancing HIV-1 Gag selectivity for PI(4,5)P$_2$-rich membranes (Inlora et al., 2014; Chukkapalli et al., 2008, 2010, 2013; Alfadhli et al., 2009). A cross-linking immunoprecipitation sequencing (CLIP-Seq) study revealed that HIV-1 MA binds almost exclusively to a subset of tRNAs in the cytoplasm (Kutluay et al., 2014) and recently, specific species of tRNA were shown to block nonspecific Gag membrane binding (Todd et al., 2017). Surprisingly, removal of the nucleocapsid (NC) domain of HIV-1 Gag abolished selective binding, suggesting NC may also play a role in membrane targeting (Todd et al., 2017).

tRNAs may also contribute to the nuclear localization of the preintegration complex (PIC) (Zaitseva et al., 2006). Following reverse transcription, the newly transcribed proviral DNA must be imported into the nucleus for integration of the viral genome into the cellular chromosome (Hu and Hughes, 2012). The CA protein is thought to assist in translocation of the PIC into the nucleus

in nondividing cells (Dismuke and Aiken, 2006; Lee et al., 2010; Yamashita and Emerman, 2004). Intriguingly, when HeLa cell cytosolic fractions containing high amounts of tRNA were added back to purified PICs and nuclei, nuclear accumulation of the PICs was observed (Zaitseva et al., 2006). Once imported into the nucleus, tRNAs and CA must dissociate from the HIV-1 proviral DNA to allow integration into the host genome (Dismuke and Aiken, 2006). Transportin 3 (TNPO3) was found to bind and export tRNAs and CA in a RanGTP-dependent manner, facilitating efficient uncoating of the viral genome after nuclear entry (Zhou et al., 2011). TNPO3 is implicated in the nuclear export of defective tRNAs, including those lacking the 3′ CCA end (Zaitseva et al., 2006). The export of defective tRNAs to the cytoplasm is counterproductive to protein translation, suggesting the defective tRNAs may function as tRFs (Zhou et al., 2011).

7SL RNA

7SL RNA is packaged at high concentrations by all retroviruses that have been examined to date including MLV, HIV-1, avian retroviruses, feline leukemia virus, visna virus, and equine infectious anemia virus (Telesnitsky and Wolin, 2016; Bishop et al., 1970; Brian et al., 1975; Cheevers et al., 1977; Duesberg and Robinson, 1966; Levin et al., 1974; Lin and Thormar, 1971; Peters et al., 1977). Besides genomic RNA and tRNAs, 7SL RNA is the most well-characterized ncRNA packaged into virions. In eukaryotes, 7SL is a 300-nt RNA named according to its sedimentation coefficient and was first identified as a prevalent RNA in RSV particles (Bishop et al., 1970; Ullu and Tschudi, 1984). Within the cell, 7SL RNA is part of the signal recognition particle (SRP) ribonucleoprotein complex (RNP), which functions in regulating the secretion of proteins in mammals (Ullu and Tschudi, 1984; Walter and Blobel, 1982). As protein translation occurs, hydrophobic sequences at the N-terminus of nascent peptides are recognized by the SRP (Cross et al., 2009), which is composed of six proteins (SRP9, 14, 19, 54, 68, and 72) and 7SL RNA. Once bound to membrane or secretory proteins, SRP is responsible for targeting these growing proteins to the endoplasmic reticulum (ER) for further distribution (Walter and Blobel, 1982; Cross et al., 2009; Luirink and Sinning, 2004). In addition to acting as scaffolding for the assembly of the SRP proteins, the RNA has roles in accelerating the binding to the SRP receptor on the ER surface and triggering conformational changes that induce GTP hydrolysis by the receptor (Telesnitsky and Wolin, 2016; Cross et al., 2009).

In the case of retroviruses, 7SL RNA is highly enriched in virions (Bishop et al., 1970; Erikson et al., 1973; Walker et al., 1974; Brameier et al., 2013; Wang et al., 2007; Keene and Telesnitsky, 2012). For example, in HIV-1 virions, there are 14 copies of 7SL packaged in comparison with 2 copies of gRNA per HIV-1 virion (Onafuwa-Nuga et al., 2006). Interestingly, although 7SL RNA is predominantly found within the SRP, major SRP components SRP19 and 54 have not been found in virions, while minimal amounts of SPR14 are encapsidated (Eckwahl

et al., 2015; Wang et al., 2008). These studies suggest that viral 7SL is newly synthesized and diverted to assembling virions prior to assembly of the larger RNP (Eckwahl et al., 2015). Although the exact mechanism of packaging remains unclear, 7SL RNA was shown to be encapsidated into minimal VLPs containing a mini-Gag construct, which contains the first 12 amino acids of matrix followed by the C-terminal domain of CA and a leucine zipper in the place of NC (Keene et al., 2010). A different report suggested NC was required for 7SL RNA packaging (Wang et al., 2007; Tian et al., 2007). Many questions remain as to the role of cellular ncRNAs that are packaged into virions. 7SL and other packaged cellular RNA may act as nonspecific nucleating factors for initiation of retroviral Gag multimerization in the cytoplasm (Telesnitsky and Wolin, 2016). In a recent study, MS2-stem loops were used to label and track 7SL RNA during HIV-1 infection (Itano et al., 2018). This study revealed that Gag and 7SL RNA arrived at the PM simultaneously, consistent with a model wherein 7SL RNA and lower-order multimers of Gag interact in the cytoplasm prior to assembly at the PM (Itano et al., 2018). Alternatively, 7SL RNA has been proposed to facilitate apolipoprotein B mRNA-editing catalytic polypeptide–like 3G and 3F (APOBEC3G, -3F) packaging (Wang et al., 2007, 2008). APOBEC family members are cytidine deaminases that modify RNA, DNA and, in the case of APOBEC3 family members, the HIV-1 genome (Jarmuz et al., 2002; Sheehy et al., 2003). In virions lacking Vif, which induces the degradation of APOBEC3G, hypermutations of the viral genome are found in the form of C- to U- changes (Harris et al., 2003; Lecossier et al., 2003). APOBEC3C, 3F, 3A, and 3B also appear to possess broad antiviral activities against viruses including simian immunodeficiency virus (SIV), MLV, hepatitis B virus, and some endogenous retroelements (Turelli et al., 2004; Bogerd et al., 2006; Chen et al., 2006; Esnault et al., 2005; Muckenfuss et al., 2006). APOBEC3G immunoprecipitated from 293 and Jurkat cells copurified with Y RNAs, specifically Y1, and Y3, and 7SL RNA (Wang et al., 2007). Overexpression of 7SL binding partner SRP19 in 293T cells reduced levels of packaged 7SL RNA and APOBEC3G, whereas overexpression of 7SL RNA increased inclusion of both components into HIV-1 virions (Wang et al., 2007). Similar results were found with APBOPEC3F, suggesting other ABOBEC3 family members may also interact with 7SL (Wang et al., 2008). The authors suggested that the potentially conserved interaction between APOBEC3G and 7SL could explain the more general antiviral nature of the protein and provide a reason for the abundant 7SL RNA present in retroviruses (Wang et al., 2007).

U Small Nuclear RNA

U snRNAs are associated with pre-mRNA splicing machinery and are between 60 and 450-nt in length (Kiss, 2004). All known U snRNAs are transcribed by RNA polymerase II with the exception of U6, which is transcribed by RNA polymerase III (Matera et al., 2007). Although U1, U2, U3, U4, U5, and U6 snRNAs have been found in MLV virions, U6 is the only one detected at levels that approach

those of 7SL RNA, whereas the others are much lower in abundance (Onafuwa-Nuga et al., 2005). Interestingly, in HIV-1 virions, 3′-extended forms of pre-U1 snRNAs were detected at low levels indicating that these RNAs had not been fully processed and are likely packaged as newly transcribed RNAs (Eckwahl et al., 2015, 2016b). RSV virions were found to contain approximately one U6 snRNA per virion and trace amounts of U1 and U2 (Giles et al., 2004). Interestingly, the authors also found products of reverse transcription that matched U6, U1, and U2 RNA suggesting that RT may use packaged cellular RNA to create recombinant viral genomes (Giles et al., 2004). It is surprising that snRNAs are frequently found in retrovirus virions as they are exclusively found in the nucleus and most retroviruses bud from the cytoplasmic membrane (Giles et al., 2004).

Y RNA

Y RNAs are small ~100-nt RNAs that are present in the cytoplasm of most vertebrates and some lower eukaryotes in complex with the Ro Protein (Hendrick et al., 1981; Smith et al., 1984; O'Brien et al., 1993; Chen and Wolin, 2004). The number of different Y RNAs depends on the species; the human genome encodes four Y RNAs denoted as hY1, hY3, hY4, and hY5 (O'Brien and Wolin, 1994). Upon transcription of Y RNAs by RNA polymerase III, Y RNA is transiently bound by the La protein and ultimately forms a complex with the Ro protein. The Y RNA–Ro complex has an important role in unfolded and mutated RNA degradation (Wolin and Steitz, 1984). Several roles for Y RNA have been proposed: (1) the Y RNA-binding site on Ro overlaps the target RNA-binding site, suggesting that Y RNA regulates RNAs, which are bound by Ro, (2) in *Xenopus* oocytes, Ro has been found to bind mutant 5S rRNA and misfolded U2 snRNA, supporting the role of the Ro complex as a scavenger of unfolded RNA, (3) Y RNA-bound Ro is exclusively localized to the cytoplasm, whereas Y RNA-depleted Ro is localized to the nucleus, suggesting Y RNA also regulates Ro trafficking, (4) Y RNA may regulate the ability of Ro to enhance cell survival following UV radiation. Free Y RNA is found in MLV and HIV-1 virions at lower concentrations than 7SL RNA, bolstering the idea that many cellular RNAs are packaged from a newly synthesized pool prior to interaction with their protein complex partners (Onafuwa-Nuga et al., 2005; Garcia et al., 2009; Chen and Wolin, 2004; O'Brien and Wolin, 1994; Reinisch and Wolin, 2007; Sim et al., 2009; Chen et al., 2003). The role of Y RNAs in viral replication is unknown; however, there is an enrichment of mouse Y1 (mY1) and mY3 RNAs even in the absence of Ro, when cellular Y RNAs are degraded, showing there is a selectivity for the virus to package these RNAs (Garcia et al., 2009).

Vault RNA

Within the cytoplasm of eukaryotes, large RNP particles consisting of three proteins [major vault protein (MVP), poly(ADP-ribosyl) polymerase (VPARP),

and telomerase/vault-associated protein (TEP1)] and multiple small ncRNAs are known as vaults. These RNPs are roughly three times larger than ribosomes with a molecular mass of 13 MDa (Kedersha and Rome, 1986; Kickhoefer et al., 2001; Stadler et al., 2009). vltRNAs are 80- to 150-nt long and vary considerably in sequence but are characterized by a GC-rich stem–loop 5′ to a box A promoter sequence (Stadler et al., 2009). The purpose of the vaults is not well understood despite the fact that they are conserved across most eukaryotic species except *Drosophila*, *Arabidopsis*, *Caenorhabditis*, and *Saccharomyces cerevisiae* (Stadler et al., 2009). Human vaults are the best characterized and are thought to primarily function in general intracellular transportation and have been implicated as a contributing factor to drug resistance by exporting chemical compounds (Kickhoefer et al., 2001; Stadler et al., 2009; Steiner et al., 2006). However, other roles have been attributed to vaults and vltRNAs, which are able to fold into structures similar to pri-miRNAs and be processed by Dicer into functional miRNA. Upregulation of vaults correlated with drug resistance to cancer therapeutics in some studies, and vltRNAs are also upregulated during Epstein–Barr virus infection (EBV) (Persson et al., 2009; Kitazono et al., 1999, 2001; Nandy et al., 2009). Of relevance to the retrovirus field is the fact that MVP alone can form vaultlike particles (Stephen et al., 2001) reminiscent of VLPs produced by Gag. Additionally, a study of all cellular RNAs packaged into MLV virions identified the presence of previously undetected vltRNAs (Eckwahl et al., 2015). The proteins associated with vaults have not been found in virions to date.

High-Throughput RNA-Sequencing Studies

With advancements in the ability to perform whole-cell RNA sequencing, more recent studies have been conducted to examine ncRNA interactions with viral proteins within the cell and to identify RNAs packaged into virions (Eckwahl et al., 2016a,b; Onafuwa-Nuga et al., 2005; Kutluay et al., 2014). CLIP-Seq was used to determine which cellular and vRNAs are preferentially bound by different domains of Gag (Kutluay et al., 2014). During the initial stages of HIV-1 viral assembly, the NC domain of Gag bound to the genomic RNA packaging signal, psi, and to the Rev response element, as well as to GU-rich mRNA transcripts. However, at the plasma membrane, NC preferentially bound to A-rich regions of both the viral genome and mRNA (Kutluay et al., 2014). Surprisingly, HIV-1 MA almost exclusively bound host tRNAs in the cytoplasm, as mentioned earlier, and did not interact with the genomic RNA (Kutluay et al., 2014). However, HIV-1 MA isolated from membrane fractions showed significantly less bound tRNA (Kutluay et al., 2014), which is in agreement with reports indicating that host tRNAs regulate HIV-1 MA–Gag plasma membrane targeting, as discussed earlier (Chukkapalli et al., 2010, 2013; Todd et al., 2017; Dick et al., 2013). A high-throughput RNA-sequencing (RNA-seq) method has also been applied to identify RNAs packaged into HIV-1 virions, revealing several

RNAs that had not been detected in previous studies, including many unprocessed RNA species, such as pre-tRNAs, mentioned earlier, and pre-snRNAs (Eckwahl et al., 2016b). Future applications of RNA-seq to other retroviruses may uncover RNAs that are universally packaged into virions and those that are selective to specific viruses.

LONG NONCODING RNA AND ENDOGENOUS RETROVIRUSES

lncRNAs are not abundantly packaged into retroviral virions with the exception of 7SL RNA and some long interspersed nuclear elements (Wapinski and Chang, 2011). Classification of lncRNA is typically more difficult than short ncRNAs, which have well-defined features (St Laurent et al., 2015). They are generally split into six groups: pseudogenes (mutated gene sequence that no longer code functional genes); long intronic ncRNA; divergent transcripts (associated with and enhance promoters); large intergenic RNA (occurring between coding regions); circular RNA; and natural antisense transcripts (Veneziano et al., 2016). Although lncRNAs are abundant within the human genome, only a few are well characterized (Geisler and Coller, 2013). Those with known functions include roles in cell cycle regulation, telomerase regulation, chromatin remodeling, and scaffolding for protein complexes. Many have been associated with diseases, including Alzheimer's disease (Mattick, 2001; Frias-Lasserre, 2012; Geisler and Coller, 2013; Groen and Morris, 2013). Several viruses, including several types of herpesviruses, encode lncRNAs known to interact with and, in some cases, inhibit host proteins, as reviewed in Tycowski et al. (2015). The human, murine, and avian lncRNAs described below adopt functions that affect retroviral life cycles in diverse ways.

NRON: HIV-1

HIV-1 latency and maintenance of virally infected reservoirs has been a central conundrum for the development of effective vaccines and antiviral therapeutic development (Groen and Morris, 2013). Several host and viral proteins are thought to regulate viral latency including nuclear factor kappa B, nuclear factor of activated T cells (NFAT) and HIV-1 Tat (Kao et al., 1987; Nabel and Baltimore, 1987; Kinoshita et al., 1998). Although controversial, host miRNAs are proposed to contribute to viral latency (Kiss, 2004). Using a large-scale siRNA screen, knockdown of the lncRNA called nonprotein-coding RNA repressor of NFAT (NRON) was found to enhance HIV-1 replication in activated primary CD4^{+} T lymphocytes (Li et al., 2016). NRON is ~2700-nt long and its expression was found to be altered over the course of HIV-1 infection; expression is reduced initially due to the viral accessory protein Nef, whereas enhanced expression is observed in the later stages of infection due to Vpu (Imam et al., 2015). NRON was found to affect HIV-1 replication in an NFAT-dependent

manner, wherein reduction of NRON resulted in increased activity of NFAT and enhanced viral transcription (Imam et al., 2015). During HIV-1 replication, the viral protein Tat has an essential role in enhancing efficient transcription of the viral genome (Leblanc et al., 2013). NRON was reported to form a complex with components of the ubiquitin/proteasome, ultimately resulting in the degradation of Tat and reduction of viral transcription in an NFAT-independent mechanism (Li et al., 2016). NRON is present at high concentrations in resting CD4^{+} T lymphocytes and therefore, may contribute to viral latency via viral transcriptional silencing (Li et al., 2016).

NEAT1: HIV-1

Many different types of nuclear and cytoplasmic bodies have been described in cells (Sleeman and Trinkle-Mulcahy, 2014). Paraspeckles are dynamic nuclear bodies, the components of which include the 3200-nt lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1). Paraspeckles respond to stress conditions by sequestering components of transcription and halting the production of specific genes; they also sequester a subset of mRNAs to be edited including those containing Alu repeats (Barichievy et al., 2015; Chen and Carmichael, 2009). Paraspeckles have also been implicated as an innate immune response to viral infections (Imamura et al., 2014). HIV-1 RNA has been reported to be localized to paraspeckles, potentially for A to I editing carried out by ADAR1 (Doria et al., 2009; Gallo and Locatelli, 2012). In one study, the expression profile of over 83 lncRNAs was analyzed during HIV-1 infection of both Jurkat and MT4 cells and NEAT1 expression was found to be increased by 5- to 10-fold (Zhang et al., 2013). Knockdown of NEAT1 resulted in reduced paraspeckle formation and increased cytoplasmic concentration of Rev-dependent instability element-containing HIV-1 RNA, enhancing viral replication (Zhang et al., 2013).

Large Intergenic RNA–p21: HIV-1

During the integration step of the retroviral life cycle, double-strand breaks must be made in the host genome to insert the proviral DNA (Craigie and Bushman, 2012). Once inserted, host machinery must repair the break in the phosphodiester bonds before damage to the host DNA triggers cell death (Houtgraaf et al., 2006). The proapoptotic protein, p53, is activated when DNA damage occurs, which also activates transcription of lincRNA-p21. The 3100-nt large intergenic RNA (lincRNA)–p21 can induce apoptotic pathways by downregulating the transcription of prosurvival genes (Huarte et al., 2010). Expression of lncRNA-p21 is regulated during HIV-1 infection in macrophages to block detection of DNA breaks, allowing HIV-1 to gain control over the MAP2K/ERK2 pathway, one of the targets of lincRNA-p21 that is needed for cell survival (Barichievy et al., 2015).

Antisense Protein RNA: HIV-1

In 1988, HIV-1 was proposed to contain an antisense protein (ASP) produced from the antisense promoter within the 3′ LTR based on computational analysis of the viral RNA (Miller, 1988). The expression of ASP has been detected in patient sera and induces CD8+ T cells (Bet et al., 2015). Possible roles for the ASP RNA include epigenetic silencing of the HIV-1 integrated DNA by recruiting chromatin remodeling proteins to the viral LTR (Zapata et al., 2017). This lncRNA is proposed to suppress viral transcription, favoring latency, by enhancing DNA methylation. It is also possible, given the degree of similarity between the 3′ and 5′ LTRs, that ASP RNA acts by forming a triple helix with the 5′ LTR of the genome (Zapata et al., 2017). ASP RNA can be detected in chronically infected cell lines and resting CD4+ T cells from patients currently taking antiretroviral therapies, demonstrating ASP RNA is expressed in vivo (Zapata et al., 2017).

Long Noncoding RNA 00173: HIV-1

Analysis of two RNA-seq studies revealed that three lncRNAs were differentially expressed during HIV-1 infection; long noncoding RNA 00173 (LINC00173) was the most evolutionarily conserved prompting further investigation (Postler et al., 2017). Intriguingly, when knocked out, LINC00173 did not impact the retroviral life cycle in Jurkat T cells. However, loss of LINC00173 resulted in higher expression of several cytokines, including interferon-γ, which is important in the adaptive immune response (Postler et al., 2017). Although the authors did not find a direct effect of LINC00173 on HIV-1 infection, they speculate that the increased production of interferon-γ could have implications on an organismal level (Postler et al., 2017).

ASP RNA: HTLV-1

The HTLV-1 accessory protein, HTLV-1 basic leucine zipper factor (HBZ) is an ASP whose gene is located near the 3′ viral LTR (Gaudray et al., 2002). The RNA transcript of this protein has been implicated in cell proliferation leading to HTLV-1-associated diseases and chronic infections (Barbeau and Mesnard, 2011). However, it has also been reported that the mRNA transcript functions by activating antiapoptotic pathways and inducing proliferation by IL-2 independent pathways (Satou et al., 2006a). Interestingly, progression to adult T-cell leukemia (ATL) is correlated with increased viral expression (Zhao and Matsuoka, 2012). However, Tax, another accessory protein associated with cell proliferation, is often mutated and inactive in ATL cases, whereas HBZ is expressed, suggesting a role for HBZ protein in chronic infection (Ma et al., 2016). The HBZ mRNA has been shown to be retained within the nucleus indicating a potential functional role in transcription regulation (Rende et al., 2011). The functional HBZ mRNA forms stem–loop structures that function

to transcriptionally activate E2F1, a transcription factor upregulated in many cancers, although the mechanism by which this occurs is not understood (Satou et al., 2006b; Matsuoka and Green, 2009). Expression of miRNAs targeting HBZ RNA in ATL cells decreased proliferation of cells (Satou et al., 2006b). In mice, HBZ mRNA has been found to activate the transcription of antiapoptotic genes including *survivin*, which may enhance the progression to ATL (Mitobe et al., 2015).

Bic: ALV and His-1: MLV

ALV infection of birds results in B-cell lymphomas. The virus often integrates at the *bic* locus and is frequently associated with *c-myc* activation (Clurman and Hayward, 1989; Tam et al., 1997). Interestingly, the expression of the proto-oncogenic *c-myc* alone is not sufficient to cause lymphoma in avian systems, suggesting that other factors are required (Adams and Cory, 1992). It was found that insertions at the *bic* locus activated the transcription of a chimeric bic-virus RNA; however, the RNA lacks an open reading frame suggesting it functions as a lncRNA (Tam et al., 1997). In a follow-up study, the expression of bic and c-myc in chicken embryonic fibroblasts induced greater cell growth than activation of *c-myc* alone (Tam et al., 2002). However, the coexpression was not sufficient to induce full transformation of cultured cells, suggesting that other genetic changes are required (Tam et al., 2002). While the exact mechanism of the bic lncRNA in cell regulation is still unclear, this discovery was the first report that an lncRNA can interact with and enhance c-myc activity (Tam et al., 2002).

In mice, MLV commonly inserts into the *His*-1 locus, which does not produce any known coding protein (Askew et al., 1991). His-1 transcripts do not contain an open reading frame and the 3000-nt transcript contains multiple stop codons suggesting that it functions through its RNA (Askew et al., 1994). In murine cell lines and mouse tissue, His-1 expression was undetected; however, in two transformed cell lines with detectable MLV insertion near the *His-1* site, increased RNA expression was observed (Askew et al., 1994). Similar to *bic* in ALV, insertion of the MLV genome into the *His-1* locus served to activate the proto-oncogene and enhance cell survival (Askew et al., 1994).

Endogenous Retroviruses

It is estimated that ~10% of the human genome comprises ERVs, which are considered a type of retrotransposon (Lower et al., 1996; Kurth and Bannert, 2010; Wildschutte et al., 2016). ERVs can arise from the integration of retroviruses in germ cells; inherited viruses are generally unable to replicate due to an accumulation of mutations, frameshifts, and deletions (Gifford and Tristem, 2003). Human ERVs (HERVs) are the best characterized, but many animal species also contain ERVs in their genomes including pigs, plants, fish, rodents,

insects, and cats (Boeke and Stoye, 1997; Herniou et al., 1998; Johnson and Coffin, 1999). ERVs are divided into three classes: class I, which resembles gamma- and epsilonretroviruses; class II, which bears similarities to betaretroviruses; and class III, which resembles spumaretroviruses (Lower et al., 1996; Gifford and Tristem, 2003). Alternative methods of classification use the primer tRNAs to categorize ERVs, see Table 12.1 (Gifford and Tristem, 2003). Initially, it was thought that ERVs were simply remnants of ancient retroviruses; however, there is increasing evidence that some ERVs have become essential regulatory elements and provide genetic diversity (Wang et al., 2014; Lu et al., 2014; Lee et al., 2017). Also, although many ERVs do not cause disease, others have been associated with multiple sclerosis, autoimmune disorders, and cancer (Mameli et al., 2007; Krieg et al., 1992). HERV-K is the most intact ERV, with a long open reading frame and ability to produce vRNA and proteins (Lower et al., 1996). HERV-K is also able to illicit a weak immune response, as antibodies to HERV-K proteins are found at very low levels following pregnancies, as well as in patients with leukemias, and certain types of tumors (Lower et al., 1996; Sauter et al., 1995). The presence of ERVs in pigs, porcine endogenous retrovirus (PERVs), is of special interest as pig tissues can be transplanted into humans. While ERVs are generally innocuous, the consequences of cross-species interactions are unknown (Weiss, 2006). A recent study examining the transplantation of porcine islet cells into humans for the treatment of type 1 diabetes found no indication of PERV infection up to 113 weeks postimplantation, lending credence to the safety of porcine transplants (Morozov et al., 2017). Interestingly, the feline ERV, RD114, was initially detected in a human cell line that had been xenografted into fetal kitten brain tissue, suggesting that xenotropic ERVs are possible (McAllister et al., 1972; Achong et al., 1976; Patience et al., 1997).

Two studies have found that ERVs are important for human stem cell function (Wang et al., 2014; Lu et al., 2014). HERV-H silencing in human embryonic stem cells was found to lead to differentiation to fibroblast-like cells (Lu et al., 2014). Using RNA-seq, the levels of HERV-H in human pluripotent stem cells were shown to be elevated compared to embryoid bodies and fibroblasts (Wang et al., 2014). Both studies revealed that HERV-H sites of integration were in regions encoding lncRNAs, prompting the authors to examine the expression of these lncRNAs and adjacent protein-coding regions (Wang et al., 2014; Lu et al., 2014). Knockdown of HERV-H also resulted in the reduced expression of neighboring lncRNAs and genes (Lu et al., 2014). It was determined that the HERV-H fragment was acting as a *cis*-gene regulator during stem cell development suggesting that other functional lncRNAs could be derived from ERVs (Lu et al., 2014). Other HERVs have been shown to play roles in cell fusion in the placenta, and fetal tolerance is linked to expression of HERV *env* genes (Blond et al., 1999; Mangeney et al., 2007). Varying levels of HERV expression are observed across many different types of cancer, prompting the examination of HERV activity in tumorigenesis (Ruprecht et al., 2008). Interestingly, HERVs

can be inserted into the genome in the antisense orientation, overlapping coding genes. This orientation results in the production of short RNAs complementary to the overlapping gene sequences, creating an inhibitory RNA able to regulate gene expression (Gogvadze et al., 2009). HERV-K, which is generally present in introns, has a functional 3′ LTR expression and was initially inserted into Old World monkey genomes (Broecker et al., 2016; Dangel et al., 1994; Mack et al., 2004). *DAP3*, a gene that is located within *HERV-K* in HepG2, 293T, and HeLa cells, is a signaling protein that when overexpressed induces apoptosis (Broecker et al., 2016; Kissil et al., 1995). HERV-K antisense RNA fragments were able to reduce levels of DAP3 and, conversely, knockdown of HERV-K transcripts enhanced DAP3 expression to induce apoptosis in HeLa cells (Broecker et al., 2016). This finding suggests HERV-K expression could potentially lead to a favorable outcome for tumor formation (Broecker et al., 2016). HERV-E was found to be differentially expressed in urotherlial carcinoma cells and coincided with a decrease in cytosolic phospholipase A2, which is often dysregulated in tumor cells (Gosenca et al., 2012). Although HERV-E transcripts are found in several cancers, including breast cancer, they are also present in normal cell lines implying more studies will need to be conducted before a link between cancers and HERV-E expression is solidified (Gosenca et al., 2012; Frank et al., 2008). Therefore, although ERVs generally do not cause diseases when inserted into host genomes, transcriptionally active portions of the genomes could inherit functional roles within the cell.

FUNCTIONAL TRANSACTIVATING RESPONSE ELEMENT RNAs

Located in the 5′UTR region of the HIV-1 vRNA, the transactivating response (TAR) element forms a stem–loop structure that specifically binds the viral protein Tat (Frankel and Young, 1998). During transcription, Tat binds to TAR and phosphorylates the C-terminal domain of RNA polymerase II, enhancing transcription of the retroviral genome (Karn and Stoltzfus, 2012). Outside of its essential role in transcription, TAR RNA has also been suggested to have a role in blocking host cellular RNAi responses to HIV-1 infection (Bennasser et al., 2006). TAR RNA–binding protein (TRBP) is known to interact with Dicer, a component of the RNAi pathway discussed in more detail in Therapeutics section, by trafficking siRNA to the multiprotein RNA-induced silencing complex (RISC) (Haase et al., 2005; Forstemann et al., 2005; Chendrimada et al., 2005). TRBP can be sequestered by TAR RNA, reducing the effectiveness of RNAi within the cell (Bennasser et al., 2006).

TAR RNA has also been implicated in both *cis*- and *trans*-inhibition of translation within host cells (Parkin et al., 1988; Edery et al., 1989; SenGupta et al., 1990). TAR RNA can block the ability of the ribosomal initiation factor eIF-4B to effectively recognize the mRNA cap (Parkin et al., 1988). Additionally, TAR RNA can be recognized by interferon inducible protein kinase (PKR), which typically recognizes dsRNA, and by 2-5A synthetase, which produces

2′,5′-oligoadenylates that activate RNase L, which can degrade single-stranded vRNA and induce autophagy in response to viral infection (SenGupta and Silverman, 1989; Roy et al., 1991). At low concentrations of TAR, PKR is activated and at high concentrations PKR is inhibited (Maitra et al., 1994). Presumably to counteract the ability of PKR and 2-5A synthetase to silence translation, when HIV-1 Tat is expressed, both PKR and 2-5A-synthetase activities are blocked (Maitra et al., 1994; Judware et al., 1993).

Most cellular mRNA is translated by a cap-dependent mechanism wherein assembling ribosomes scan along the 5′ UTRs to find start codons (Jackson et al., 2010; Deforges et al., 2017). However, the HIV-1 5′ UTR is highly structured and contains stable stem loops including TAR that are capable of hindering ribosomal scanning (Yilmaz et al., 2006). Within the 5′ UTR of several retroviruses, including HIV-1, a posttranscriptional control element (PCE) helps recruit host proteins essential for efficient translation (Bolinger et al., 2007, 2010; Hull and Boris-Lawrie, 2002; Russell et al., 2001; Roberts and Boris-Lawrie, 2003). Dhx9/RNA helicase A (RHA) is known to interact with PCEs to destabilize structured elements allowing for cap-dependent translation (Hartman et al., 2006). RHA interacts with TAR RNA, is packaged into HIV-1 virions, and is important for efficient translation of the HIV-1 vRNA and progeny virion infectivity (Bolinger et al., 2010). In addition, some cap-dependent cellular translation is downregulated during HIV-1 infection but vRNA is still translated, the possibility of IRESs within the HIV-1 genome has been explored (Agy et al., 1990; Brasey et al., 2003). Indeed, IRES-like elements within the 5′ UTR and in the *gag* coding frame have been characterized (Deforges et al., 2017; Brasey et al., 2003; Buck et al., 2001).

Surprisingly, the TAR element was recently shown to be one of the regions of vRNA to bind to integrase (IN) in HIV-1 virions (Kessl et al., 2016). Previously, allosteric IN inhibitors (ALLINIs) had been shown to inhibit late stages of HIV-1, disrupting viral maturation and resulting in impaired viral infectivity (Jurado et al., 2013; Fontana et al., 2015; Desimmie et al., 2013), although the mechanism was unknown. Using CLIP-seq, IN was found to bind discreet regions of the viral RNA including TAR and RRE. Disruption of IN–viral RNA interactions by mutagenesis or treatment with ALLINIs resulted in eccentric viral core formation and reducing infectivity (Kessl et al., 2016). The functional significance of this interaction is not completely understood, although it is postulated that the IN–viral RNA interaction may ensure the presence of IN in the CA core and thereby facilitate maturation of the core (Kessl et al., 2016).
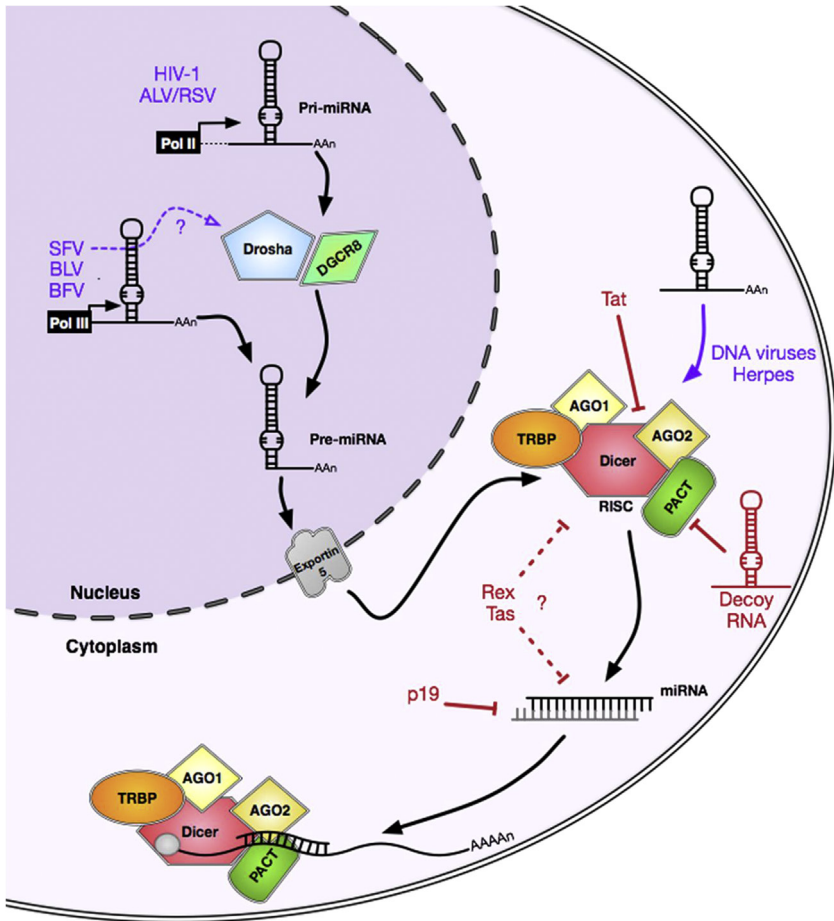
RNA INTERFERENCE AND miRNAs

Although plants do not have an immune system in the typical mammalian sense, higher-order plants are able to mount targeted immune responses to viral threats using RNAi (Voinnet, 2001; Plasterk, 2002). RNAi was first described in transgenic petunias, wherein introduced genes were silenced through an unknown

pathway (van der Krol et al., 1990; Napoli et al., 1990). Eventually, it was found that short 21–23 nt siRNAs were targeting mRNAs within the cell, causing the degradation of the RNA and suppression of protein expression (van der Krol et al., 1990). Over 90% of viruses that infect higher-order plants are transmitted through RNA at some stage of the viral life cycle (Voinnet, 2001). Exogenous viral dsRNA, showing no homology to the host genome, has been shown to trigger the RNAi pathway to suppress vRNA invaders (Elmayan and Vaucheret, 1996). It was observed that viruses containing similar gene sequences to those of the plant cell could cause virus-induced gene silencing (Ruiz et al., 1998; Ratcliff et al., 1999). Essentially, viral ssRNA can catalyze the synthesis of dsRNA by plant RNA-dependent RNA polymerases (Plasterk, 2002). The typical RNAi pathway can then occur, ultimately creating siRNAs targeted to the viral genome (Voinnet, 2001). Importantly, this pathway can lead to the production of secondary siRNAs, effectively amplifying the "immune response" (Plasterk, 2002). As for retroviruses discussed below, plant viruses adapt to the host RNAi pathway by producing virally encoded suppressors of RNA silencing (Pruss et al., 1997). For example, tomato bushy stunt RNA viruses produce a protein called p19, an inhibitor of Dicer, which blocks the host plant cell's immune response to initial viral infection (Voinnet et al., 1999).

RNAi, miRNA, and siRNA Production

The RNAi pathway was initially thought to be unique to plants, but was later identified in many eukaryotic species (Plasterk, 2002; Almeida et al., 2011). Briefly, RNA Pol II and III recognize specific promoters in DNA to begin transcription of long primary miRNA transcripts (pri-miRNA), usually containing a 33-bp stem loop (Lee et al., 2004; Borchert et al., 2006) (Fig 12.1). Pri-miRNAs produced from RNA Pol II are sensitive to alpha-amanitin, allowing for the identification of the polymerase responsible for transcription (Lee et al., 2004). These transcripts are polyadenylated and capped via a similar mechanism to that used for mRNAs, and like mRNAs, can be edited (Cai et al., 2004; Luciano et al., 2004). The nuclear microprocessor complex composed of Drosha, an RNase III enzyme, and DGCR8, which contains two dsRNA-binding motifs, cleaves the pri-miRNA 11 bp from the base of the stem–loop structure and the product of this step is pre-miRNA (Lee et al., 2003; Han et al., 2004). Although most miRNAs are processed through Drosha and DGCR8, some miRNAs are formed after intron splicing and can bypass this step (Ruby et al., 2007). At this stage, the pre-miRNA is exported to the cytoplasm and further processed by the RISC-loading complex, which consists of the RNase Dicer, TRBP, the protein activator of PKR (PACT) and Ago2, the main component of Argonaute-2 (Gregory et al., 2005; Lee et al., 2006). TRBP and PACT help to stabilize the pre-miRNA–protein complex, whereas Ago2 creates a nick in the 3′ arm of the stem loop (Lee et al., 2006; Diederichs and Haber, 2007). Dicer cleaves the remaining loop resulting in a 21–23 nt RNA with 2-nt overhangs on both the

FIGURE 12.1 MicroRNA (miRNA) production pathway and viral interaction with RNA interference (RNAi) machinery. Host pri-miRNAs are transcribed by RNA polymerase II (Pol II) or III (Pol III) and can be processed by Drosha and DGCR8 into pre-miRNAs. Pre-miRNAs are then exported from the nucleus by exportin-5 and cleaved into a 21–22 nt miRNA duplex by Dicer of the RNA-induced silencing complex (RISC) complex. One miRNA strand is loaded onto the Argonaut (AGO)-RISC complex and used to select mRNAs for degradation or translational silencing. This process is depicted by *black arrows*. Viral miRNA entry into the RNAi pathway is shown in *purple text*. Inhibition of the host RNAi pathway by viral proteins or RNA is indicated by *red text* and *arrows* directed towards their proposed inhibitory target. *ALV*, avian leukosis virus; *BFV*, bovine foamy virus; *BLV*, bovine leukemia virus; *RSV*, Rous sarcoma virus; *SFV*, simian foamy virus; *TRBP*, TAR RNA–binding protein. (Adapted from Winter, J., Jung, S., Keller, S., Gregory, R.I., Diederichs, S.S., 2009. Many roads to maturity: microRNA biogenesis pathways and their regulation. Nat. Cell Biol. 11, 228–234; Trobaugh, D.W., Klimstra, W.B., 2017. MicroRNA regulation of RNA virus replication and pathogenesis. Trends Mol. Med. 23, 80–93; Klase, Z.A., Sampey, G.C., Kashanchi, F., 2013. Retrovirus infected cells contain viral microRNAs. Retrovirology 10, 15; Soifer, H.S., Rossi, J.J., Saetrom, P., 2007. MicroRNAs in disease and potential therapeutic applications. Mol. Ther. 15, 2070–2079.)

3′ ends (Bernstein et al., 2001). Although both strands could be utilized as the guide RNA for silencing, it is typical that the one with the least stable 5′ end becomes the functional miRNA, whereas the other one is degraded (Schwarz et al., 2003; Khvorova et al., 2003). Generally, miRNAs target the 3′ UTRs of mRNA blocking protein translation (Ouellet and Provost, 2010). A majority of the mRNAs that are completely complementary to the seed sequence, the minimal portion of miRNA required to recognize the target RNA, will be translationally suppressed, whereas targeted mRNAs with partial complementarity to guide RNAs tend to be degraded (Yekta et al., 2004; Mansfield et al., 2004; Lewis et al., 2005). Many of the steps of this process can be bypassed or altered depending on cellular conditions; for a more detailed review see Winter et al. (2009). Processing bodies (P-bodies) within the cytoplasm of cells appear to be concentrated areas of translationally silenced RNAs, mRNA degradation, and nonsense-mediated decay (Liu et al., 2005; Sen and Blau, 2005). Since the first identification of miRNAs, over 5500 human and 130 viral miRNAs have been predicted (Griffiths-Jones et al., 2006, 2008; Londin et al., 2015; Trobaugh and Klimstra, 2017). Expression of miRNAs is tightly regulated within cells and is often tissue specific, leading to the use of miRNAs in diagnostics for various types of cancers, cardiovascular diseases, autoimmune diseases, and neurodegenerative diseases (Almeida et al., 2011).

Effective viral infection requires regulation of various cellular processes including mRNA translation (Barichievy et al., 2015). HIV-1 infection has been found to modulate the expression of over 300 genes including miRNAs (Barichievy et al., 2015; Ouellet and Provost, 2010; van 't Wout et al., 2003). The ability of host miRNAs to impact viral replication in mammals has been well characterized. The question remains whether these miRNAs are physiologically capable of directly regulating retroviral replication (Grassmann and Jeang, 2008). Additionally, many different types of viruses have been found to produce miRNAs from their genomes (Tycowski et al., 2015; Ouellet and Provost, 2010; Klase et al., 2013; Umbach and Cullen, 2009). The most widely characterized viral miRNAs are produced from DNA viruses including *Herpesviridae* and mouse cytomegalovirus (Ouellet and Provost, 2010). The discovery of viral miRNAs in RNA viruses, such as EBV, was surprising and remains controversial (Tycowski et al., 2015; Klase et al., 2013; Houzet and Jeang, 2011; Cullen, 2012). First, many RNA viruses replicate exclusively in the cytoplasm, thereby avoiding nuclear Drosha cleavage. In addition, if nuclear RNA genomes were processed into miRNAs very little full-length gRNA would be available to be packaged (Umbach and Cullen, 2009; Cullen, 2012). However, some retroviruses have adapted to produce miRNAs by the less frequently used RNA Pol III, addressing the issue of genomic RNA degradation of Pol II transcripts (Klase et al., 2013). Conversely, Drosha and the RNAi pathway can act to inhibit viral replication resulting in potentially beneficial or detrimental outcomes (Barichievy et al., 2015; Umbach and Cullen, 2009). Cellular miRNAs are proposed to regulate viral replication (Houzet and Jeang, 2011; Yeung et al., 2007). To counteract cellular antiviral RNAi responses,

retroviruses have adapted by degrading RNAi machinery, diversifying the roles attributed to viral proteins, and producing "decoy" RNA transcripts (Bennasser et al., 2006; Houzet and Jeang, 2011; Yeung et al., 2007).

Cellular MicroRNAs Made in Response to Viral Infections

Mammalian miRNAs are estimated to regulate up to 30% of protein-coding mRNA and the expression patterns of some miRNAs are modulated upon viral infection (Trobaugh and Klimstra, 2017; Houzet and Jeang, 2011). Host miRNAs can impact viral life cycles both directly and indirectly, leading to either enhanced viral production or suppression of the viral life cycle (Trobaugh and Klimstra, 2017; Watanabe et al., 2007). The specificity of the host miRNA response to specific viral infection and whether the RNAi pathway is used as a general antiviral response are active areas of investigation. miRNA pathways identified in specific retroviruses are described below.

Avian leukosis virus subgroup J (ALV-J). ALV can be transmitted vertically and chicken eggs are used in the development of human vaccines (Gao et al., 2010; Hussain et al., 2003). Thus, understanding the mechanism of this oncogenic virus' life cycle has been a major undertaking and seems linked to host miRNAs (Dai et al., 2015; Li et al., 2014, 2015; Wang et al., 2013a). Microarray analysis of chicken (*Gallus gallus*) tumors showed differential expression of several miRNAs known to interact with MAPK and Wnt signaling pathways, both associated with tumorigenesis in exogenous ALV-J infections (Wang et al., 2013a). These miRNAs include gga-miR-125b, gga-miR-193a, gga-miR-193b, and gga-miR-221. gga-miR-1650 was found to bind the 5′ UTR of the ALV-J gRNA resulting in decreased viral replication (Wang et al., 2013b). However, both WT and gga-miR-1650-resistant viruses were able to replicate under endogenous gga-miR-1650 expression indicating a higher level of miRNA expression would be needed to suppress the virus (Wang et al., 2013b). Another miRNA found to be upregulated during ALV-J infection was gga-miR-34b-5p, which enhances viral replication by downregulating interferon regulatory factor-1, preventing host responses to viral infections and promoting tumorigenesis (Li et al., 2015). Another viral sensing target of gga-miR-34b-5p is melanoma differentiation–associated gene 5 (MDA5). MDA5 also controls proliferation, cell cycle progression and migration of ALV-J infected cells, suggesting that gga-miR-34b-5p regulation of host immune responses has a substantial impact on viral replication and disease progression (Li et al., 2017). Like miRNAs, piwi-interacting RNAs (piRNAs) are also able to silence ALV expression (Sun et al., 2017). These RNAs interact with a subclass of Argonaute proteins, known as PIWI proteins, which result in the cleavage of the targeted RNA (Sun et al., 2017). However, the resulting cleavage products can then be used as secondary piRNAs amplifying the effect (Sun et al., 2017). Using RNA-seq, 73 active transposable elements were identified in White Leghorn testis that elicited piRNA-mediated suppression, suggesting piRNAs have evolved to maintain the integrity of germline genomes (Sun et al., 2017).

Prototype foamy virus type 1 (PFV-1). Expression of a silencing suppressor, p19, was found to enhance PFV-1 viral expression in 293T cells leading the authors to speculate that the RNAi pathway was involved in viral regulation (Trobaugh and Klimstra, 2017; Lecellier et al., 2005). This study further showed that human miR-32 shared homology with the 3′UTR of all PFV-1 mRNAs and repressed viral expression in a manner that depended on a complementary sequence (Lecellier et al., 2005). The countermechanism utilized by PVF-1 will be discussed below.

HTLV-1. Human miR-28-3p targets the gRNA of HTLV-1 within the *gag/pol* gene causing a halt in translation of the virus in resting T cells (Trobaugh and Klimstra, 2017; Bai and Nicot, 2015). Interestingly, subtype 1a, the Japanese AKT-1 strain of HTLV-1, contains a single-point mutation within the target sequence creating resistance to miR-28-3p and allows the virus to transmit efficiently (Trobaugh and Klimstra, 2017; Bai and Nicot, 2015). Computational studies predicting host miRNAs that could target HTLV-1 gRNA revealed several potential candidates, including plus-strand miR-653, -648, -596, -644, -496, -431, -326, -125b, -432, -125a, -663, -939, -1538, and -1908 (Houzet and Jeang, 2011; Ruggero et al., 2010; Hakim et al., 2008). Two miRNAs, miRNA-130b and miRNA-93, have been shown to be upregulated in HTLV-1 infected transformed cells, leading to the speculation that miRNAs may play a role in development of ATL as the normally functioning miRNAs regulate tumor suppressor protein TP53INP1 (Houzet and Jeang, 2011; Yeung et al., 2008).

HIV-1. It has been proposed that miRNAs could regulate several steps of the HIV-1 life cycle, either directly by targeting the genomic RNA or indirectly by controlling the cellular environment (Barichievy et al., 2015; Trobaugh and Klimstra, 2017). Expression of 62 miRNAs was reported to be altered between uninfected and HIV-1-infected individuals (Houzet et al., 2008). Interestingly, knockdown of Drosha and Dicer increased HIV-1 expression, suggesting that the RNAi pathway may regulate HIV-1 infection (Houzet and Jeang, 2011; Triboulet et al., 2007). Host miRNAs that have been proposed to target the RNA genome include miR-29a, which is complementary to a region in the *nef* gene (Nathans et al., 2009; Ahluwalia et al., 2008). In addition to simply blocking translation, miR-29a is implicated in the sequestration of HIV-1 RNA in P-bodies and association of the vRNA with RISC components, perhaps functioning in the regulation of viral latency (Nathans et al., 2009; Chable-Bessia et al., 2009). Multiple in silico studies have been carried out to predict additional host miRNAs that could target the HIV-1 genome directly, and the list of hits includes miR-149 (*vpr*), -378 (*env*), and -324-5p (*vif*) (Hariharan et al., 2005). Many studies were performed in specific cell lines or conditions leading to confusion over reproducibility and physiological relevance of miRNAs found to inhibit viral replication; however, the miRNAs uncovered computationally and in some cases experimentally include miR-133b, -138, -149, -326, -92a, -28b, -125b, -150, -223, -382, -29b-3p, -33a-5p, 423, -301a, and -155 (Barichievy et al., 2015; Trobaugh and Klimstra, 2017; Houzet and Jeang, 2011; Ahluwalia et al., 2008; Houzet et al., 2012; Huang et al., 2007; Reynoso et al., 2014; Whisnant et al.,

2013). A cluster of miRNAs, miR-28, miR-125b, miR150, miR-223, and miR-382, are proposed to bind to the 3′UTR of the HIV-1 RNA, suppressing expression of viral proteins and ultimately contributing to viral latency in resting CD4+ T cells (Huang et al., 2007). Certain cells are less susceptible to HIV-1 infection, including peripheral blood monocytes, whereas tissue macrophages are efficiently infected (Kedzierska and Crowe, 2002; Orenstein et al., 1997). As miRNA expression is generally tissue specific, the levels of putative anti-HIV-1 miRNAs (miR28, -150, 223, and 382) were examined in monocytes and macrophages (Wang et al., 2009). Interestingly, monocytes were found to have higher expression levels of these miRNAs than those differentiated into macrophages. Moreover, monocytes in which the targeted miRNAs were knocked down were more permissive to infection, suggesting that the differences in miRNA expression may contribute to viral permissiveness (Wang et al., 2009). Several cellular miRNAs indirectly impacting the HIV-1 life cycle have also been described including miR-20a, -17-5p, -1236, -15a/b, -16, -93, -106b, -198, -27b, -29b, -223, -150, -155, -146a, -888, -132, and -217 (Barichievy et al., 2015; Triboulet et al., 2007; Ma et al., 2014; Shen et al., 2012; Sung and Rice, 2009; Chang et al., 2012; Swaminathan et al., 2012; Chen et al., 2014; Chiang et al., 2013; Zhang et al., 2012). These miRNAs are proposed to have a wide array of functions including suppressing HIV-1 infection by restricting nuclear import of the PIC, cell cycle regulation, and enhancing transcriptional activation of latent viral genomes (Barichievy et al., 2015; Ma et al., 2014; Swaminathan et al., 2012; Chiang et al., 2013). During the progression of HIV-1 infection, many patients develop HIV-associated neurocognitive disorders (HAND) (Xu et al., 2017). Numerous miRNAs were found to have abnormal expression in brain tissue of patients with HAND, including miR-500a-5p, miR-93-3p, miR34c-3p, and miR-381-3p, which were found to be upregulated (Xu et al., 2017). These miRNAs target peroxisome biogenesis factors, resulting in depletion of peroxisomes during HIV-1 infection, which typically plays a role in lipid metabolism and antiviral signaling (Xu et al., 2017). Reduction in peroxisomes over time may contribute to neurological disorders in HIV-1 patients (Xu et al., 2017).

Viral MicroRNAs Encoded Within Genomes

The existence of miRNAs produced from a viral genome was first described for EBV genomic RNA, wherein five miRNAs were initially discovered in 2004 (Pfeffer et al., 2004). Since this early report, computational predictions and experimental evidence support the existence of miRNAs produced from viral genomes, including retroviruses (Tycowski et al., 2015; Groen and Morris, 2013; Ouellet and Provost, 2010; Klase et al., 2013; Houzet and Jeang, 2011). However, many of these miRNAs appear to be expressed at very low levels within the cell and specific functions have yet to be identified for the majority. Coupled with difficulties in reproducibility, the relevance of these transcripts remains a topic of debate (Berkhout and Jeang, 2007; Ouellet and Provost,

2010; Houzet and Jeang, 2011; Lin and Cullen, 2007). A general set of guidelines for the identification of viral miRNAs has been suggested (Tycowski et al., 2015; Klase et al., 2013) including: (1) any ncRNA produced must have importance in the viral life cycle due to space limitations of the genome; (2) the levels of miRNA should be detectable by deep sequencing, indicating that they are expressed at functional concentrations; and (3) the miRNA must have a defined role and should be conserved across clades. Specific examples of miRNAs in retroviral genomes are described below.

Bovine leukemia virus (BLV). One of the early questions regarding miRNA production from retroviruses revolved around how the genome could avoid being processed by the RNAi machinery (Cullen, 2012). Pol II transcripts are the main substrate for the RNAi pathway; however, as mentioned above, Pol III transcripts are occasionally used (Lee et al., 2004; Borchert et al., 2006). Pre-miRNAs transcribed by Pol III are able to bypass Drosha processing, protecting the vRNA from cleavage (Cullen, 2012; Kincaid et al., 2012). As an example, BLV was found to encode a cluster of five miRNAs within SL1 and SL2 stem loops in the 5′UTR named BLV-miR-B1-5 (Kincaid et al., 2012). Interestingly, BLV-miR-B4 has an identical seed sequence to host miR-29, which has previously been implicated in transformation of B cells in mice, and is sufficient to induce tumor formation (Kincaid et al., 2012; Han et al., 2010; Santanam et al., 2010). The natural hosts of BLV are cattle, which develop atypical B-cell (CD5$^+$) tumors that are BLV+ but produce very little viral mRNA, leading to the hypothesis that BLV-miR-B4 may contribute to tumorigenesis (Gillet et al., 2007; Letesson et al., 1990). BLV-miR-B2-5p also shares sequence identity with a host miRNA, miR-943, which has been tied to tumor suppressor p53, hinting at roles for the other BLV-miRs in tumor formation (Kincaid et al., 2012; Chang et al., 2011). In another study, BLV miRNAs were found to be present in leukemic B cells isolated from sheep infected with BLV without detectable levels of Pol II driven viral LTR transcription, supporting the conclusion that miRNAs contribute to a tumorigenic state even in the absence of detectable viral production (Rosewick et al., 2013). The viral miRNAs constituted a high percentage of the host miRNA pool (~40%) and were present in amounts up to 80,000 copies per cell (Rosewick et al., 2013). While the BLV miRNAs may contribute significantly to tumorigenesis, it is also possible that they could lead to viral latency, as suggested for miRNAs produced from other retroviral genomes (Rosewick et al., 2013; Klase et al., 2007). A recent report examined the transcriptomic profile of cells transduced with the BLV miRNAs to identify potential direct and indirect targets and to delineate their impact on the BLV life cycle and B-cell transformation (Gillet et al., 2016). Several mRNAs were found to be targeted by BLV miRNAs, including GZMA, FOS, PPT1, ANXA1, MAP2K1 and PIK3CG, whose gene products are involved in apoptosis, immunity, cell signaling, and oncogenesis pathways (Gillet et al., 2016; Hagn and Jahrsdorfer, 2012; Lieberman, 2010; Grossman et al., 2004). Deletion of miRNAs from the BLV genome leads to decreased viral loads, arguing for a potential role in the

viral life cycle; however, the specific role of miRNA is still unknown (Gillet et al., 2016). Intriguingly, BLV is also associated with breast cancer and it has been suggested that a new BLV vaccine in development may exclude attenuated viruses containing miRNAs due to their potential role in tumorigenesis (Gillet et al., 2016; Buehring et al., 2015; Gutierrez et al., 2014).

Bovine foamy Virus (BFV). Three BFV miRNAs produced from the viral genome have been described (Whisnant et al., 2014). BFV miRNAs are transcribed by RNA Pol III as a single transcript from the *bet* gene (Tycowski et al., 2015; Whisnant et al., 2014). However, unlike BLV where the pre-miRNA is exported into the cytoplasm bypassing Drosha, it appears that initial processing of the pri-miRNA transcript may be carried out by Drosha (Whisnant et al., 2014). BFV miR-BF2-5p and miR-BF1-5p are highly expressed in chronically infected cells, accounting for over 50% and 19% of all small RNA within the cell, respectively (Whisnant et al., 2014). These miRNAs are also detected in calves 6 months postinfection, indicating that they are expressed in vivo, although the impact of miRNA expression remains unknown (Whisnant et al., 2014). The seed sequence of miR-BF1-5p is identical to miR-B5, a miRNA expressed from the bovine herpesvirus 1, suggesting they may have a common target (Whisnant et al., 2014; Glazov et al., 2010).

ALV and RSV. A *cis*-acting element within ALV-J genomes, E (XSR), encodes a 148-nt ncRNA that has the ability to fold into a stem–loop structure similar to those processed by Dicer (Yao et al., 2014; Chesters et al., 2006). The XSR element is conserved across most ALV-J isolates and appears to contribute to oncogenesis in some cases (Chesters et al., 2006; Wu et al., 2010). Deep sequencing of an ALV cell line revealed the XSR element produced a miRNA (Yao et al., 2014). Unlike the other retrovirus miRNAs described above, alpha-amanitin blocked expression of the viral miRNA, indicating that transcription is Pol II dependent (Yao et al., 2014). This was the first description of a retrovirus using the canonical RNAi pathway to produce viral miRNAs.

Simian foamy Virus (SFV). Putative viral miRNAs were also predicted to be produced from the SFV genome using a combined computational and synthetic approach (Klase et al., 2013; Kincaid et al., 2014). Two miRNAs, SFVagm-miR-S4 and SFVagm-miR-S6, were shown to be produced in cells transfected with the proviral African green monkey SFV genome and corresponded to sequences in the LTR (Tycowski et al., 2015; Kincaid et al., 2014). While the miRNAs are transcribed by RNA Pol III, knockdown of Drosha resulted in decreased viral miRNA production, indicating Drosha processing is necessary for expression (Kincaid et al., 2014). Like other viral miRNAs, SFVagm-miR-S4 and SFVagm-miR-S6 share seed sequences with host miRNAs, miR-155, and miR-132/212, respectively (Kincaid et al., 2014). Host miR-155 is associated with cell survival and proliferation, and mimics of this miRNA have been found encoded in several herpesvirus genomes (Kincaid et al., 2014; Gottwein et al., 2007; Linnstaedt et al., 2010; Skalsky et al., 2007). Similarly, the miRNA family 132/212 is implicated in innate immunity, and the miRNAs are upregulated during Kaposi's sarcoma–associated

herpesvirus infection (Kincaid et al., 2014; Lagos et al., 2010). Although the SFV miRNAs resemble host miRNAs that play roles in herpesvirus infection, the relevance of their expression to the SFV life cycle is unknown.

HIV-1. Although several miRNAs are predicted to originate from the HIV-1 genome, the topic remains controversial due to difficulties in reproducibility (Groen and Morris, 2013; Klase et al., 2013; Umbach and Cullen, 2009; Lin and Cullen, 2007; Pfeffer et al., 2005). Although many retroviral miRNAs appear to mimic host miRNAs that modulate the cellular environment, HIV-1 viral miRNAs appear to target the virus itself to regulate latency (Groen and Morris, 2013; Ouellet and Provost, 2010; Klase et al., 2013; Houzet and Jeang, 2011). In silico methods initially predicted that HIV-1 encoded five miRNAs within the TAR stem loop, R region, *gag*, *gag-pol* frame shift, and *nef* (Houzet and Jeang, 2011; Bennasser et al., 2004). Subsequently, a study was published illustrating the ability of miR-N367, produced from the *nef* region of the viral genome, to negatively regulate HIV-1 expression, potentially contributing to viral latency (Omoto et al., 2004). The 5′UTR of HIV-1 is highly structured and contains many features critical to the viral life cycle including the Psi packaging signal (Balvay et al., 2007) and TAR; the latter forms a stable stem–loop integral to efficient transcription through binding to the Tat protein (Gatignol et al., 1991). In the absence of Tat, for instance, potentially during latency, only short viral transcripts are made that contain TAR RNA (Feinberg et al., 1991; Van Lint et al., 2013). In addition to sequestering TRBP, TAR RNA is capable of being processed by dicer and miRNAs derived from this region were detected by RNase-protection assays in infected T cells (Klase et al., 2007). One TAR-derived miRNA was found to recruit HDAC-1, a histone deacetylase associated with HIV-1 latency, to the viral LTR (Klase et al., 2007). TAR RNA-derived miRNAs, miR-TAR-5p and -3p, have also been identified at low levels (Ouellet et al., 2008). Another conserved double-stranded region of the HIV-1 RNA genome is formed when tRNA^{Lys3} is annealed to the PBS (Hu and Hughes, 2012). This region was found to associate with Ago2 of the RISC complex, potentially activating the RNAi pathway as an antiviral response to infection (Yeung et al., 2009). Intriguingly, the PBS:tRNA hybrid region appears to be processed into miRNAs in ERVs from mice and humans, implicating the host RNAi machinery in viral suppression (Calabrese et al., 2007; Kawaji et al., 2008). Although, the HIV-1 gRNA–tRNA hybrid-derived ncRNA was also found in a later deep sequencing study, the authors concluded it was more likely a degradation product of tRNA^{Lys3} due to its presence in uninfected controls (Schopman et al., 2012). Another in silico alignment of matching regions of the HIV-1 genome and host mRNAs involved in immune responses predicted multiple targets for viral miRNA, though they remain to be validated (Groen and Morris, 2013; Couturier and Root-Bernstein, 2005). An *env* derived miRNA was found to inhibit HIV-1 expression similar to TAR-derived miRNA; however, in the presence of Tat, this inhibitory effect was largely abolished suggesting the virus had found a way to adapt to the host RNAi response (Bennasser et al., 2005).

Viral Suppressors of RNA Silencing

Retroviruses are notorious for their ability to evade host defenses, whether directly through accessory proteins or by modulating translation to favor viral protein production (Malim and Emerman, 2008). Many plant viruses and some insect viruses have adapted to RNAi immune responses by evolving suppressors of RNA silencing (SRS) with the ability to bind and block the function of RISC components or to sequester miRNAs directed against the virus (Voinnet et al., 1999; Umbach and Cullen, 2009; Li et al., 2002). As mentioned above, tomato bushy stunt virus encodes a protein, p19, which functions by binding specifically to short dsRNAs containing the typical 2-nt overhang associated with miRNAs, effectively blocking RISC:miRNA association (Umbach and Cullen, 2009; Qian et al., 2009; Scholthof, 2006). Therefore, it was natural, given the involvement of RNAi in other viral life cycles, to suspect that retroviral genomes might also contain SRS proteins or broaden the functions of existing viral proteins to serve this role (Houzet and Jeang, 2011). Tat has also been implicated as an SRS protein, possibly through hindering Dicer activity (Bennasser et al., 2005; Bennasser and Jeang, 2006). HTLV-1 encodes an accessory protein, Rex, which binds to the Rex-response element and facilitates export of incompletely spliced viral mRNAs (Ballaun et al., 1991; Kusuhara et al., 1999; Younis and Green, 2005). As a potential SRS, Rex is able to block the processing of pri-miRNA by Dicer, although whether the suppression is mediated through dsRNA sequestration or direct binding to Dicer is unknown (Abe et al., 2010). The traditional role of the PFV Tas protein is as a transactivator of PFV transcription (Falcone et al., 2003). As mentioned above, host miR-32 targets PFV to inhibit translation of viral proteins (Lecellier et al., 2005). However, Tas expression caused an accumulation of host miRNA and ameliorated translational repression, supporting Tas as a general RNAi suppressor (Lecellier et al., 2005). Several studies have also been published showing little effect of Tas, Rex, and Tat proteins on the host RNA silencing pathway and argue that the interferon system is much more sensitive and effective than the SRS pathway in mammals (Umbach and Cullen, 2009; Lin and Cullen, 2007).

THERAPEUTICS

Current retroviral treatments for HIV-1 require daily doses of highly active antiretroviral therapy, a combinational regimen targeting multiple steps of the retroviral life cycle (Gulick et al., 1997). Unfortunately, over time the virus is able to adapt, requiring the patient to switch antivirals to avoid viral rebound (Clavel and Hance, 2004; Taylor and Hammer, 2008). Additionally, the side effects caused by treatment are often severe and worsen over time, resulting in nonadherence to the therapy schedule, which can result in selective pressure for viral mutagenesis under suboptimal concentrations of inhibitors (d'Arminio Monforte et al., 2000). With the discovery of RNAi, a potential new approach to viral treatment became available, wherein viral translation could be targeted

and suppressed by introduction of engineered small-hairpin RNAs (shRNAs) (Janssen et al., 2013). Applying siRNA strategies to other viral and cancer targets has been employed with varying degrees of success (Trobaugh and Klimstra, 2017; Barnes et al., 2008; van Rooij et al., 2008; Lanford et al., 2010; Dunning et al., 2016; Soifer et al., 2007). Several problems have plagued the development of siRNA-based therapeutics, including efficient delivery to targeted tissues, viral escape through mutagenesis, saturation of RNAi machinery, and stability of introduced siRNAs (Almeida et al., 2011; Trobaugh and Klimstra, 2017; Houzet and Jeang, 2011; van Rooij et al., 2008; Krutzfeldt et al., 2005; Hutvagner et al., 2004). An shRNA vaccine for poliovirus has been tested and found comparable to the Sabin type 1 poliovirus vaccine in mice, although partial deletions of the target viral sequence occur (Barnes et al., 2008). Hepatitis C virus (HCV), a causative agent of liver disease, was the target of another study, as miR-122 is necessary for HCV infection (Jopling et al., 2005, 2008). Weekly injections of a locked nucleic acid–modified oligonucleotide complementary to miR-122 reduced levels of HCV RNA in infected chimpanzees without viral mutation or deleterious side effects (Lanford et al., 2010). Additionally, a more recent study attempted to create a siRNA therapeutic against Ebola virus disease. Unfortunately, the siRNA-loaded lipid nanoparticles did not significantly increase survival rates (Dunning et al., 2016).

Single siRNA species were initially used to target specific regions in the HIV-1 genome (Das et al., 2004; Boden et al., 2003; Leonard et al., 2008; Westerhout et al., 2005). For example, a single shRNA directed against *tat* was able to repress HIV-1 transcription by 95% (Boden et al., 2003). However, when cultured for longer periods of time, HIV-1 was able to adapt by a single-point mutation rendering the shRNA ineffective (Boden et al., 2003). Continuous inhibition of HIV-1 using an siRNA against *nef* was found to induce viral mutation and eventual escape (Das et al., 2004). Interestingly, while viral escape has been linked to point mutations conferring resistance to siRNAs, a follow-up study found that some HIV-1 viral escape mutants resulted in mutations outside of the target sequence resulting in structural changes in the viral RNA (Westerhout et al., 2005). In another example of unusual viral escape, siRNAs against the TAR stem loop resulted in compensatory mutations in the promoter region that enhanced viral transcription (Leonard et al., 2008). As with antiretroviral drugs, siRNA therapy would most likely need to be given in combination for successful inhibition (Das et al., 2004; Boden et al., 2003). In silico predictions suggested that expression of at least four shRNAs would be needed to maintain a high degree of viral repression and decrease the ability of HIV-1 to evade silencing (Applegate et al., 2010). This was corroborated with lentiviral transduction of a combination of four siRNAs targeting Gag, Pol, and R/T-5 regions of HIV-1. Using this approach, HIV-1 replication was inhibited for 40 days without viral escape, although some viral spread was observed, suggesting the RNAi pathway could have been saturated (ter Brake et al., 2008). It also became clear that to sustain expression of siRNAs, lentiviral vectors lacking any sequence repetition

would be necessary to avoid recombination and to induce stably expressing cells (Applegate et al., 2010; ter Brake et al., 2008). Intriguingly, HIV-1 mutations tend to follow predictable routes, leading to the concept of coupling second generation siRNA species targeting likely resistance mutations to primary siRNA treatments, thereby enhancing the effectiveness of siRNAs (Schopman et al., 2010). Unfortunately, even with the use of second-generation siRNAs, the virus was still able to escape restriction, adapting with novel mutations (Schopman et al., 2010). An additional concern of shRNA therapy is the reduced expression of Dicer in monocytes (Coley et al., 2010). However, a subset of shorter shRNAs are able to bypass dicer, instead being processed by Ago2 directly and creating a single guide strand, AgoshRNAs (Liu et al., 2013). This approach presents several advantages to traditional shRNAs, including limited off-target toxicity from the passenger strand (Herrera-Carrillo et al., 2017; Herrera-Carrillo and Berkhout, 2017). Successful AgoshRNAs have been designed against the CCR5 coreceptor, Gag, and Pol (Herrera-Carrillo et al., 2017; Herrera-Carrillo and Berkhout, 2017).

Another approach to RNA-based therapeutics is to cleave or delete portions of the integrated or RNA HIV-1 genome through targeted enzymatic activities to disrupt the life cycle (Mitsuyasu et al., 2009; Herrera-Carrillo and Berkhout, 2016; Amado et al., 2004; Rossi, 1999). Transducing CD34+ hematopoietic stem cells with a ribozyme targeted to the *vpr/tat* reading frames and introducing them into HIV+ patients resulted in a slightly decreased viral load (Mitsuyasu et al., 2009). Although the transduced stem cell percentage was likely low, there were no reported negative effects, providing evidence that gene therapy is possible (Mitsuyasu et al., 2009). Zinc-finger nucleases, recombinases and transcription activator–like effector nuclease strategies have been developed for HIV-1 treatment and several have been examined in clinical trials (Sarkar et al., 2007; Tebas et al., 2014; Qu et al., 2013). With the development of the clustered regularly interspaced short palindromic repeat (CRISPR)-CRISPR-associated (Cas) editing system, new approaches to gene therapy have become available (Herrera-Carrillo and Berkhout, 2016). This system relies on guide RNAs that target specific sequences of DNA, which in turn can be cleaved by the endonuclease, Cas9 (Hsu et al., 2014). Although this technique has several advantages, it does require the introduction of the relatively large CRISPR and Cas9 into the genome, which is accomplished by production of stable target cell lines expressing humanized Cas9 and several guide RNA sequences by lentiviral transduction (Wang et al., 2016). However, HIV-1 has been shown to alter nucleotides around the cleavage site to reduce effectiveness of Cas9 (Hsu et al., 2014). Additionally, introduction of CRISPR/ Cas can actually accelerate viral escape because once the viral DNA is cleaved, nonhomologous end joining machinery can repair the dsDNA breaks creating resistant viruses within 36 h of infection (Wang et al., 2016; Liang et al., 2016). Alternative nonviral targets have been suggested to limit the spread of HIV-1 infection, including the coreceptors CXCR4 and CCR5. Mutation of CXCR4

and CCR5 has been successful in conferring resistance against viral infection, which could be used in combination therapies (Hou et al., 2015; Ye et al., 2014). Although there are still many aspects of gene therapy that need to be studied and understood in more detail, great strides have been made in the area of RNA-based therapeutics. Many of the lessons learned have been applied to general techniques in the field of virology and cell biology, including the development of stable lentiviral gene–silencing approaches (Hsu et al., 2014; Stewart et al., 2003).

CONCLUDING REMARKS

The discovery that the human genome is predominantly composed of ncRNA has propelled the field of RNA biology into many new areas, such as exogenous siRNA gene regulation, and has led to a deeper understanding of cellular biology. It is now clear that ncRNAs are critical to cellular responses ranging from general homeostasis to the disease states of viral infection and cancer. RNAs that were once considered to be well understood, such as tRNAs, are now thought to possess many alternative functions, including those mediated by tRNA fragments. Many newly discovered ncRNAs, such as vltRNAs, are still being characterized at a basic level. The impact of RNA on retroviral life cycles will undoubtedly grow as novel roles for cellular and viral ncRNA continue to be elucidated. Breakthroughs that have been made in the field to date lay the groundwork for future endeavors that could lead to the development of effective RNA-based therapies.

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