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MicroRNAs and Exosomes: Key players in HIV pathogenesis

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Conflicts of interest
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Abstract

Objective.—Human Immunodeficiency Virus (HIV) is well-known to cause impairment of the human immune system, and until recently was a leading cause of death. It has been shown that T-lymphocytes are the main targets of HIV. The virus inactivates T-lymphocytes by interfering with a wide range of cellular and molecular targets leading to suppression of the immune system. The obljective of this review is to investigate to what extent microRNAs (miRNAs) are involved in HIV pathogenesis.

Methods.—The scientific literature (Pubmed and Google scholar) was searched between 1988 and 2019.

Results.—Mounting evidence has revealed that miRNAs are involved in viral replication and immune response, whether by direct targeting of viral transcripts, or through indirect modulation of virus-related host pathways. In addition, exosomes have been found to act as nano-scale carriers involved in HIV pathogenesis. These nanovehicles target their cargos (i.e., DNA, RNA, viral proteins, and miRNAs) leading to alteration of the behavior of recipient cells.

Conclusion.—miRNAs and exosomes are important players in HIV pathogenesis. Additionally, there are potential diagnostic applications of miRNAs as biomarkers in HIV infection.

Keywords

Human immunodeficiency virus; AIDS; microRNA; exosomes; pathogenesis mechanisms; diagnostic biomarkers

Introduction

Human immunodeficiency virus 1 (HIV-1) is a member of the lentiviral family of retroviruses which causes human infection, and drastically decreases the number of CD4 T-lymphocytes as the infection progresses. Consequently, the affected subjects become highly susceptible to acquired immunodeficiency syndrome (AIDS) (1–3). According to a World Health Organization report, since the discovery of the HIV/AIDS, it has been estimated that the number of patients who acquired HIV/AIDS was 70 million, of whom 35 million have died. At the end of 2017, around 36.9 million HIV-infected people were living throughout the world (4, 5).

Since inflammation and dysfunction of immune response are hallmarks of chronic untreated HIV disease, this could be a cause of serious non-AIDS events (SNAEs), and various clinical sequelae that afflict AIDS patients (6, 7). There are some reports have documented the effect of early anti-retroviral therapy (ART) on the development of inflammatory diseases in AIDS. The impact of early ART on markers of inflammation is less clear. Early ART has been related to a significant decrease in the frequency of latently infected cells,

which is more pronounced if ART is initiated within days to weeks (rather than months) following infection. Although early ART can potentially decrease serious non-AIDS events (such as inflammatory end-stage organ disease) and related mortality, longer prospective studies with clinical endpoints are still required to determine the benefits of early ART (8–12).

Due to the success of ART, HIV has transitioned into a more long-term chronic disease in most countries, where the previous serious effects of AIDS are not now a major concern (13). Instead of addressing acute immune suppression that threatens patients' lives, clinical professionals now manage persistent disease, which may continue for several years. HIV care now requires clinicians and health care organizations to change from focusing on acute care, to long-term management (13). Clinical professionals not only require to be experts in anti-retroviral control, but also require additional skills for the prevention and management of cardio-vascular disease, and other co-morbidities related to aging. Bio-medical studies should also provide new approaches in this regard (13). One of the high priorities for handling HIV in the long term, is to understand the reasons for the persistent inflammation arising during ART, and how it results in morbidity and additional health problems. Moreover, there should affordable methods for preventing non-transmissible diseases and tuberculosis (TB) in populations who live in regions lacking robust care health systems (13).

MicroRNAs (miRNAs) are small non-coding RNAs that have been implicated in the causation and progression of a wide range of different diseases, and have recently been proposed as therapeutic targets in cancer, infections, cardiovascular disease, and diabetes (14–19). miRNAs in serum (circulating miRNAs) or in PBMC of HIV-1 infected patients can play a role in the progress of HIV-1 infections, by modulating HIV-1 proteins or affecting HIV-1 replication-associated host parameters (20). Several different miRNAs may inhibit the replication HIV-1; however they are not expected to influence the integration of viral DNA. Although viral protein expression may be reduced or blocked, HIV-1 latency could still be observed, which is one of the big barriers for treatment of HIV-1 infections (20). Integrated pro-virus within the HIV-1 latency reservoir, is able to be reactivated under proper stimulation leading to HIV-1 recurrence. This situation suggests the possible involvement of cellular miRNAs in establishing HIV-1 latency. Promising strategies for clearing the viral reservoir could result from studies on the mechanism of how miRNAs influence viral protein expression (20).

Lipid membrane particles or vesicles with nanometer dimensions are widely released by mammalian cells. These particles contain different cargos related to their cells of origin, including nucleic acids and proteins (21). These cell-secreted vesicles have been shown to important in inter-cellular communication. There is still uncertainty concerning the terminology and precise dimensions of different vesicles secreted by cells. These vesicles have been called exosomes, extra-cellular vesicles, oncosomes, micro-vesicles, and so forth (22). In this review, they are called exosomes for clarity.

Numerous definitions that have been provided for cell-derived vesicle subtypes have led to significant overlap with some properties of viruses. In practice, cell-related vesicles and viruses can both play a role in inter-cellular communication by traveling in the circulation,

attaching to, and being taken up by cells, and delivering their cargo to the target or recipient cells (23). There are similarities between viruses and exosomes in terms of function and composition, which is caused by their overlap in biogenesis and functions. In the infected cells, exosomes and viruses are generated at the same time, and result in the incorporation of viral-derived materials into exosomes. Such considerations lead to difficulties in differentiation and separation of these two types of particles. It is necessary to better distinguish between viruses and exosomes in biological specimens. Purification and isolation procedures should be designed to distinguish between viruses and exosomes, but even recent separation protocols have disadvantages, which can affect the conclusions (24). Due to varying specific features of exosomes, the absence of a global marker, and the possibility that exosomes can contain viral materials, validation of homogenous purification from a heterogenous population is still problematic.

In the current review, we summarize the role of microRNAs and exosomes in the pathogenesis of HIV infection. Moreover, we highlight the potential diagnostic roles of microRNAs and exosomes in HIV patients.

MicroRNAs and Exosomes: Insights into HIV pathogenesis

miRNAs belong to the class of non-coding RNAs, and are about 19–25 nucleotides in length. They are generated from endogenous primary miRNA precursors by RNA polymerase II acting on genomic DNA sequences. Primary miRNAs are catalyzed and processed into single-strand mature miRNAs by two ribonucleases (RNase) III enzymes, “Drosha and Dicer” (Figure 1) (25).

One role of miRNAs may be to control virus propagation and replication. For instance, the regulatory effects of miRNAs on the propagation of viral infection have been recently demonstrated. Furthermore, some viral miRNAs encoded by viral genomes are expressed within host cells and play a role in the cell cycle and cellular outcomes of infection (26).

While several viruses have been shown to encode for viral miRNAs, controversy persists over whether a functional miRNA is encoded in the HIV-1 genome (27). However, it has been reported that HIV-1 infectivity is influenced by cellular miRNAs. Either through directly targeting the viral genome, or by targeting the host cellular proteins required for successful virus replication, multiple cellular miRNAs may modulate HIV-1 infection and replication. Perhaps as a survival strategy, HIV-1 may modulate proteins in the miRNA biogenesis pathway to subvert the miRNA-induced antiviral effects (27).

miRNAs regulation is anchored on genomic information processing on four scenarios that may possibly explain the confounded nature of their effects in virus-infected host systems. First, HIV-1 infection alters host miRNAs networks to initiate successful viral invasion and latency, thus, affecting global host microRNA regulome. Second, HIV-1 miRNAs are produced from both sense and antisense transcripts to target either its own viral transcript or host genes for immune compromise. Third, the host miRNAs systems may consequentially target the HIV-1 genomic elements or its genes to innate immune responses. Fourth, the interplay of miRNAs and target mRNA between host and HIV-1 can be organized into

regulatory modules (*cis*-and *trans*- regulation) of essential biochemical pathways as critical determinants of host cell fate and survival.

It has also been reported that viral protein Tat, by targeting PTEN, up-regulates the expression of miR-21 and miR-222 contributing to apoptosis resistance in CD4+ T cells infected by HIV-1 (28). In addition, some miRNAs such as miR-29a, miR-128, miR-28, and miR-223 can lead to a decrease in HIV replication by targeting the HIV 3'-UTR region, PTEN, and the 3'-end of HIV mRNA, respectively (29–31). Thus, miRNAs can not only facilitate viral replication, but also promote disease progression. On the other hand some other miRNAs can decrease or inhibit the virus life cycle.

In general, HIV-1 infection may be affected by miRNAs via several mechanisms. Anti-HIV-1 miRNAs inhibits HIV-1 activity via CCR5 or CXCR4, auxiliary receptors for HIV-1, or target HIV-1 directly through *env*, *pol*, *gag*, *vif*, and *tat* genes of HIV-1 genome (32). Hariharan et al. applied a consensus scoring technique, and demonstrated that miR-29a and miR-29b targeted *nef*, miR-149 targeted *vpr*, miR-378 targeted *env*, and miR-324–5p targeted *vif* inside the HIV-1 genome (33). Huang et al. found that miR-28, miR-125b, miR-150, miR-223, and miR-382–5p targeted 3′UTR region of HIV-1 mRNA in the cells, which declines $CD4^+$ T-cell actuation during the resting time (34). Monocytes have numerous anti-HIV-1 miRNAs, which may be down-regulated in macrophages after differentiation, and could render macrophages more vulnerable to HIV-1 infection. Inhibiting such miRNAs enhanced the susceptibility of mononuclear cells to HIV-1 infection (34). The 3′UTR region of the HIV-1 RNA genome has been identified as the target of miR-196b and miR-1290 (35). Suppressing these 2 miRNAs may result in the activation of latent HIV-1, which could lead to clearance of the latent viral reservoirs through virus-generated cytolysis and the host anti-viral immune response generated in the presence of ART (35, 36).

It can be concluded that the reason for the low number of validated HIV-1 encoded miRNAs in the miRBase database, reflects difficulties in their detection, and makes them among the least described virus-induced miRNAs (37). The reason for this low number may be due to the small genome size of HIV-1, or to low levels of expression that cannot easily be detected by common biochemical methods. Therefore, improved procedures for detection are needed (38). A previous study estimated that retroviral miRNAs comprise just 0.5% of the total miRNAs that can be detected in cells infected with HIV-1 (39). Additionally, the biogenesis of viral miRNAs could be limited due to the poor accessibility of the primiRNAs to nuclear miRNA processing machinery, and natural destabilization (37). Moreover, numerous studies have reported that Dicer or Drosha can carry out endonucleolytic destruction of viral RNA genomes, which will eventually reduce the production of viral miRNAs (40).

Nonetheless, the emergence of technologies with higher sensitivity such as next generation sequencing, RNAse protection assays (RPA), and improved computational power could play a role in the discovery of novel HIV-1-derived miRNAs. Recently a pyro-sequencing approach suggested that not less than 40% (or 125) of the candidate HIV-1 miRNAs originated from the TAR, RRE and *nef* regions, and constituted the majority of non-coding RNAs in cells infected with HIV-1 (41). Deep sequencing studies have further confirmed

these findings, since it has been reported that HIV-1 miRNAs resulting from the structured regions of the genome, facilitate Drosha and Dicer mediated RNA processing (42).

It seems likely that interactions between HIV-1 miRNAs and the targeted mRNAs function as a regulator of the viral genome. More investigation is needed to confirm additional functionality of HIV-1 miRNAs, such as targeting host cellular transcripts for immune evasion (43).

Exosomes are biological nanovehicles, which are characteristic of many pathological and physiological processes (44, 45). Nearly all the different types of mammalian cells release exosomes into the extracellular environment (46) and they have been found to be abundant in several biological fluids, such as, blood, saliva, breast milk, semen and urine (47–53). Exosomes possess lipid-bilayer membranes, and have a roughly spherical shape (54). The contents of the exosomes depend on the cell type from which they were formed by a budding process, and on the condition of the host cells (e.g. virally infected or cancer cells) (55–57). Exosomes normally contain a range of different molecules, such as nucleic acids (DNA, RNA, mRNA, viral genome and microRNAs), annexins, tetraspanins (i.e., CD9, CD63, CD81, CD82), enzymes, cytoskeletal proteins, MHC molecules, signal transduction proteins and heat shock proteins (54, 58). It has been proposed that exosomes are involved in cell-cell communication. By regulation of cell signaling, as well as the ability to be taken up by targeted cells, they are thought to play significant roles in intercellular communications via interactions with membrane receptors (46, 59). Moreover, exosomes have the ability to transfer miRNAs into target cells, and may take part in intracellular communication by the repression of target mRNAs in recipient cells. Consequently, after merging with target cells, the viral and cellular miRNAs delivered by exosomes alter the levels of gene expression, by inhibition of mRNA translation (60). There are several studies that show that exosomes contain HIV proteins and fragments of the HIV genome (61, 62). Furthermore, as has been shown in HIV-infected patients, exosomes also contain HIV-derived transactivating responsive (TAR) RNA which can inhibit apoptosis by decreasing the expression of pro-apoptotic proteins, such as Cdk9 and Bim (61). Recently, several studies have suggested that exosomes isolated from the semen of healthy men, and from the breast milk of healthy women suppressed HIV infection (62).

HIV Long-Term Non-Progressors and microRNAs

To control viral replication, the majority of HIV-infected patients require long-term antiretroviral therapy (ART). However, approximately 1% to 5% of affected individuals (which are called long-term non-progressors (LTNPs) can control their HIV infection for more than 7 years without receiving ART (63, 64). Elite controllers (ECs) and viremic controllers (VCs) have been identified as small subsets of patients with HIV infection (65, 66). Without ART, the viral load in ECs can reach an undetectable level (<50 copy/ml) and the CD4-cell count remains high (200 to 1000/μl) (67–70). However, the viral load of VCs usually lies between 200 and 2000 copies/ml in the absence of ART. Viremic progressors (VPs) are HIV-positive patients who have high levels of viral load and progress towards AIDS if they do not receive ART (71, 72). The exact mechanism of this LTNP phenomenon has not yet been completely elucidated (73). The effects of miRNAs on HIV replication have

been reported (74–76), but their roles in ECs have not been adequately studied. However, some studies have shown deregulated expression of some miRNAs in ECs compared to non-infected controls (77).

In 2012, Witwer and colleagues conducted an investigation to evaluate the expression profile of miRNAs, and their correlation with viral load versus number of CD4+ T-cell in three groups (uninfected controls, untreated viremic patients, and ECs). They found that in both ECs and viremic patients, miR-125b and miR-150 were significantly down-regulated. Also, there was a negative correlation between miR-181b and CD4 counts, while the correlation between miR-150, miR-31 and miR-29a was remarkably positive; however, no significant rcorrelation was observed between miRNAs expression and viral load (78). Reynoso and colleagues reported that, in plasma obtained from ECs, the expression of miR-29b-3p, miR-146a-5p and miR-33a-5p was up-regulated in comparison with chronically HIV-infected patients. In addition, up-regulation of miR-33a-5p and miR-29b-3p correlated with a notable decrease in viral production in primary CD4+ T cells and MT2 cells (69). In another study, Egana-Gorrono et al., screened 286 miRNAs in phyto-hemagglutinin-stimulated PBMCs from 29 individuals divided into four groups: ECs, VPs, patients receiving ART, and uninfected individuals, using TaqMan low-density arrays (TLDA). The results showed that the expression pattern of23 miRNAs was significantly different between ECs and VPs (Table 1). Next, all the subjects were divided into two groups and the alteration of mRNA expression levels were analyzed in two blocks (block 1: ECs and uninfected individuals; and block 2: viremic-progressors and patients receiving ART). The outcomes of their analysis confirmed that miR-27a, −27b, −29b and −221 were up-regulated in block 1, and the expression of the miRNAs was down-regulated in block 2. In addition, 19 other miRNAs were down-regulated in block 1, while they were up-regulated in block 2 (77). Overall, the assessment of the altered expression patterns of miRNA in ECs, which was similar to non-infected subjects, and different from chronically HIV-infected patients, could provide useful information to identify novel and prognostic biomarkers for predicting HIV disease progression towards AIDS, and could contribute to anti-HIV drug discovery efforts.

Egaña-Gorroño et al. evaluated the differential miRNA profile in CD8+ T cells between patients infected with HIV, who had differences with regard to control of viral replication and immune response (79). They reported down-regulation of miRNA when comparing samples from elite suppressors (ES), ART-treated, and viremic HIV-infected groups, and showed that hsa-miR-4492 had the highest down-regulation. Even though miRNA down-regulation was more pronounced when comparing stimulated CD8+ T cells with their resting counterparts, viremic patients (VP) still exhibited a differential miRNA expression pattern. Indeed, hsa-miR-155 and hsa-miR-181a were down-regulated in VP, while up-regulation or no difference was found after stimulation in the other groups. In general, functional enrichment analysis showed that the expected target genes contributed to activation of signal transduction pathways, metabolic modulation, apoptosis, and immune responses (79).

Examination of the miRNA profile in patients infected with HIV at various stages of the infection might show a dysregulated miRNA pattern with diagnostic and prognostic value for HIV-1 treatment (79). Moreover, the differential modulation of miRNAs in CD8+ T-

lymphocytes might be helpful in further understanding the basic mechanisms of host anti-viral responses.

So far, researchers have not observed a relationship between level of miRNA expression and resistance of the resting memory $CD4^+$ T cells to HIV-1 infection. In comparison with activated $CD4^+$ T cells, resting memory $CD4^+$ T cells exhibited up-regulation of five miRNAs: miR-28, miR-125b, miR-150, miR-223, and miR-382, which negatively target the 3′-ends of HIV-1 mRNAs (34). For this reason, in resting $CD4^+$ T cells infected with HIV-1 (infected clones or isolated from cART-treated HIV-1 patients) knock-down of miRNAs using antisense suppressors increased the generation of viral proteins and virions. Moreover, over-expression and knockdown studies suggested there was a negative relationship between miR-125b expression and HIV-1 infection in a T cell line (80). Additionally, specific miRNAs apparently indirectly regulate HIV-1 infection in resting $CD4^+$ T cells, via regulation of the expression of cellular co-factors. Levels of cyclin T1 protein, which is critically involved in the viral Tat-mediated trans-activation of HIV-1 LTR-driven gene expression, were up-regulated, regardless of transcript levels, when the resting $CD4^+$ T cells were activated (81). It is interesting that up-regulation of cyclin T1 was followed by a considerable down-regulation of a group of miRNAs, including miR-27b, miR-29b, miR-150, and miR-223 in activated $CD4^+$ T cells. Researchers confirmed this observation via over-expression or depletion of miRNAs, which decreased or enhanced the cyclin T1 protein levels, respectively. Nonetheless, it was found that only miR-27b directly modulated the expression of cyclin T1, while miR-29b, miR-150, and miR-223 had an indirect impact on the levels of cyclin T1.

Monocytes do not allow HIV-1 replication; however, they are susceptible to infection upon differentiation into monocyte-derived macrophages (MDM) or monocyte-derived dendritic cells (MDDC). Although multiple mechanisms have been proposed for the post-entry restriction of HIV-1 in monocytes, some reports suggested a relationship between levels of miRNA expression and the resistance of monocytes to HIV-1 infection. Wang et al. (82) observed that monocytes expressed higher levels of cellular miRNAs, miR-125b-5p, miR-28–5p, miR-150–5p, miR-223–3p, and miR-382–5p. Huang et al. (34) reported that these miRNAs inhibited HIV-1 replication in resting $CD4^+$ T cells. Since knock-down of these miRNAs in monocytes increased HIV-1 infection, and miRNA over-expression in the MDMs suppressed HIV-1 replication, researchers suggested that levels of miRNA expression could define the susceptibility of monocytes or MDMs to HIV-1. Figure 2 illustrates the various miRNAs involved in HIV pathogenesis.

HIV-encoded miRNAs

Despite the efforts that have been made to find a permanent cure for HIV/AIDS, the HIV virus unfortunately uses a range of strategies to escape recognition and elimination by the host immune system (83, 84). These strategies depend on viral products which mimic some host cell-specific components to evade immune recognition (85). It has been revealed that the virus and viral proteins are able to encode small non-coding RNAs (miRNAs) leading to manipulation of cellular and viral transcripts contributing to the proliferation and infectivity of the virus, as well as actively curtailing the host immune responses against the virus (86).

Recently, it has been demonstrated that both non-coding and coding region of the HIV genome can produce miRNAs, which regulate both host and viral gene expression (Table 2). The essential functions of viral mi RNAs (vmiRNAs) have not yet been addressed in depth (87, 88). Several studies have indicated that vmiRNAs originate from the trans-activation response (TAR) and negative regulatory factor (Nef) proteins of HIV(89–92). Klase et al. showed how to isolate vmiRNAs (TAR-miR-3p and −5p) from TAR, which protect the HIV-infected cells against apoptosis through decreasing ERCC1 and IER3 gene expression involved in apoptosis (91). The results suggested that TAR-miRNA shelters HIV-infected cells from programmed cell death by down-regulation of cellular genes implicated in apoptosis (91). You et al. reported that by targeting the PABPC4 in lymphokine cells, miR-N367 could suppress the expression of lymphokine mRNA, and also contribute to the maintenance of viral latency (93). Furthermore, Omoto and colleagues demonstrated that Nef-derived miRNAs were produced persistently in HIV infected cells. Their results showed that miR-N367 inhibited Nef expression, as well as transcription of the long terminal repeat (LTR), possibly reducing HIV transcription (92). The miR-H3 sequence is embedded in the HIV reverse transcriptase coding region, which is highly conserved between HIV subtypes. This provides possibilities for miR-H3 to target the HIV TATA box at 5′-LTR, leading to the activation of viral promoter transcription. Subsequently, up-regulation of miR-H3 can result in massive production of the virus; however, mutations within miR-H3 sequence significantly decrease the replication of wild-type HIV viruses (94). The production of the antagonizing transcription factor (AATF) has a role in DNA damage, cell cycle, transcriptional regulation, and in apoptosis. Thus, it is possible that, by silencing the AATF gene, apoptosis induction would increase (95). Kaul et al. reported that miR-H1 down-regulates AATF gene expression and induces apoptosis in infected cells, caused by vmiR-TAR. Consequently, miR-H1 decreases the expression of miR-149 which has been identified as a target-transcript of HIVVpr (96).

Studies have shown that specific families of viruses encode certain miRNAs that are commonly called viral miRNAs or vmiRNAs. These vmiRNAs affect viral replication (97), and are an important factor in the activity of DNA viruses (98, 99). Although most RNA viruses do not encode for vmiRNAs, the question of whether retro-viruses (and specifically HIV-1) do or do not encode for any functional miRNA(s) is still under dispute (100). Another member of the Retroviridae family, called bovine leukemia virus clearly does encode for a functional vmiRNA (101). Hence, researchers have argued that retroviruses that have access to both the nuclear and cytoplasmic miRNA processing machinery may indeed express vmiRNAs.

A recently conducted study used bio-informatic prediction algorithms, and suggested that the HIV-1 genome might encode for five candidate vmiRNAs (102). Reports showed that the HIV-1 Nef coding region contained specific vmiRNAs (Nef-U3-miR-N367) (103). Additionally, the 3′ end of HIV-1 RNA encodes for a vmiRNA (HIV-1-miR-H1) (104). HIV-1 trans-activation RNA (TAR) that attaches to the HIV-1 protein Tat, and modulates viral translation, encodes for a vmiRNA (known as TAR-miR-5p & 3p) (105, 106). Although the above studies demonstrated the presence of vmiRNAs inside the HIV-1 RNA genome, other studies reported contrary findings, and could not demonstrate vmiRNA expression post-HIV-1 infection. Another recent study used sensitive deep sequencing

technology to show that HIV-1 did not express any functional vmiRNAs in infected cell lines, primary peripheral blood mono-nuclear cells (PBMCs), and in primary macrophages (107). Moreover, the researchers conducted photo-activatable, ribonucleoside-induced cross-linking, togther with immuno-precipitation (PAR-CLIP) assays, and provided evidence implying that HIV-1 genome would not be likely to be targeted by cellular miRNAs (107). Zhang et al. showed the presence of a new vmiRNA encoded by HIV-1 and known as miR-H3 (108). They found that miR-H3 was located in the region of the HIV-1 RNA genome, which encodes for reverse transcriptase, and attached to the TATA binding sites on HIV-1 5′LTR to increase viral transcription (108).

Contradictory findings regarding whether vmiRNAs are encoded by HIV-1 can be partly explained by the differences in the types of cells investigated, different technology employed, or different strategies employed for detecting and confirming vmiRNA expression. Further research is necessary to reconcile the differences, using standardized protocols, and improving collaboration and exchange of data between research groups who work in this field. The actual practical contributions of vmiRNAs encoded by HIV-1, should be followed by careful monitoring of their role in HIV-1 infection and replication.

MicroRNAs as diagnostic and prognostic biomarkers in HIV

MicroRNAs (miRNAs), 18–25 nucleotides in length, are non-coding RNAs that are able to target mRNAs and regulate their expression (110–112). In terms of functionality, miRNAs are important agents for gene silencing and post-transcription regulation of proteins. During viral infection, some of the viral genes that play essential roles in the pathogenesis of infection, also cause miRNA production through interacting with the virus or host cell mRNAs (113). Mounting data suggests that these biomarkers can be considered appropriate for screening and monitoring of HIV patients in various phases of infection. Some investigations have focused on the elaboration of HIV miRNAs and their expression levels. It has been found that a dysregulated profile of miRNA expression would be helpful to differentiate HIV infection, and the phase of infection in affected patients. Recently, it was concluded that miRNAs and their expression levels could be different in different phases. For instance, miR-3162–3p is down-regulated in the plasma of patients in the acute phase of HIV infection. Therefore, this biomarker could useful to detect new infections (114, 115).

In HIV patients, the expression levels of miRNAs have been evaluated by several investigations. Although some miRNAs have shown variability in expression levels between both plasma and infected cells, their expression levels can be useful to determine HIV infection progression. For example, miR-146b-5p and miR-150 are dysregulated in various phases of HIV infection in plasma and in PBMC. Additionally, it has been reported that miR-150 and miR-146b-5p are up-regulated in plasma, but down-regulated in PBMC of HIV patients in the AIDS phase (116). It has been reported that miR-34a up-regulation can increase trans-activation of the virus by affecting Tat expression and increasing its functionality (117). Several studies have reported the expression levels of miRNAs in different cells from AIDS patients in different phases of infection. In primary CD4+ T cells, the expression of miR-124a, miR-29a, miR-223, miR-27a, miR-19b, miR-151–3p, miR-28–5p, miR-766 and miR-30a-3p were up-regulated, while the expression of miR-125b which

increases the virus entry to the cells, was down-regulated. In addition, miR-181b was up-regulated in monocyte-derived dendritic cells (MDDCs) in the AIDS phase (118–121).

During HIV infection, the virus recruits employs several mechanisms to induce the latency phase inside the host cells. The mechanisms that the virus uses for induction of the latency phase, are not yet fully understood. In the latent phase of HIV infection, the virus does not replicate. HIV latency in resting primary $CD4^+$ T cells is one of the most important problems affecting treatment of this infection, even when using HAART (highly active antiretroviral therapy) (122–124). Investigations on HIV latency and its correlation with miRNA expression support this idea that miRNAs play a part in this process. Huang and colleges found that miR-28, miR-125b, miR-150, miR-223, and miR-382 were up-regulated in HIV infected cells in the latency phase. By targeting the 3′ ends of HIV messenger RNAs, these miRNAs inhibit virus production in infected resting $CD4^+$ T cells (125). Other studies have strengthened the correlation between HIV latency and miRNAs, in which miRNAs expression could regulate virus replication in infected cells. It has been found that, during the latency phase of HIV infected cells, miR-17–5p, miR-20a and, miR-29a were up-regulated and also could suppress viral replication. It was shown that miR-17–5p and miR-20a could reduce virus replication, meanwhile, they affect the Tat cofactor PCAF (p300/CBP-associated factor) (74, 126). Another relevant issue for HIV replication concerns the simultaneous up-regulation of some cellular and viral miRNAs that promote HIV replication in infected cells. It has been found that miR-TAR reduced apoptosis and promoted viral replication. Also, miRNA-H3 (viral miRNA) and miRNA-132 can act as viral replication promoters and their expression levels increase in infected cells (91, 94, 127). Wang et al. showed that miR-196b and miR-1290 were up-regulated in infected cells, and also reported that, through targeting the 3’ untranslated region of HIV, these miRNAs reduced viral replication. This study suggests that the inhibition of some cellular miRNAs could affect HIV latency, leading to the eradication of a reservoir of infection (128).

HIV infected individuals do not solely suffer from immune suppression, but they may also suffer from other complications, such as HIV-associated neurocognitive disorders (HAND), further exacerbating the severity of the condition. The HAND syndrome is a result of excessive macrophage activation, and this condition even occurs in patients who successfully respond to ART. Investigations on miRNAs and HAND have found that there are some miRNAs that could be related to this condition. An in-vitro study showed that miR-196a induced apoptosis in neuronal cells. Moreover, miR-500a-5p, miR-381–3p, miR-93–3p and miR-34c-3p were up-regulated in macrophages in human brain tissue. By decreasing neuroprotective proteins, they play a role in neuronal pathogenesis and also affect the innate immune responses leading to neurocognitive dysfunction. In addition, there are other miRNAs playing a crucial role in HIV neuronal complications. For instance, up-regulation of miR-101 in human brain microvascular endothelial cells caused destruction of endothelial permeability, and miR-128a disrupted the neuronal activity in primary cortical neurons, and could contribute to HIV encephalopathy (HIVE) (129–132). Nowadays, it is well-accepted that miRNAs play a role in other HIV complications, such as HIV cardiomyopathy (HIVCM) caused by increased monocyte adhesion to the endothelium in HIV patients. This adhesion is caused by increased ICAM-1 expression induced in infected cells by HIV Tat. Also, Tat can recruit miR-221 and miR-222 to cause an increase in ICAM-1 leading to

cardiomyopathy in the untreated infection animals (133). It has been demonstrated that miRNAs are important agents in the regulation of glomerular hemostasis in different conditions. The role of miRNAs in HIV-associated nephropathy (HIVAN) has not been fully documented, but in a study conducted by Cheng et al. on transgenic mice (Tg26) and in vitro human podocytes, they observed that miR-200 and miR-33 were down-regulated during HIV infection (untreated infection). They suggested that these miRNAs could play a role in the pathogenesis of the proliferative phenotype of HIVAN (134).

Regardless of the disease phase, different levels of miRNAs in HIV infected patients when compared to controls, show that expression patterns of miRNAs in different cells are more complicated than what could be first thought. For instance, several studies demonstrated that in monocytes and monocyte-derived macrophages (MDMs), miR-198, miR-155, miR-1236, miR-221, miR-15a, miR-15b, miR-16 and miR-93 were up-regulated. Furthermore, the expression of miR-21, miR-222, miR-29, miR-34a, miR-125b, miR-28–5p, miR-150, miR-223 and miR-290 were also up-regulated in lymphocytes, and vice versa for miR-34c-5p, miR-20a, miR-106, miR-155, miR-29 and miR-2 (Table 3).

Approximately 10~15% of the patients infected with HIV-1 exhibit a sharp decline in $CD4^+$ T-cell counts in the initial phase of infection, followed by a rapid progression to full-blown AIDS. Researchers compared miRNA expression profiles in PBMCs isolated from rapid and slow progressors, and showed different levels of miR-31, miR-200c, miR-526a, miR-99a, and miR-503, which might be useful as bio-markers for fast progressors (135). Duskova et al. demonstrated miR-19b, miR-146a, miR-615–3p, miR-382, miR-34a, miR-144, and miR-155 that modulate innate immune-associated and inflammation-associated genes, were remarkably up-regulated in PBMCs with the increased viral loading in the people infected with HIV-1 (136).

Munshi et al. compared the expression levels of miR-16, miR-146b-5p, miR-150, miR-191, miR-223, and miR-146b-5p in plasma taken from normal individuals without AIDS, patients infected with HIV who had not been given ART, patients who had taken ART, and those who had been given ART but did not respond (116). The researchers found that levels of miR-146b-5p in plasma and PBMCs varied between groups, and predicted the response to ART. Additionally, it may be possible to use miR-150 as a biomarker to monitor HIV/AIDS prevalence and the impact of ART (116). Rocca et al. observed an inverse relationship between miR-29a levels and HIV viral load and the degrees of immunosuppression (numbers of $CD4^+$ T cells and the $CD4^+$ T/$CD8^+$ T ratio) in 165 young patients chronically infected with HIV-1 (137). MiR-29a levels and response to treatment varied among patients. Low miR-29a levels were observed in the patients who failed treatment (CD4 < 350 cells/μL). Hence, it may be possible to use miR-29a as a biomarker of long-term survivors and response to ART. Moreover, miR-29a may predict disease prognosis and progression (137).

Longitudinal studies of miRNAs in non-treated patients who suffer HIV-1 progression may give insights into disease progression and potential therapeutic targets. However, guidelines to start ART as soon as possible after diagnosis of HIV-1 infection, have made this type of study more difficult to carry out.

MicroRNAs as therapeutic targets in HIV

The cellular RNAi machinery, such as miRNAs, plays a pivotal role in controlling several diseases, such as viral infection, cancer, and probably HIV. Some details of the interaction between host-cellular miRNAs and HIV have been reported. In fact, the expression profile of miRNAs changes during HIV infection supporting the idea that dysregulation of cellular miRNAs is associated with HIV disease progression (180–182). It has been observed that some miRNAs hinder HIV infection via several mechanisms. Some cellular miRNAs target HIV accessory genes and host protein/genes involved in the life cycle of HIV(183), affecting the interaction between cell surface glycoprotein CD4 and the HIV ligands, leading to HIV entry (184). Lodge et al. demonstrated that, through down-regulation of CD4 expression, miR-221 and miR-222 were up-regulated in macrophages infected with HIV, resulting in the inhibition of CD4-mediated HIV entry (156). Moreover, the co-receptor CXCR4 is another facilitator which helps HIV entry into T lymphocytes and myeloid cells (185, 186). Quaranta and colleagues performed an investigation to test the efficacy of treatment with AMD3100 and promyelocytic leukemia zinc finger (PLZF) on the CXCR4 and miR-146a expression levels in human primary CD4+ T lymphocytes infected by HIV. They showed that PLZF, an amiR-146a repressor, increased the expression levels of TRAF6 and CXCR4 proteins in CD4+ T lymphocytes. Therefore, using gene-silencing treatment of PLZF or AMD3100, it was observed that the up-regulation of miR-146a restricted HIV entry into leukemic monocytic cells and CD4+ T lymphocytes through suppression of CXCR4 (176). The mechanism of HIV replication is associated with host cellular factor cyclinT1, which binds to viral trans-activator protein (Tat) leading to the activation of transcription of the integrated virus (provirus) (187). A new anti-HIV property of miR-198 was recently shown by Sung and colleagues. They showed that up-regulation of miR-198 restricts HIV replication via targeting 3UTR of cyclinT1 mRNA in monocytes (142). Previous studies have indicated that TNPO3 regulates nuclear import and replication of HIV in host cells (188, 189). Through induction of type I interferon, miR-128 directly targets TNPO3 mRNA. Consequently, TNPO3 mRNA expression levels and protein are remarkably reduced, and miR-128 suppresses virus replication in HIV-infected cells (30). miRNAs can also target Nef, an important virulence factor of primate lentiviruses, such as HIV (190). Ahluwalia et al. suggested that repression of miR-29a notably promoted HIV infection. Furthermore, it was demonstrated that miR-29a decreased the expression of Nef protein, which causes interference with HIV replication (157). In addition, Waminathan and colleagues reported that miR-155 coulkd serve as an anti-HIV agent via affecting some HIV-dependent factors, such as LEDGF, Nup153, TNPO3 and ADAM10 involved in pre-integration and post-entry events (144). Triboulet et al observed that down-regulation of pri-miR-17/92 enhanced HIV production in Jurkat cells, and it is known that HIV actively down-regulates the expression of the miR-17/92 cluster. By affecting the PCAF (p300/CBP-associated factor) levels, these miRNAs could decrease HIV transcription, because PCAF enhances Tat binding to CDK9/P-TEFb as well as transcription of HIV genes (74, 191).

As mentioned earlier, studies have reported that several cellular miRNAs contribute to HIV replication by targeting both cellular and viral factors. As seen in table 4, some miRNAs can enhance HIV infection by repressing cellular inhibitors of viral replication. For instance, miR-217 and miR-34a down-regulate SIRT-1, a Tat and p65 deacetylase, leading to

increased efficiency of HIV transcription (118, 143, 192). miR-132 is the first miRNA shown to elevate HIV replication. Chiang et al. found that miR-132 was over-expressed due to the activation of CD4+ T cells. They also reported that, by targeting of MeCP2, miR-132 may be potentially associated with enhanced HIV replication (127). The phosphatase 1 nuclear targeting subunit (PNUTS) is involved in regulation of HIV transcription. Kapoor et al. reported that miR-34a was up-regulated in HIV-infected T cells. They also indicated that miR-34a could overcome the suppressive effects of PNUTS and increase HIV replication (153). In one investigation, Farberov et al. showed that the up-regulation of miR-124a, miR-34a and let-7c increased virion release and the viral genome copy number in the infected Jurkat cell line. These miRNAs, by targeting TASK1 and p21, inhibited cellular proteins that restrict viral replication, and enhanced viral replication and release from HIV-infected cells (161). As well, Zhang and colleagues suggested that HIV-Tat protein induces the over-expression of miR-34a (long terminal repeat (LTR) trans-activation via the SIRT1/NF-kB pathway) in TZM-bl cells(117). These findings suggest that some miRNAs can be considered as novel agents to control HIV infection or in conjunction with antiviral drugs contributing to improve the viral disease.

In conclusion, most studies were carried out in vitro. Whether miRNAs can inhibit latency, boost immune function, prevent re-infection with HIV-1, or allow long-term proviral latency remains to be answered in humans. Therefore, future research studies need to confirm the functional relevance of miRNA in HIV-1 infection.

HIV and Exosomes

A majority of the cells are able to release membrane-surrounded vesicles, usually known as extra-cellular vesicles (EVs), into the extra-cellular spaces for inter-cellular communication at local and distant sites. They mediate molecular transfer between cells, and may carry out immune modulation (195). EVs have a high degree of heterogeneity and dynamic interconversion, and are commonly categorized into exosomes (200), macro-vesicles (196), and apoptotic bodies, on the basis of biogenesis and vesicle cellular origin (197). Exosomes are produced as intra-luminal vesicles, by budding away from the cytoplasm into an intermediate endocytic compartment, that is called a “multi-vesicular body” (MVB). Exosomes are shed from the cells when the MVB is combined with the plasma membranes (198). Exosomes include different molecular cargoes depending on their cells of origin, such as RNAs and proteins (198). Even though widely-employed exosome purification protocols in some past publications, have frequently co-isolated various kinds of EVs, differential ultra-centrifugation technique can separate EVs containing CD63, CD81, and CD9 tetraspanins, and endosome marker-enriched vesicles that are considered to be the characteristic markers of exosomes (199). Figure 3 illustates a schema of exosome biogenesis.

It is possible to isolate exosomes from the medium of HIV-1-infected cells, and from sera of individuals with HIV infection (Table 5) (200). The exosomes from latent HIV-1-infected Jurkat cells (J1.1) do not contain intact HIV-1 viral particles, even though these exosomes include some viral proteins, including Gag and the precursor form of Env protein (p160) (201). The HIV transactivation response (TAR) element RNA, which is a precursor of

several HIV-encoded miRNAs, establishes a stem–loop folded structure in the nascent transcript, that facilitates the attachment of viral transcriptional trans-activator (Tat) protein to enhance transcription and replication of HIV (202). Exosomes isolated from HIV-1-infected cell culture supernatants, or from HIV-infected patient sera contained TAR RNA in the total viral RNA (201). TAR RNA-bearing exosomes generated the pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-β (TNF-β) when added to primary macrophages (200).

Currently, the usefulness of exosomes and other extracellular vesicles (EVs) is an evolving approach to diagnose or even treat HIV infection (203). Determining the possible correlation between HIV and release patterns of exosomes may be helpful to tackle HIV and its related complications, leading to production of new medications or therapeutic agents (203–206). Despite all the attempts that have been made during the prior 20 years, to discover an effective and potent vaccine to protect the immune system against HIV, there are still numerous puzzles to be solved (207, 208). These problems may originate from unknown mechanisms related to host-pathogen interactions and the ability of the virus to evade the immune ssytem. For instance, one of the ways to escape immune detection is to take advantage of intercellular communication processes. Cytoplasmic tunnels that resemble cell-to-cell channels or tunneling nano-tubes are other possibilities. In this way, macromolecules and cellular constituents can be physically transported from one cell to another cell. These channels can be used in microbial propagation, when two immune cells form synapses to present antigens in humoral immunity. This virus can then move from one T cell to infect all of them (209).

The complexity of performing studies on exosomes secreted from cells infected with HIV-1 is due to particular features of exosomes and HIV-1 viruses. Their biophysical molecular properties, biogenesis and uptake mechanisms are complex and different. The density of HIV-1 ranges from 1.16 to 1.18 $g \cdot mL^{-1}$, while the density of exosomes ranges from 1.13 to 1.21 $g \cdot mL^{-1}$ (210, 211). HIV-1 is slightly larger in size than exosomes, with the virus diameter ranging from 100–120 nm, in comparison with the diameter of exosomes being 40–100 nm (24). Moreover, it is believed that HIV-1 could be produced via similar pathways that apply to exosome biogenesis (212). HIV-1 budding is suggested to be involved with numerous cellular processes, such as Alix and TSG101 that are also involved in exosome biogenesis (213). The convergence of the biogenesis of HIV-1 and exosomes, suggests that HIV-1 products, such as proteins and RNAs might be encased within the exosomes, and the fact that exosomes can be isolated from fluids of indivuduals infected with HIV-1 raises the question of whether this could be contamination. However, rigorous purification methods, including immune-affinity methods and centrifugation on density gradients are able to separate exosomes from HIV-1 particles (24, 214). The remarkable similarity between the biogenesis of exosomes and enveloped viruses generally, and HIV-1 in particular, resulted in the “Trojan exosome” hypothesis of HIV-1 assembly and cell-cell transmission. This suggests that the HIV-1 virus evolved to use the biogenesis of exosomes and their cell uptake pathways, to allow envelope-independent entry of the virus (215). The constituents of the HIV virus may be packaged into the intraluminal vesicles (ILV) while there is uncertainty as to whether the cells are infected by mature progeny viral or not (216). It is possible that, exosomes that bind via their unique cell surface receptors, or by engagement of intact virus

could be involved in viral infections (217). In other words HIV could employ exosomes to increase the infection rate and to escape from immune defense. This process, by which exosomes may facilitate the viral access into cells of the innate and adaptive immune system is very important, and could be a mechanism by which HIV develops resistance to some neutralizing antibodies (217).

The composition of exosomes derived from biological fluids is extremely variable, and it has been proposed that the composition may govern their biological effects. Accumulating evidence suggests that the effects of exosomes on HIV pathogenesis may depend on their cellular source (218). In most cases (but not all) exosomes derived from HIV-infected cells are more virulent and boost infection, while exosomes derived from uninfected cells have more protective properties (219). Regarding the source of exosomal release, It appears that the origin of the exosomes is the determining factor for their effects on HIV (218). For example, exosomes derived from human blood infected with HIV, may be derived from various types of cells, including both HIV-infected cells as well as uninfected cells. It has been postulated that HIV hijacks the exosome biogenesis pathway which transports various viral proteins and RNAs for the viral dissemination process(220).

In recent years, some studies have focused on the exosomal contents in HIV patients and HIV infected cells. Roth et al. used MDM cells (human monocytes differentiated to macrophages) to show that miR-548a, miR-30e, miR-338, miR-454, miR-518f, miR-1243, miR-1247a, miR-150, miR-29a, miR-302c, miR-636, miR-872, miR-875 were all up-regulated in HIV infected cells (221). Also, Aqil et al. used MicroRNA Array screening to measure miR-149, miR-382, miR-378, miR-324–5p, miR-223, miR-150, miR-125b, miR-29a, miR-29b, miR-29c, miR-92a, miR-28, miR-26a, miR-20a, miR-19a, miR-19b, miR-17. They demonstrated that these miRNAs were down-regulated in HIV Nef expressing human monocytic U937 cells. They also, found that some miRNAs could prevent replication of HIV (222). Regardless of the miRNAs, there are other factors which they could have an impact on HIV progression. McNamara and colleagues investigated expression of HIV Nef proteins in HEK-293 cells, and they showed that HIV Nef protein could be involved in extracellular communication and viral pathogenesis (223). It has also been suggested that exosomal Nef could have an effect on $CD4^+$ T lymphocytes and could activate resting lymphocytes (109). Further results reported by Konadu et al. using a TUNEL assay and immune blot analysis suggested that the secretion modification region (SMR) motif of HIV Nef could play an important role in viral pathogenesis (224).

It has also been found that there are components in the exosomes of HIV infected cells, which can alter immune response and induce apoptosis. In this regard, Lenassi and et al. showed that exosomal Nef induced cell death in HIV-1 infected peripheral blood lymphocytes (PBLs) (225). Furthermore, it was found, that TAR miRNA could down-regulate apoptosis by targeting the Bim protein. These results led Narayanan et al. to investigate exosomes in PBM cells from uninfected controls, HAART-treated, and long term non-progressor patients (61). Lee et al. investigated exosomes obtained from myeloid cells isolated from HIV patients, and found that the exosomes contiained Nef and the myeloid tyrosine kinase, Hck leading to the release of pro-inflammatory cytokines which correlated with immune suppression in chronic HIV Infection (226). Analysis of the exosomal cargoes

obtained from plasma, has been reported by Konadu et al, who showed that cytokines and chemokines such as IL-1, IL-2, IL-2Ra, IL-4, IL-5, IL-7, IL-9, IL-12p70, IL-15, IL-16, TNF- α, IFN-β and CXCL10, CCL2/3/4, CD-40L, G-CSF, sFasL, and sICAM could be found accompanying the Nef in exosomes. Researchers observed that the levels of each cytokine and chemokine, measured in the exosomal fraction, were higher in the infected individuals compared to non-affected cases. It should be noted that a relationship between the majority of cytokines/chemokines and exosomes or MVs has not yet been confirmed by mass spectrometry or other protein detection techniques. Nonetheless, higher amounts of these immune mediators in the EV fraction of patients infected with HIV, emphasize the potential significance of an exosome-based delivery mechanism for HIV infection, and other pathological conditions (Table 5) (227).

Nowadays the use antiretroviral therapy has lessened many of the complications of HIV infection, but HIV-associated neurocognitive disorder (HAND) is still troubling. Investigations into HIV infected exosomes have shown a connection between the exosomal cargoes and HAND. In one study, Rahimian and colleagues showed that Tat protein derived from primary astrocytes could induce death in neurons (228). Khan et al. using neuroblastoma cell lines showed that Nef could be important in HAND pathogenesis by increased secretion of beta-amyloid (Aβ) and Aβ peptides. They also showed that Nef mRNA could induce secretion of beta-amyloid (Aβ) (229). Exosomal Nef can also affect the blood-brain barrier and its integrity, and can induce microglial cells to secrete cytokines and chemokines (230). It has been shown that exosomes derived from HIV infected cells, were able to transport different mRNAs derived from HIV. Arenaccio and colleagues found that HIV derivatives in the exosomal cargo could increase the susceptibility of unstimulated T CD4+ cells (231). It was also sugested by Aqil et al. that, AATK, SLC27A1, and CDKAL mRNAs could be important for triggering apoptosis in Nef-expressing U937 monocytic cells (232).

It seems that EVs obtained from human semen may possess a significant anti-retroviral activity. Madison et al. demonstrated the ability of EVs isolated from semen taken from healthy males to inhibit viral replication when incubated with various strains of HIV (233). Researchers argued that EV-mediated disruption of the reverse transcriptase activity caused defective viral replication. Interestingly, anti-retroviral activity has been found in semen-derived EVs, but not in the EVs isolated from blood (233). Researchers showed that EVs isolated from the healthy semen were capable of inhibiting HIV spread into vaginal cells and of disrupting viral replication in the vaginal epithelium (234). These results strengthened the significance of the examination of anti-retroviral activity of exosomes (and other vesicles extracted from semen) for contributing to the discovery of novel treatments for HIV. Moreover, studies on the isolation of EVs from breast milk provided fascinating findings concerning HIV suppression. Reports showed that EVs isolated from breast milk provided regulatory activity on the immune system (235). Näslund et al. demonstrated that EVs extracted from human breast milk from normal donors suppressed HIV infection of MDDC and viral transmission to CD4+ T cells (236). A reason for this protection against infection, may be that the EVs attach to the DC-SIGN receptor, thus competing with the virus, and inhibit infection of CD4+ T cells (236). Analyzing exosomal proteins extracted from saliva might be used for monitoring the positive or negative impacts on the progress of HIV

infection and AIDS. Dominy et al. studied heroin abusers, and provided evidence for the effect of HIV infection on the release of proteins contained in EVs from salivary glands and oral epithelium (237). They explained that EVs isolated from saliva contained cargo proteins modified by HIV infection (237). Researchers have examined EVs in the urine as effectors of innate immunity (innate immune proteins with anti-microbial activities). For instance, urinary EVs suppressed the growth of *Escherichia coli* (two pathogenic and commensal strains). This indicated a probable immune defense system of the host urinary tract (238). As far as we know, there have not yet been any reports examining the relationship between HIV infection and EVs isolated from urine. The use of urinary exosomes (and other EVs) may possibly provides a replacement for normal blood samples for monitoring spread of infection in HIV-positive individuals. Urinary EVs might also be applied for the investigation of any relationship between kidney diseases and HIV (239). Similarly, EVs derived from vaginal fluid have been suggested to be a protective agent against HIV infection (240). It is still necessary to do further work on the contribution of exosomes and EVs in various body fluids and tissues. Investigation of exosomes extracted from other biological fluids, particularly the cerebro-spinal fluid (which has a close relationship to the immuno-privileged state of the brain) might provide more information on the transport of immuno-modulatory molecules in the context of HIV-associated brain manifestations. Moreover, a greater understanding of the mechanistic basis of how exosome derived from different bio-fluids inhibit HIV-1 replication may be useful in future strategies to design HIV-1 vaccines.

The isolation and purification of nano-vesicles can constitute a methodological concern because of the variation of the phenotypic properties of exosomes. Isolation and purification may be carried out by centrifugation, which involves using filters and density gradients. Moreover, a growing variety of commercial kits now exist for facilitating the procedure. Assessment of protein markers is necessary for isolating and purifying exosomes so that the resulting material is well-characterized (241). It is possible to directly visualize exosomes using electron microscopy, where they frequently show a cup-shaped morphology, but this may be produced by the electron microscopy preparation process (242). In addition, the similar features of exosomes and retro-viral particles, adds another layer of complication to the characterization and isolation of vesicles from HIV infections. One popular approach is to use density gradient isolation to separate exosomes from viral particles, accompanied by an enzymatic assay for acetylcholinesterase (AChe), which is a marker of exosomes (203). However current thinking is to consider Ache to be a marker of ectosomes or micro-vesicles instead of exosomes, as demonstrated by numerous proteomic studies accessible on Exocarta (http://www.exocarta.org/) and Vesiclepedia (http://www.microvesicles.org/). It is clear that protocols for the separation of HIV from EVs (with similar dimensions) has no effect on separating various EV sub-populations. Thus, it is necessary for further progress in the existing separation techniques in order to further understand the contributions of exosomes (and other EVs) to the pathophysiology of HIV infection.

To summarize, the influence of exosomes on HIV is still poorly understood. In a general way, exosomes can modulate immune responses and may affect HIV pathogenesis, playing arelevant role in HIV pathophysiology. This seems to be mediated by the exosomal cargo,which comprises mainly membrane proteins and non-coding RNAs. The current state

of the field can be summarized as follows: (I) A lack of distinction between exosomes and other EVs creates much confusion in the literature. The labeling of other types of vesicles as “exosomes” makes the comparison of results from different studies very difficult. Besides, a range of experiments were performed using a mixture of exosomes with other types of EVs; (II) Over the years, mounting evidence has left little room for the hypothesis of HIVexploiting the MVB/exosome export machinery for its release (thought to occur especially ininfected macrophages), although it is clear that the virus may explore components that areshared between exosome and vesicles budding at the plasma membrane; (III) An alternative hypothesis of the exploitation of exosome/EV release by HIV is acamouflage of the viral particles by surrounding themselves with exosomes, which couldenhance the infectivity of viral particles by facilitating their contact with target cells; (IV) Nef plays an important role in increasing import/export processes in infected cellsand regulating exosomal cargo. Nef is long known to be secreted, and a body of work sustainsthat most of it is secreted in EVs. Although most of the experimental evidence implicatesectosomes as the primary source of secreted Nef, exosomes could also play a role. Nefsecreted in EVs was suggested to have a range of effects on target cells, such as induction ofapoptosis and, at a neurological level, Beta-Amyloid induction and the disruption of theblood-brain barrier; (V) HIV induces the expression of several types of RNA, such as vRNA-TAR, that are incorporated in exosomes and have been reported to have important functions in target cells, suggesting an important role in HIV infection. Conversely, host miRNAs carried by host exosomes could exert a protective effect against HIV pathogenesis. The viral protein Nef was described to influence miRNA export in exosomes/retention in Nef-expressing cells, thusinfluencing gene expression; (VI) The identification of the biomolecules transported by exosomes and the elucidation of their immune regulatory effect in HIV-positive individuals will provide new insights into the role of these immunomodulatory nanovesicles in AIDS pathogenesis; (VII) Exosomes from different cell sources play different roles in HIV pathogenesis. Whereas exosomes/EVs from infected cells may promote viral replication and thedissemination of infection, exosomes/EVs from uninfected tissues or cells could protect theimmune system against the virus, as described in CD8 cells. The direction of the actiondepends on the cargo, the type of their cell of origin, and the interaction with viral proteins;(VIII) Exosomes from semen and breast milk have a potential anti-HIV activity. Thebiomonitoring of HIV/AIDS progression could be performed through the evaluation ofexosomes derived from different biological fluids; (IX) Engineered exosomes could be used as vectors for therapeutic molecules and nanosystems.

Conclusions

In recent decades, several studies have confirmed that microRNAs are major players in the pathogenesis of various diseases such as cancer, cardiovascular diseases, and also some infectious diseases. These molecules are able to inhibit, activatie, and modulate a wide range of different cellular processes, and can affect molecular targets mediating their pleiotropic effects. It has been shown that the HIV virus can affect the regulation and modulation of miRNA networks dictating their effects on the infected cells. Deregulation of miRNAs is associated with HIV progression in infected patients. Hence, identification of the miRNA

sequences in patients infected with HIV, will facilitate ongoing research providing a better understanding of underlying cellular and molecular pathways involvied in HIV pathogenesis. Moreover, it is likely that miRNAs could be employed as diagnostic biomarkers for monitoring patients who are infected with HIV. Besides miRNAs, exosomes are another factor involved in HIV pathogenesis. Exosomes by targeting their cargos (i.e., DNAs, RNAs, miRNAs, viral proteins) to recipient cells could be involved in HIV pathogenesis. To understand the interaction between exosomes and/or EVs and their respective cargos, with HIV, and the modulation of the immune system occurring during viral infection, it is necessary to improve, standardize, and better describe techniques for isolation and characterization. A clear determination of the type(s) of vesicles contributing to Nef transfer might help researchers to find methods for specific blockage of the pathways involved in controlling viral transmission. Studies of exosome or EVs and viral infection is still an emerging area of HIV research. Nonetheless, our assumption is that researchers can overcome these problems during the coming years. so that more applications of exosomes will be used for disease management and drug discovery of HIV infection. Apparently, HIV controls cell export mechanisms in multiple ways. It is possible that there is a relationship between viral and host RNA export and exosomal pathways, whereas intact virus export and secretion of Nef are apparently a cell membrane-driven process. Nevertheless, there is insufficient information available on the pathways due to difficulties in distinguishing exosomes from ectosomes or micro-vesicles. Our belief is that a clear understanding of the relationship between HIV infection and progression, and micro-vesicles or exosomes, would make it possible to better understand HIV infection and may provide new opportunities for an effective cure.

In conclusion, identification of various miRNAs and exosomes involved in HIV pathogenesis could pave the way for the development of new and effective therapeutic approaches which offer new hope in patients infected with HIV. On the other hand, utilization of microRNAs and exosomes are subject to some limitations, such as the variation of microRNA expression patterns in different samples, and the high cost of isolation and characterization of exosomes, which are partly responsible for the fact that no microRNA and exosome applications have yet been introduced into clinical practice.

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Abbreviations

AARSD1	Alanyl-TRNA Synthetase Domain Containing 1
AATF	Apoptosis Antagonizing Transcription Factor
AATK	Apoptosis Associated Tyrosine Kinase
AIDS	acquired immune deficiency syndrome
AP-1	activating protein-1

ART	Antiretroviral Therapy
ATF2	Activating Transcription Factor 2
Cdk9	cyclin-dependent kinase 9
CXCR	C-X-C chemokine receptor
DAP3	death-associated protein 3
ECs	Elite controllers
EVs	extracellular vesicles
FOXO3	Forkhead box O3
G-CSF	Granulocyte colony-stimulating factor
HAART	highly active antiretroviral therapy
HAND	Human immunodeficiency virus-associated neurological disorders
Hck	hemopoietic cell kinase
HEK 293	Human embryonic kidney 293 cells
HIV	Human Immunodeficiency Virus
HIVCM	Human Immunodeficiency Virus cardiomyopathy
HIVE	Human Immunodeficiency Virus Encephalopathy
HMOX1	hemeoxygenase (decycling) 1
IER3	immediate early response 3
ILV	intraluminal vesicle
IRF	Interferon regulatory factor
LTNP	Long term non-progressor
LTR	Long terminal repeat
MAPK	Mitogen-activated protein kinase
MDCCs	monocyte-derived dendritic cells
MDM	monocyte-derived macrophages
MECP2	methyl CpG binding protein 2
microRNA	microRNA
NAMPT	Nicotinamidephosphoribosyltransferase
Nef	Negative Regulatory Factor

NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cell
Nup153	Nucleoporin 153
PABPC4	poly(A) binding protein cytoplasmic 4
PBL	Peripheral blood lymphocyte
PBMC	Peripheral blood mononuclear cell
PCAF	P300/CBP-associated factor
PLZF	promyelocytic leukemia zinc finger
PNUTS	phosphatase 1 nuclear-targeting subunit
PTEN	Phosphatase and tensin homolog
RNase	ribonucleases
SIRT1	Sirtuin 1
SLC27A1	Solute Carrier Family 27 Member 1
SMR	secretion modification region
Sp1	specificity protein 1
TAR	Trans-activation response element
Tat	Trans-Activator of Transcription
TLDA	TaqMan low-density array
TLR	Toll-like receptor
TNPO3	Transportin-3
TRAF6	TNF receptor associated factor 6
UTR	Untranslated region
VCs	viremic controllers
Vif	Viral infectivity factor
VPs	viremic progressors

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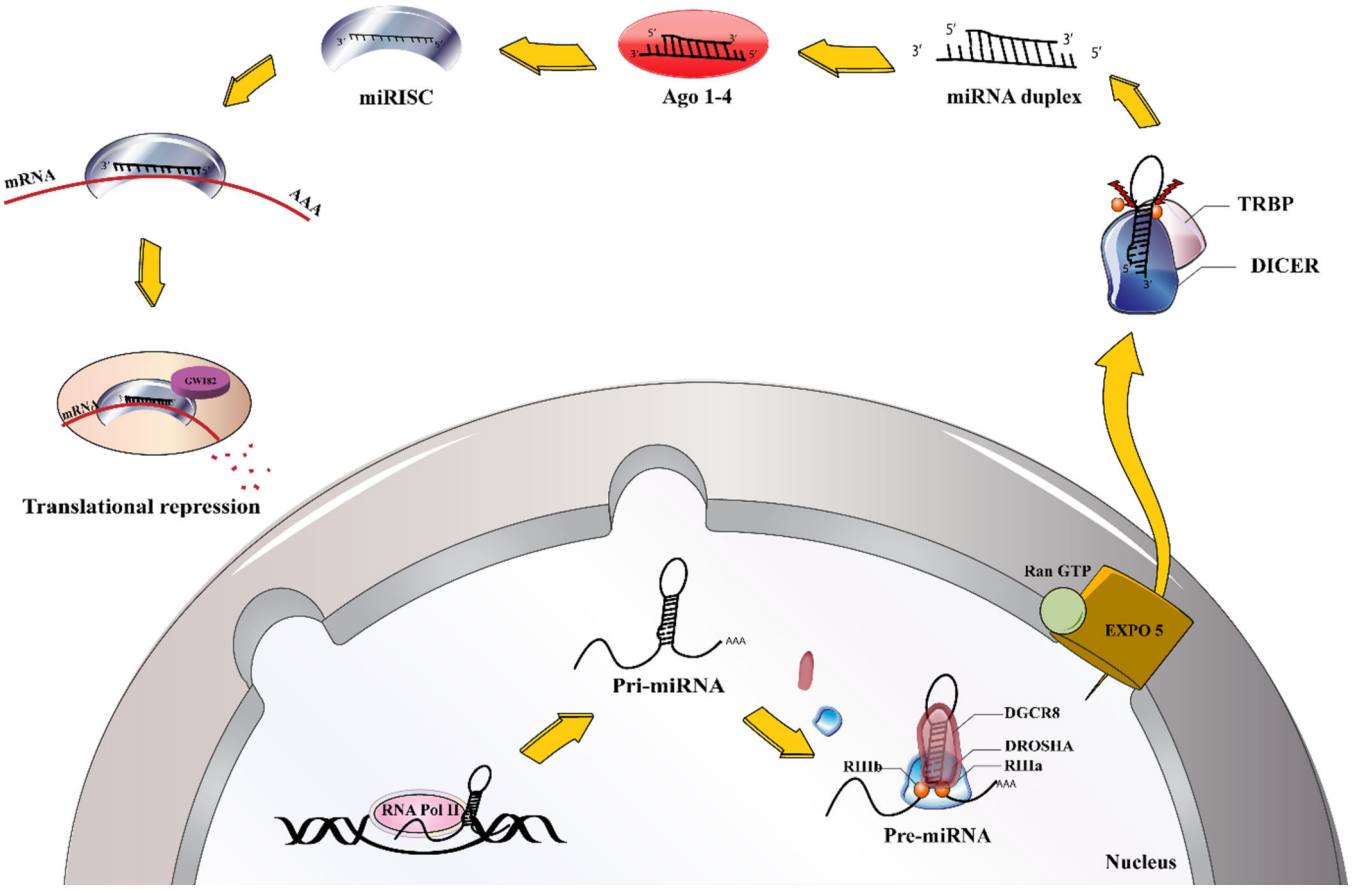

Figure 1.
microRNA biogenesis

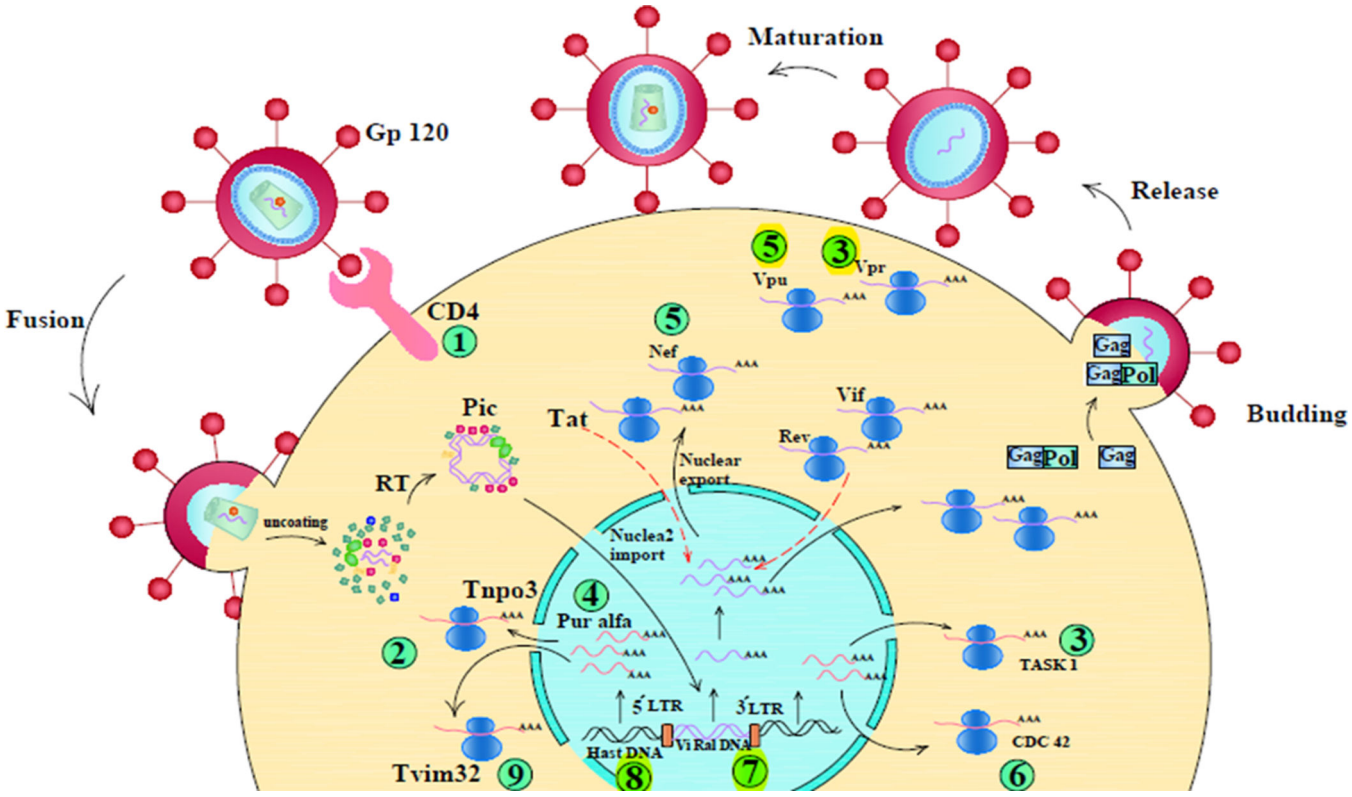

Figure 2. A schematic of microRNA networks affected by HIV virus.

(1) Up-regulation of miR-221 & 222 blocks CD4 receptor and inhibits entry of virus into the cell. (2) Up-regulation of miR-128 represses nuclear import of the virus. (3) Down regulation of miR-34a enhances release of virus and increases vpu activity. (4) Up-regulation of miR-20a decreases tat activity, inhibits binding of pur α to the LTR promoter, and represses virus replication in monocytes. (5) Up-regulation of miR-223 represses nef, vpr and blocks apoptosis in non-infected CD4 T-cells; miR-n367 decreases nef protein and virus virulence. (6) Down-regulation of miR-29 a/b increases cdc42 expression and promotes apoptosis in CD4 T-cells, (7) Up-regulation of miR-H3 interacts with the tata box in 5́ LTR, enhances promoter activity and increases RNA transcription and protein expression. (8) Up-regulation of miR-TaR3p decreases virus replication via targeting the TaR element in the 5́ LTR. (9) Up-regulation of miR-155 maintains the virus in the latent phase and reduces Nf-κβ signaling pathway

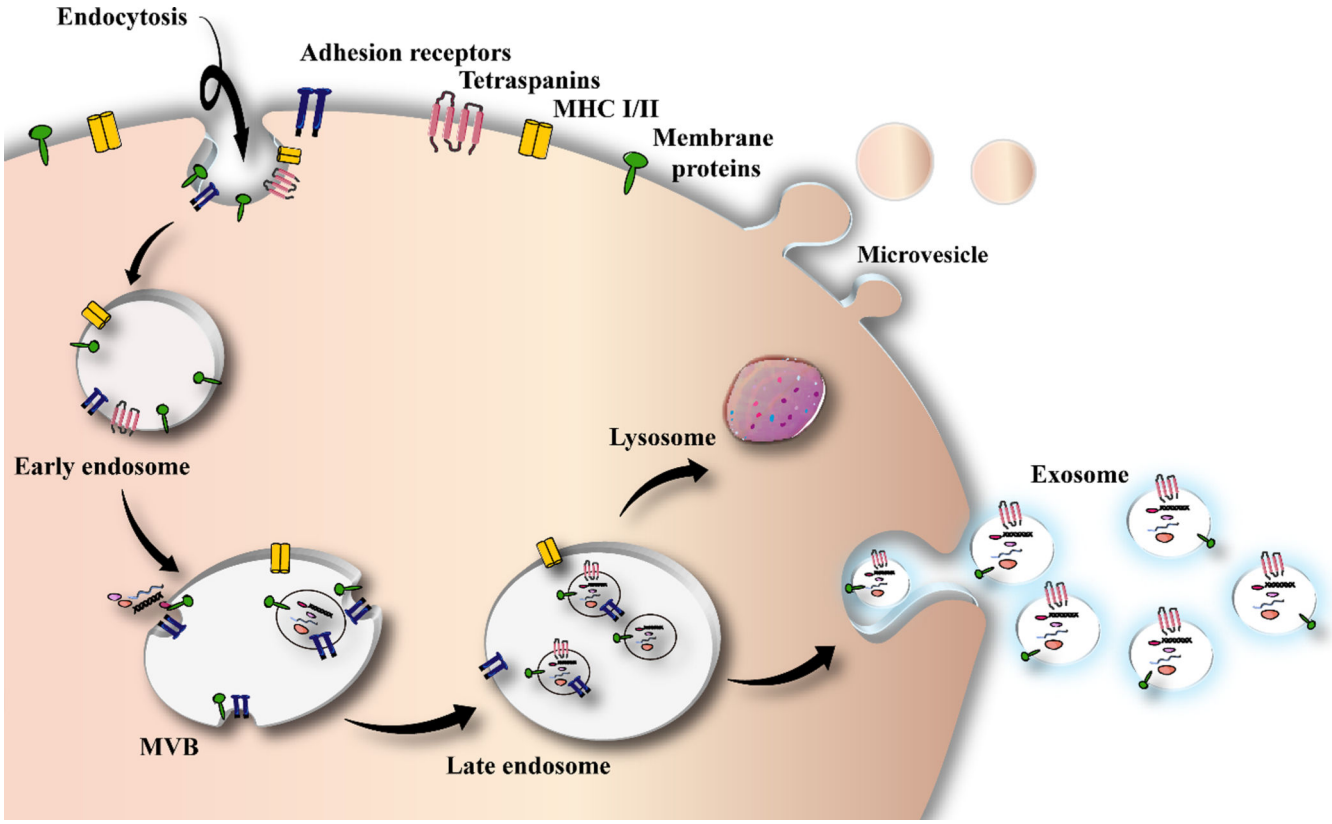

Figure 3.
Exosome biogenesis

Table 1:

Expression of Long term non-progressor (LTNP) microRNAs and Viramic progressors microRNAs

microRNA	EC/VC/VP	Expression	Method	Matrial (Plasma, PBMC, T cell)	Sample (n)	Note	Ref
miR-16	EC and untreated viremic patients	Up	TaqMan low-density arrays (TLDA), qPCR	PBMC	13 (EC+VC)		(78)
miR-22	EC and untreated viremic patients	Up	TLDA	PBMC	13 (EC+VC)		(78)
miR-155	EC and untreated viremic patients	Up	qPCR	PBMC	13 (EC+VC)		(78)
miR-34a	Untreated viremic patients	Up	qPCR	PBMC	6	Significantly correlated with CD4 counts only in elite controllers	(78)
miR-21	Untreated viremic patients	Up	qPCR	PBMC	6		(78)
miR-27a	Untreated viremic patients	Up	qPCR	PBMC	6		(78)
miR-181b	Untreated viremic patients	Up	Nanostring, qPCR	PBMC	6	Negatively correlated with CD4 counts	(78)
miR-181d	Untreated viremicpatients	Up	Nanostring	PBMC	6		(78)
miR-155	Untreated viremic patients	Up	Nanostring	PBMC	6		(78)
miR-9	Untreated viremic patients	Up	Nanostring	PBMC	6		(78)
miR-29b-3p	EC	Up	Real-time qPCR	Plasma	18 (9 EC+9 CH)	The expression level of miR-29b-3p was higher in plasma from ECs than chronic HIV progressors (CH).	(69)
miR-33a-5p	EC	Up	Real-time qPCR	Plasma	18 (9 EC+9 CH)	The expression level of miR-33a-5p was higher in plasma from ECs than CHs	(69)
miR-146a-5p	EC	Up	Real-time qPCR	Plasma	18 (9 EC+9 CH)	The expression level of miR-146a-5p was higher in plasma from ECs than CHs.	(69)
miR-221	EC	Up	TLDA	PBMC	8	Upregulated in Ec and uninfected individuals while downregulated in VCs and patients under ART	(77)
miR-27b	EC	Up	TLDA	PBMC	8	Upregulated in Ec and uninfected individuals while downregulated in VCs and patients under ART	(77)
miR-29b	EC	Up	TLDA	PBMC	8	Upregulated in Ec and uninfected individuals while downregulated in VCs and patients under ART	(77)

microRNA	EC/VC/VP	Expression	Method	Matrial (Plasma, PBMC, T cell)	Sample (n)	Note	Ref
miR106a	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
mir-155	EC and VC	Up	Microarray	$CD8^+$T- cells	30 (EC+VC)	Upregulated mir-155 expression when resting CD8+ T-cells were stimulated	(66)
miR-140	VP	Up	TLDA	$CD8^+$ T-cells	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-146a	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-4484	EC, VC and VP	Up	Microarray	$CD8^+$T- cells	43 (EC+VC +VP)	Upregulated mir-4484 expression when resting CD8+ T-cells were stimulated	(66)
miR-125a	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-484	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-590	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-17	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-146b	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-155	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-16	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-186	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-27a	EC	Up	TLDA	PBMC	8	Upregulated in Ec and uninfected individuals while downregulated in Vcs and patients under ART	(77)
miR-191	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-197	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-339	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-374	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)

microRNA	EC/VC/VP	Expression	Method	Matrial (Plasma, PBMC, T cell)	Sample (n)	Note	Ref
miR-200b	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-200c	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-422	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-454	VP	Up	TLDA	PBMC	8	Upregulated in VCs and patients under ART while Downregulated in ECs and uninfected individuals	(77)
miR-125b	Untreated viremic patients	Down	TLDA	PBMC	6		(78)
Let-7g	Untreated viremic patients	Down	Nanostring, TLDA	PBMC	6		(78)
miR-146b-5p	Untreated viremic patients	Down	Nanostring, TLDA	PBMC	6		(78)
miR-150	Untreated viremic patients	Down	Nanostring	PBMC	6	Considerably positively correlated with CD4 counts	(78)
miR-150	EC and untreated viremic patients	Down	qPCR	PBMC	13 (EC+VC)	Considerably positively correlated with CD4 counts	(78)
miR-29a	Untreated viremic patients	Down	Nanostring, TLDA, qPCR	PBMC	6	Considerably positively correlated with CD4 counts	(78)
miR-29b	Untreated viremic patients	Down	Nanostring	PBMC	6		(78)
miR-29c	Untreated viremic patients	Down	Nanostring	PBMC	6		(78)
miR-221	VP	Down	TLDA	PBMC	8	Downregulated in VCs and patients under ART while upregulated in ECs and uninfected individuals	(77)
miR-27a	VP	Down	TLDA	PBMC	8	Downregulated in VCs and patients under ART while upregulated in ECs and uninfected individuals	(77)
miR-27b	VP	Down	TLDA	PBMC	8	Downregulated in VCs and patients under ART while upregulated in ECs and uninfected individuals	(77)
miR-29b	VP	Down	TLDA	PBMC	8	Downregulated in VCs and patients under ART while upregulated in ECs and uninfected individuals	(77)
miR106a	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-125a	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)

microRNA	EC/VC/VP	Expression	Method	Matrial (Plasma, PBMC, T cell)	Sample (n)	Note	Ref
miR-140	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-146a	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-146b	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-155	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-16	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-17	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-186	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-191	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-197	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-200b	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-200c	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-339	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-374	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-422	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-454	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-484	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-590	EC	Down	TLDA	PBMC	8	Downregulated in ECs and uninfected individuals while Upregulated in VCs and patients under ART	(77)
miR-4734	VP	Down	Microarray	$CD8^+$ T-cells	13	Downregulated miR-4734 in VPs Compared with uninfected individuals	(66)
miR-4505	EC	Down	Microarray	$CD8^+$ T-cells	15	Downregulated miR-4505 in ECs Compared with uninfected individuals	(66)

microRNA	EC/VC/VP	Expression	Method	Matrial (Plasma, PBMC, T cell)	Sample (n)	Note	Ref
miR-4505	VC	Down	Microarray	$CD8^+$ T-cells	15	Downregulated miR-4505 in VCs Compared with uninfected individuals	(66)
mir-4508	EC	Down	Microarray	$CD8^+$ T-cells	15	Downregulated miR-4508 in ECs Compared with VP	(66)
miR-3620	EC	Down	Microarray	$CD8^+$ T-cells	15	Downregulated miR-3620 in ECs Compared with VP	(66)
miR-4492	EC	Down	Microarray	$CD8^+$ T-cells	15	Downregulated miR-4492 in ECs Compared with VP	(66)
miR-4507	EC	Down	Microarray	$CD8^+$ T-cells	15	Downregulated miR-4507 in ECs Compared with VP	(66)
miR-181a	VP	Down	Microarray	$CD8^+$ T-cells	13	Downregulatedmir-181a expression when resting CD8+ T-cells were stimulated	(66)
let-7b-5p	VP	Down	Microarray	$CD8^+$ T-cells	13	Downregulated let-7b-5p expression when resting CD8+ T-cells were stimulated	(66)
miR-150	VC	Down	Microarray	$CD8^+$ T-cells	15	Downregulated mir-150 expression when resting CD8+ T-cells were stimulated	(66)
miR-1202	VC	Down	Microarray	$CD8^+$ T-cells	15	Downregulated mir-1202 expression when resting CD8+ T-cells were stimulated	(66)

Table 2:

HIV-encoded miRNAs

vmiRNA	Target	Function	Ref
miR-N367	*Nef*	Block HIVNef expression in vitro (long term non-progressors) miR-N367 corresponding to suppression of Nef expression in vivo (Inhibition of Nef expression by siRNA/miR-N367 in mice)	(92)
miR-N367	PABPC4 (iPABP)	MiR-N367 might repress the activation of lymphokine mRNA expression through targeting PABPC4 to help maintain viral latency.	(93)
HIV-1-miR-H1	AATF	Induced AATF gene knockdown within human mononuclear cells initiates their apoptosis.	(96)
miR-H3	*HIV 5′ LTR*	Interacts with the TATA box in HIV 5′ LTR miR-H3 upregulates HIV RNA transcription and protein expression.	(94)
vmiR99		Stimulated human macrophage TNFα release	(109)
vmiR88		Stimulated human macrophage TNFα release	(109)
vmiR-TAR	IER3, *ERCC1,* Caspase 8, Ikaros, Aiolos	Protects infected cells from apoptosis	(91, 109)
vmiRNA#1–5	-	Proteins involved in, for example, signal transduction, protein synthesis, and degradation, DNA methylation	(87)
miR-TAR-3p	TAR (HIV)	Inhibitory effect on viral replication	(101)

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Table 3:

Expression of microRNAs in different phases of HIV infection

miRNA	Expression	Type of cell	HIV-associated phase/disease	Model	Method	Note	Ref
miR-28, 125b, 150, 223, 382	Up	Resting primary CD4+ T cell	Latency	Human, in vitro	Microarray stem-loop RT-PCR	Targets the 3′ ends of HIV messenger RNAs	(125)
miR-17-5p, 20a	Up	CD8+ T cell	Latency	Human, in vitro	Northern blot	Suppression of HIV replication by reducing PCAF (Tat co factor) expression	(74)
miR-132	Up	Active CD4+ T cell	Latency	Human, in vitro	Real-time RT-PCR	Promotes HIV Replication	(127)
miR-H3	Up	Resting CD4+ T cell	Latency	In vitro	Deep sequencing	Enhances viral production and Replication activates HIV latency	(94)
miR-196b, 1290	Up	-	Latency	In vitro, Human	Microarray Real-time RT-PCR	Keep the virus in the latent phase	(128)
miR-155	Up	-	Latency	In vitro	Real-time RT-PCR	Keep the virus in the latent phase and decrease of NF-KB Signaling pathway	(138)
miR-29a	Up	-	Latency	Human, in vitro	Real time PCR	Repress active HIV replication in Latent phase	(126)
miR-128	Up	CD4+ T cells blood-derived monocytes	Maybe in Latency	In vitro	-	Type I interferon induce expression of mir-128 and inhibition of viral nuclear entry and viral replication	(30)
miR-34a	Up	-	AIDS	In vitro	Real time PCR	Up regulation n of miR-34a enhanced Tat-induced LTR transactivation through repressing SIRT1 and increasing the transcriptional activity of NF-kB	(117)
miR-181b	Up	Monocyte-derived dendritic cells (MDDCs)	AIDS	in vitro	Real time PCR	Gp 120 increase level of miR-181b and induce of IL-6 expression, As a result, chronic inflammation occurs	(139)
miR-124a	Up	CD4+ T cells	AIDS	HUman	Real-time RT-PCR	Decrees level of SIRT1 protein and activating Th2 type CD4+ T cells leads to secretion of IL-10 and TGF-β cytokines	(119)
miR-29a, 223, 27a, 19b, 151-3p, 28-5p, 766, 30a-3p,	Up	CD4+ T cells	HIV/AIDS	Human	Real-time RT-PCR TaqMan Low-Density Array		(120)
mir-146a	Up	Microglial cells	Neuro AIDS	Human	Real-time RT-PCR	Keeping HIV-mediated chronic inflammation of the brain, induce the latency of the virus in microglial cells	(140)
miR-101	Up	human brain microvascular endothelial cells	HIV-associated neurological disorders	In vitro	Real-time RT-PCR	TAT C protein induces expression of miR-101 and block VE-Cadherin, Destruction of endothelial permeability	(130)

miRNA	Expression	Type of cell	HIV-associated phase/disease	Model	Method	Note	Ref
miR-34c-3p, 93-3p, 381-3p, 500a-5p	Up	Primary macrophages	HIV-associated neurocognitive disorders	Human, in vitro	Microarray	Decline levels of peroxisomal proteins and defense against anti-viral	(131)
mir-128a	Up	Primary cortical neurons	HIV Encephalopathy (HIVE)	Human, in vitro	Microarray Real-time RT-PCR	TAT induced expression of mir-128a and disrupt neuronal activity	(141)
miR-198	Up	Monocytes (macrophage)	-	In vitro	Microarray	Decreased cyclin T1 protein and repress of HIV replication and gene expression in monocytic	(142)
miR-217	Up	Galactosidase indicator (MAGI) cells	-	In vitro	Real time PCR	miR-217 promotes Tat-induced HIV LTR transactivation by inhibit of SIRT1 expression and decrease AMPK signaling pathway, promote NF-κB activation	(143)
miR-155	-	Macrophages	-	In vitro	Microarray	TLR3 and TLR4 stimulation in Macrophage, promote expression of miRNA and inhibit Inhibition of the post-entry, pre-integration steps	(144)
miR-32	Up	Microglia cell	-	In vitro	Real time PCR	The Tat C protein induces miRNA and down regulate the expression level of TRAF3, over expression IRF3 and IRF7	(145)
miR-29a	Up	T lymphocytes	-	In vitro	Real Time RT-PCR	Represses HIV Replication	(29)
miR-223	Up	CD4+CD8-	-	In vitro	microarray Real time PCR	Inhibit of Vif. Vpr and Nef proteins	(146)
miR-9	Up	Macrophages	-	Human, in vitro	Real time PCR	Methamphetamine and HIV promote expression of miR-9. Induce neurotransmitter release in dopaminergic neuron	(147)
miR-34a	Up	vascular endothelial cells	-	Human, in vitro, in vivo	Real time PCR	TAT protein, p53, lopinavir/ritonavir induce miR-34a expression and increased EC senescence	(148)
miR-TAR-3p	Up	monocyte-derived macrophages(MDMs)	-	In vitro	Real time PCR	MiR-TAR-3p Decrease virus replication via targeting the TAR element in the 5´ LTR and reduce genome transcription	(149)
miR-1236	Up	Monocytes	-	In vitro	Real-time RT-PCR	Repress HIV Infection in Monocytes	(150)
miR-222	Up	CD4 T cell	-	In vitro	Real-time RT-PCR	Up regulation mir-222 by HIV tat and NFKB, decreasing rate of CD4	(151)
miR-150, 28-5p, 125b	Up	CD4+ T cell	-	Human, in vitro	Real-time RT-PCR	Methamphetamine reduces HIV Replication via up regulation of mir-125b, miR-150 and miR-28-5p	(152)
miR-34a	Up	T-cells	-	In vitro	Real time PCR	Promotes HIV replication in t cell	(153)
miR-29 family	Up	CD4+ T lymphocytes CD14+ monocytes	-	Human	Real time PCR	-	(154)
miR-29	-	primary lymphoid CD4 T cells	-	Human, in vitro, in vivo	Real time PCR	IL-21 increase level of mir-29 and inhibit HIV replication	(155)

miRNA	Expression	Type of cell	HIV-associated phase/disease	Model	Method	Note	Ref
miR-221, 222	Up	monocyte-derived macrophages (MDMs)	-	In vitro	RNA-seq	TNFα induce expression of mir-222/221 and restrict HIV entry in Macrophages	(156)
hsa-miR-21, 222	Up	CD4+ T cells	-	In vitro	Microarray	Inhibition of apoptosis through reduction of PTEN-AKT-FOXO3a signaling pathway, enhance hiv1 replication and promote energy and depletion of CD4+ T Cell, Increasing the expression of miRNA by tat protein	(28)
hsa-miR-29a	Up	-	-	In vitro	Real time PCR	Block Nef expression and decrease of virus levels	(157)
miR-326	Up	-	-	In vitro	Real time PCR	Inhibit of 3´ LTR genome and decreased HIV replication	(158)
miR-182	Up	-	-	In vitro	Real time PCR	Increase in Tat-induced HIV LTR transactivation and promoting the transcriptional activity of NF-kB	(159)
miR-19b, 146a, 615-3p, 382, 34a, 144, 155	Up	-	-	Human, in vitro	Real-time RT-PCR	Useful biomarker for the determination of prognosis	(160)
let-7c	Up	-	-	In vitro	Real time PCR	Increase viral replication and spread, promote virion release and higher copy number of viral genome transcripts in infected cells	(161)
miR-34a, 124a	Up	-	-	In vitro	Real time PCR	Increase viral replication and spread, promote virion release and higher copy number of viral genome transcripts in infected cells	(161)
miR-15a/b, 16, 20a, 93, 106b	Up	Monocytes monocyte-derived DCs (MDDCs)	-	In vitro	Microarray Real-time RT-PCR	Decrease of tat and Pur-α proteins, Represses HIV replication in monocytes	(162)
hsa-miR541-3p, 518f-3p, 195-3p	Up	-	-	Human, in vitro	Real-time RT-PCR	Represses HIV replication and induce antiviral responses	(163)
miR-9	Down	CD4+ cells	Latency	Human, in vitro	Real-time RT-PCR	Inhibit of IL2 transcription and development of T cell exhaustion during chronic HIV infection	(164) (165)
miR-31, 29b, 590-5p	Down	CD4+ T cell	Latency	Human	Real time PCR	Useful for prognostic and diagnostic, strategy to choose patients who would benefit from earlier ART	(166)
hmiR-che-1	Down	CD4+ T cell	Latency AIDS	Human, in vitro	Real time PCR	Increase Vpr protein and over expression of hiv1-mir-H1	(167)
miR-125b	Down	Primary CD4+ T cells	AIDS	Human, in vitro	Microarray Real Time RT-PCR	Cocaine promotes HIV replication and increase of virus entry	(121)
miR-146b-5p	Up Down	-	AIDS	Human	Real-time RT-PCR		(116)
miR-150	Up	-	AIDS	Human	Real-time RT-PCR		(116)

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miRNA	Expression	Type of cell	HIV-associated phase/disease	Model	Method	Note	Ref
miR-21, 155	Down	Monocyte-derived dendritic cells (MDDCs)	Suggest in AIDS	In vitro	Real time PCR	Gp 120 decreases level of miR-21/155 and induces IL-6 expression, as a result, chronic inflammation occurs	(139)
miR-221, 222	Down	Monocytes	HIV-Associated Cardiomyopathy	In vitro, in vivo	Real-time RT-PCR	TAT promotes Expression of ICAM-1 and increase NF-kB, MAPK signaling pathways	(133)
miR-200, 33	Down	Podocytes	HIV-associated nephropathy (HIVAN)	In vitro, in vivo	microarray Real time PCR	Contributes to the progress of the proliferative phenotype of HIVAN	(134)
miR-196a	Down	Neuronal	HIV associated neurocognitive disorders (HAND)	In vitro, in vivo	Real time PCR	TAT induce of p73, p53 and inhibit miR-196a Increase apoptosis in neuronal cells	(132)
miR-3162-3p	Down	-	Acute	Human, in vitro	microarray Real time PCR	Potential biomarker to identify HIV new infections in HIV infected persons	(114)
miR-29a/b	Down	CD4+CD8-	-	In vitro	microarray Real time PCR	Increase Nef and cdc42 promotes apoptosis in cd4 cells	(146)
miR-155, 21	Down	CD4+CD8-	-	In vitro	microarray Real time PCR	-	(146)
miR-155, 20a	Down	Monocyte-derived dendritic cells (MDCCs)	-	In vitro	Real-time RT-PCR	Cocaine reduces CD83 and enhances DC-SIGN, LTR and pu.1 levels in monocyte-derived dendritic cells (MDCCs), elevates HIV Infectivity	(168)
miR-106b	Down	CD4+ T cell	-	In vitro	Real time PCR	Increase of p21 expression, Useful to provide a new therapeutic approach	(169)
miR-20a	Down	CD4+ T cell	-	In vitro	Real time PCR	Increase of p21 expression, Useful to provide a new therapeutic approach	(169)
miR-34c-5p	Down	Naïve CD4 T cells	-	Human, in vitro	miR RT-qPCR assays	Promotes HIV replication	(170)
miR-21	Down	Monocytes	-	Human, in vitro	Real time PCR	Increased levels of NFKB and IFN-stimulated gene 15 lead to promoting inflammation	(171)
miR-181a	Down	Astrocytes compared to microglia	-	In vitro	Real-time RT-PCR	Suppression of HIV replication	(172)
hsa-miR1225-5p, 18a, 335	Down	-	-	Human, in vitro	Real-time RT-PCR	-	(163)
miR-29a-5p	Down	-	-	Human	Real time PCR	-	(173)
miR-27b	Up	Resting CD4+ T cell	-	In vitro In vivo	Microarray	In resting CD4+ T cells this miRNA directly binds the 3′-UTR of cyclin T1 and inhibits expression, repressing HIV replication	(174)
miR-29b, 150, 223	Up	Resting CD4+ T cell	-	In vitro In vivo	Microarray	In resting CD4+ T cells this miRNA directly binds the 3′-UTR of cyclin T1 and inhibits expression, repressing HIV replication	(174)

miRNA	Expression	Type of cell	HIV-associated phase/disease	Model	Method	Note	Ref
miR-28, 150, 223,	Up	Monocytes/macrophages	-	In vitro	Real-time RT-PCR	Represses HIV replication in macrophages and enhances replication in monocytes	(175)
miR-382	Up	Monocytes/macrophages	-	In vitro	Real-time RT-PCR	Represses HIV replication in macrophages and enhances replication in monocytes	(175)
miR-146a	Down	Resting primary CD4+ T lymphocytes	-	In vitro	Real time PCR	In resting primary CD4 T lymphocytes prevents HIV entry into T lymphocytes and myeloid cells In active CD4+ T lymphocytes enhances HIV entry	(176)
miR-N367	-	T cell	Latency	In vitro, in vivo	Northern blot	Blocks Nef expression, decreases HIV virulence	(92)
miR-TAR-5p, TAR-3p	-	-	Latency	In vitro	Sequencing	Reducing apoptosis and promotes virus replication	(91)
miR-H1	-	CD4+ T cell	Latency AIDS	Human, in vitro	Real time PCR	Promote CD4+ lymphopenia by decreasing AATF gene	(167)
vmiR88, 99	-	Macrophage	AIDS	In vitro	Real-time RT-PCR	Stimulated human macrophage TNFα release	(109)
miR-N367	-	T cell	-	In vitro	Northern blot	Decreases HIV transcription via the NRE of the 5′-LTR U3 region and Nef sequences at the 3′-UTR	(177)
miR-TAR-5p, TAR-3p	-	-	-	In vitro, in vivo	Northern blot	Effective on virus replication and Increased efficiency of host antiviral defense	(178)
hiv1-mir-H1	-	-	-	In vitro	-	Suppression of mir149 expression and blocks AATF, Bcl-2, c-myc, Par-4 and Dicer genes, up-regulates Vpr protein, and increases apoptosis	(96)
hsa-miR-148	-	-	-	Human	Real time PCR		(179)

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Table 4:

MicroRNA as therapeutic targets in HIV

microRNA	Expression	Target	Model	Method	Function (s)				Ref
					Reversal of latency	Apoptosis inhibition	Prevention of HIV entry	Other	
miR-132	Up	MeCP2	Human					miR-132 enhances HIV replication	(127)
mir-146a	Up	CCL8/MCP-2	In vitro	Real-time PCR				the maintenance of HIV-mediated chronic inflammation of the brain	(140)
miR-34a	Up	PNUTS/PPP1R10	In vitro	Real-time PCR				enhances HIV replication	(153)
hsa-miR-21, 222	Up	PTEN	In vitro	Microarray		*			(28)
miR-29a	Up	HIV 3 UTR region	In vitro					Represses HIV Replication	(29)
miR-222, 221	Up	CD4 mRNA	In vitro	RNA-seq			*		(156)
miR-217	Up	SIRT1	In vitro					miR-217 promotes Tat-induced HIV LTR transactivation	(115)
let-7c	Up	p21	In vitro	Real-time PCR				Enhance viral replication and spread	(161)
miR-34a	Up	TASK1	In vitro	Real-time PCR				Enhance viral replication and spread	(161)
miR-34a	Up	SIRT1 3′-UTR	In vitro	Real-time PCR				Promotes Tat-induced HIV transactivation	(117)
miR-217	Up		In vitro	Real-time PCR				miR-217 influenced promotes Tat-induced HIV transactivation via decreases of SIRT1 expression	(143)
miR-124a	Up	TASK1	In vitro	Real-time PCR				Enhance viral replication and spread	(161)
miR-29 family	Up		63	Real-time PCR				Influence the clinical progression of HIV infection, the HIVproviral load and the innate immune response against HIV	(154)
miR-34a	Up	Sirt1	In vivo, In vitro	Real-time PCR					(193)
let-7, miR-124a, 34a	Up	p21 protein	In vitro	Real-time PCR				Enhances viral production and Replication	(161)
miR-146a	Down	CXCR4 TRAF-6	In vitro				*		(176)
miR-34c-5p	Down		Human	miR RT-qPCR assays				Promotes HIV replication	(170)
miR-21	Down	IP-10	Human, In vitro	Real-time PCR				miR-21 has the ability to inhibiting the expression of IP-10 via monocytes, that is a significant source of inflammation in HIV positive patients.	(171)

microRNA	Expression	Target	Model	Method	Function (s)				Ref
					Reversal of latency	Apoptosis inhibition	Prevention of HIV entry	Other	
miR-20a	Down	p21	In vitro	Real-time PCR				HIV can exploit host cellular machinery through miR-20a to regulate the selective gene in target cells.	(169)
miR-106b	Down	p21	In vitro	Real-time PCR				HIV can exploit host cellular machinery through miR-106b to regulate the selective gene in target cells.	(169)
miR-27b	Down	3′-UTR of cyclin T1	In vitro	Microarray				Regulation of HIV Replication in Resting $CD4^{+}$T Lymphocytes	(174)
miR-196b, 1290		3′ untranslated region of HIV	In vitro	*				Contribute to HIV latency suppressing effects on HIV infectivity	(128)
miR-1236		VprBP	In vitro					Inhibits HIV Infection of Monocytes	(194)
hsa-miR29a		Nef (HIV protein)	In vitro					Downregulates the expression of Nef protein and interferes with HIV replication	(157)
miR-128		TNPO3 mRNA	In vitro				*	Inhibition of viral replication	(30)
miR-182		NAMPT Mrna	In vitro	Real-time PCR				Increase in Tat-induced HIV LTR transactivation	(159)
miR-155		3′-UTR of TRIM32	In vitro	Real-time PCR	*				(138)
miR-198		Cyclin T1 mRNA	In vitro	Real-time PCR				Restrict HIV replication in monocytes	(142)
miR-155		LEDGF ADAM10 TNPO3 Nup153	In vitro	Real-time PCR				Inhibits PIC nuclear import	(144)

Table 5:

Exosomal cargoes released from HIV-infected cells

Type of cargo		Expression	Exosome Source	Sample (n)	Ref
MicroRNA	miR-155	Up regulation	Plasma	43	(243)
	miR-223	Up regulation	Plasma	43	(243)
	miR-548a	Upregulation	HIV-infected macrophage		(221)
	miR-30e	Upregulation	HIV-infected macrophage		(221)
	miR-338	Upregulation	HIV-infected macrophage		(221)
	miR-454	Upregulation	HIV-infected macrophage		(221)
	miR-518f	Upregulation	HIV-infected macrophage		(221)
	miR-1243	Upregulation	HIV-infected macrophage		(221)
	miR-1247a	Up regulation	HIV-infected macrophage		(221)
	miR-150	Up regulation	HIV-infected macrophage		(221)
	miR-29a	Up regulation	HIV-infected macrophage		(221)
	miR-302c	Up regulation	HIV-infected macrophage		(221)
	miR-636	Up regulation	HIV-infected macrophage		(221)
	miR-872	Up regulation	HIV-infected macrophage		(221)
	miR-875	Up regulation	HIV-infected macrophage		(221)
	vmiR-88	Up regulation	Serum	14	(109)
	vmiR-99	Up regulation	Serum	14	(109)
	miR-29b	Up regulation	-	16	(244)
	TAR miRNA	Up regulation	PBMC	6	(61)
	miR-130a	Up regulation	IV-infected and cocaine-treated human monocyte derived macrophages		(245)
	miR-17	Up regulation	Human monocytic U937 cells		(222)
	miR-382	Down regulation	Human monocytic U937 cells		(222)
Protein	Tat	Up regulation	Engineered human cellular exosomes to express HIV Tat	14	(246)
	Nef	Up regulation	Expresstion of HIVs Nef proteins in HEK-293		(223)
	Hck (hemopoietic cell kinase), ADAM17	Up regulation	Plasma, Myeloid cells	8	(226)
	Nef and ADAM17	Up regulation	Plasma	8	

Type of cargo		Expression	Exosome Source	Sample (n)	Ref
	Nef	Up regulation	Induce pro-inflammatory vesicles		(226)
	DAP-3	Up regulation	Dendritic cells		(247)
	Nef	Up regulation	A3.01 T cell line		(224)
	Nef-ADAM17-TNFα	Up regulation	U937 cells		(248)
	Nef	Up regulation	Astrocyte cultures		(249)
	Fibronectin and Galectin-3	Up regulation	HIV infected DC	-	(250)
	Nef	Up regulation	HEK 293 cells		(251)
	Nef	Up regulation	Plasma, neuroblastoma cell line SH-SY5Y	12	(229)
	Nef domain (the^{62}EEEE^{65}acidic)	Up regulation			(252)
	Nef	Up regulation			(253)
	Nef	Up regulation	PBLs		(225)
	Gag	Up regulation	Jurkat T cells		(254)
	Nef	Up regulation	Microglial cells		(230)
	Tat	Up regulation	Tat-expressing primary astrocytes		(228)
Cytokin/ chemokine	Nef and IL-1, IL-2, IL-2Ra, IL-4, IL-5, IL-7, IL-9, IL-12p70, IL-15, IL-16, TNF-α2/α, IFN-β, CXCL10, CCL2/3/4,CD-40L, G-CSF, sFasL, sICAM,	Up regulation	Plasma	25	(227)
RNA	Trans-activation response (TAR) RNA and TAR-*gag*	Up regulation	Jurkat E4 cells (HIV-infected T cells) and othere cell lines	In vitro, human PBMC	(255)
	Nef messenger RNA	Up regulation	SH-SY5Y cells, HEK293		(229)
	AATK, SLC27A1, and CDKAL	Up regulation	Nef-expressing U937 monocytic cells		(232)
	MECP2, HMOX1, AARSD1,ATF2	Up regulation	Nef-expressing U937monocytic cells		(232)
	nef messenger RNA	Up regulation	Neuroblastoma cell line SH-SY5Y		(229)
	TAR RNA	Up regulation			(256)
Defective HIV	defective HIV (F12/Hut-78 cells) andNef_{F12}	E Up regulation	Hut-78, D10/Hut-78, F12/Hut-78, and Rev-CEM and HEK293 wich infected by virus		(231)