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MicroRNA: implications in HIV, a brief overview

Sudheesh Pilakka-Kanthikeel, Zainulabedin M. Saiyed, Jessica Napuri, and Madhavan P. N. Nair

Department of Immunology, Institute of Neuroimmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, HLS-1, 418A 11200 SW 8th Street, Miami, FL 33199, USA

Madhavan P. N. Nair: nairm@fiu.edu

Abstract

MicroRNAs (miRNAs) are 20–22 nucleotide length noncoding RNA molecules that represent key regulators of many normal cellular functions. miRNAs undergo two processing steps which transform a long primary transcript into the mature miRNA. Available literatures demonstrate the association between alterations in the expression of miRNAs and the progression of numerous human disorders. Even though significant advances have been made, many fundamental questions about their expression and function still remain unanswered. Identifying factors that block the negative action of drugs of abuse on the miRNAs could help in identifying new therapeutic strategies. In this review, we briefly discuss the importance of miRNAs on HIV, strategies used by virus to avoid the cells' antiviral miRNA defenses, and how HIV might control and regulate host cell genes by encoding viral miRNAs.

Keywords

miRNA; HIV-1; HAND; Drugs of abuse

Introduction

As the name suggests, microRNAs (miRNA) are tiny regulatory RNA molecules ~20–22 nucleotides (nt) in length. miRNAs are encoded by the genome but are not translated into protein. MicroRNAs are produced from a single arm of imperfect, 80-nt-long RNA hairpins located within polymerase II-derived transcripts referred to as a primary transcript (pri-miRNA) which is then trimmed in the nucleus by the microprocessor complex containing RNase Drosha and DGCR8. The resulting product is ~70-nucleotide-long stem-loop precursor miRNA (pre-miRNA). Pre-miRNA is exported out of the nucleus to the cytoplasm via the exportin-5. In the cytoplasm, pre-miRNA is processed by type III RNase Dicer to miRNA/miRNA* duplex of 19 to 25 nucleotides. miRNA/miRNA* is incorporated into the RNA-induced silencing complex (RISC) where miRNA* is degraded, while miRNA serves

as a “guide strand” for messenger RNA (mRNA) targeting. RISC is a multiprotein complex consisting of argonautes, RNA processing/degrading enzymes, Dicer, HIV-1 TRBP, a cofactor, and several other proteins that is required for miRNA-mediated silencing (Bartel 2004; Kim et al. 2009; Lee et al. 2004).

miRNAs control the gene expression by contributing significantly to posttranscriptional regulation by binding to the 3′ untranslated region (UTR) of mRNAs, thereby repressing the translation or inducing mRNA degradation. The seed sequence, 5′ nucleotides 2–7 of the mature miRNA, must be complementary to the viral target for silencing or inhibiting virus replication (Bartel 2004).

miRNAs in disease

There are evidences from recent reports that miRNAs are critical key regulators for normal cellular functions like proliferation, differentiation, development, apoptosis, signal transduction, and establishment of cell lineage (Eisenberg et al. 2007; Kloosterman and Plasterk 2006; Lu et al. 2005; Wang et al. 2009). Expression of several miRNAs has been shown to be elevated or repressed in activated T cells in vitro (Cobb et al. 2006). Appealing evidences have accumulated to suggest the role of aberrant miRNA expression in various human diseases, such as cancer (Calin and Croce 2006; Croce and Calin 2005; Huang et al. 2007), autoimmune disease (Dai et al. 2007; Stanczyk et al. 2008; Zhao et al. 2010), neurodegenerative disease (Kim et al. 2007; Wang et al. 2008), inflammatory diseases (Sonkoly et al. 2007), muscular (Eisenberg et al. 2007) and cardiovascular disorders (Care et al. 2007; Ikeda et al. 2007), and developmental abnormalities and psychiatric disorders, such as schizophrenia (54). miRNAs can influence host–virus interaction in a variety of ways such as direct modulation of viral replication, by affecting viral susceptibility, and also by indirect modulation of cellular genes that influence viral propagation (Kumar and Jeang 2008; Scaria et al. 2007; Yeung et al. 2007).

Cellular miRNA in AIDS

The first evidence for the antiviral activity of cellular miRNAs came from a study, where researchers showed knockdown of miR-32 expression or deletion of the miRNA target sequence from the viral genome significantly enhanced primate foamy virus type 1 (PFV-1) replication suggesting that miR-32 inhibited infection by PFV-1 (Lecellier et al. 2005). Significant advances have been made in the field of miRNA since then. Recent findings of cellular change in miRNA expression during human immune deficiency virus (HIV) infection (Triboulet et al. 2007; Yeung et al. 2005a), contributing to HIV-1 latency in primary CD4⁺ T lymphocytes (Huang et al. 2007) and distinct patterns of miRNA in HIV-1 provirus plasmid-transfected HeLa cells (Sung and Rice 2009), provide supporting evidences to the fact that different expression profiles of cellular miRNAs associate with different stages in HIV-1 disease progression.

Several cellular miRNAs which potentially target a set of accessory genes of HIV-1 have recently been identified. Using computational approach, five human T-cell miRNAs targeting the highly conserved regions across all clades of HIV-1 were predicted (Hariharan et al. 2005). Significant change in at least 62 miRNAs from HIV-infected PBMC (Houzet et

al. 2008) and change in miRNA profile in human cells after HIV-1 protein expression have also been reported (Yeung et al. 2005b). Table 1 summarizes the list of cellular miRNAs identified in relation to HIV/AIDS, the functions of which are discussed in this review.

HIV suppresses miRNA silencing pathway

Both Dicer and Drosha have been shown to contribute to the suppression of HIV-1 replication, suggesting a role of miRNA silencing machinery in the control of HIV-1 in vitro. Even though it is not clear whether this effected through direct or indirect mechanism, it is proposed that miRNAs are involved in negatively controlling HIV-1 replication (Triboulet et al. 2007).

Upregulation of 11 miRNA, including miR-122, miR-370, miR-373, and miR-297, moieties detected only in HIV-1 infected cells was noted during infection in Jurkat cells (Triboulet et al. 2007). HIV-1 also suppresses expression of the polycistronic miRNA cluster, miR-17/92, which encodes for miR-17-(5p/3p), miR-18, miR-19a, miR-20a, miR-19b-1, and miR-92-1. There was enhancement of HIV-1 production in Jurkat cells after the knockdown of specific siRNA against pri-miR-17/92, which suggests that downregulation of miR-17/92 affects virus replication. Since miR-17/92 does not directly target the viral genome, it seems that the effect of miR-17/92 on HIV-1 replication might be by targeting cellular protein(s). miRNA cluster miR-17/92 inhibits HIV-1 replication through repression of the histone acetyltransferase P300/CBP-associated factor (PCAF), an important cofactor for Tat in HIV-1 gene expression (Triboulet et al. 2007). miR-17-5p and miR-20a target the 3' UTR region of histone acetylase PCAF to inhibit mRNA translation (Kiernan et al. 1999; Ott et al. 2004). This miRNA inhibition pathway is required for efficient viral replication (Lagos-Quintana et al. 2001; Triboulet et al. 2007).

Cellular miRNA contributes to HIV latency

During HIV-1 latency, the provirus gets stably integrated into the host genome without producing any viral transcripts or proteins. This latency helps HIV-1 to evade immune responses and the action of antiretroviral drugs (Berkhout 2008). HIV-1 uses miRNA-mediated downregulation of viral gene expression to its own advantage by allowing it to be in a state of viral latency.

Several cellular miRNAs target a set of accessory genes of HIV (Ahluwalia et al. 2008; Nathans et al. 2009; Sung and Rice 2009; Wang et al. 2009). The potential miRNA target sites were mapped in the 3' UTR of HIV-1 RNAs in resting T cells (Huang et al. 2007). Among the cellular miRNAs with predicted binding sites in these regions, five (miR-28, miR-125b, miR-150, miR-223, and miR-382) are abundant in resting T cells compared to activated T cells (Huang et al. 2007) and monocytes (Wang et al. 2009). Increased HIV-1 production from pNL4-3-transfected cells upon neutralization of inhibitory effects of these five miRNAs suggests that these differentially expressed cellular miRNAs inhibit HIV-1 expression in primary resting CD4⁺ T cells through their interactions with the 3' end of HIV-1 RNA, thereby contributing to viral latency observed in quiescent cells. However, these miRNA inhibitors do not affect cellular proliferation status (Huang et al. 2007).

Altered expression of cellular miRNA on immune cell differentiation and viral infection

In addition to their direct effect on HIV-1 replication, miRNAs also have significant roles in host innate immune defense regulation. Monocyte differentiation into dendritic cells is regulated and coordinated by different miRNAs (Noorbakhsh et al. 2010; Wang et al. 2009). Even though cells of the monocyte/macrophage lineage are susceptible to HIV-1 infection, monocyte-derived dendritic cells (MDDCs) are poor producers of HIV-1 compared with monocyte-derived macrophages. Wang et al. (2009) recently reported that although both monocytes and macrophages expressed anti-HIV-1 miRNAs like miR-28, 150, 223, and 382, their levels were different in monocytes and macrophages, freshly isolated monocytes expressing significantly higher levels of anti-HIV miRNAs than donor-matched macrophages. The modulation of the anti-HIV-1 miRNA levels in monocytes/macrophages could alter the cell's susceptibility to HIV-1 infection (Wang et al. 2009). The suppression of these anti-HIV-1 miRNAs in monocytes facilitates HIV-1 infectivity, whereas increase of the anti-HIV-1 miRNA expression in macrophages inhibited HIV-1 replication. It is suggested that monocyte differentiation and HIV-1 susceptibility are linked by a common set of miRNAs. The negative association of intracellular miRNA expression and cell differentiation from monocytes to either macrophages or MDDCs may confer resistance to HIV infection in monocytes. The miRNA's profiling analysis showed miR-223 to target HIV-1 in the 3' end of the viral genome repressing its expression (Sung and Rice 2009).

miR-198, another miRNA which is downregulated during monocyte to macrophage differentiation, is capable of repressing HIV-1 replication through downregulation of cyclin T1 protein expression without affecting cyclin T1 mRNA levels supporting its anti-HIV-1 function (Sung and Rice 2009). The expression of cyclin T1, required for transactivation by HIV-1 Tat, increases during macrophage differentiation and enhances HIV-1 replication within macrophages (Liou et al. 2002). It is suggested that a cellular negative-feedback loop is activated that results in elevated levels of miR-198 following cyclin T1 upregulation and a subsequent dampening of the induction of cyclin T1 (Sung and Rice 2009).

Out of the five miRNAs identified against HIV targets, miR-29a, miR-29b, and miR-149 are expressed in T cells. miR-29a and miR-29b, which have highly related sequence similarity, not only inhibit Nef expression but also HIV virus replication in HEK293T cells and Jurkat T cells (Ahluwalia et al. 2008). miR-29a and miR-29b target the nef gene, whereas miR-149, miR-324-5p, and miR-378 target vpr, vif, vpu (Hariharan et al. 2005), nef, vpr, vif, and vpu being the four accessory genes of HIV-1. Their predicted target site is highly conserved in the sequences from all clades of HIV-1 (A, B, C, D, F, and H), except clade O.

Target prediction analysis by Nathans et al. suggested that the HIV-1 3'-UTR can be targeted by 11 miRNAs (miR-29a, 29b, 29c, 149, 147, 138, 513, 516-5p, 581, 644, and 646, Nathans et al. 2009). Even though the inhibition of miR-29a, b, or c increased HIV-1 production, highest effect was associated with miR-29a.

miRNA in neuro-AIDS

Activation of macrophages/microglia is thought to play a key role in development and progression of neuro-AIDS. Increased expression of miR-146a has been documented in T

cells following proinflammatory stimuli (Taganov et al. 2006), or during viral infection (Motsch et al. 2007). Similarly, HIV-1-infected primary human fetal microglia also expresses increased level of miR-146a (Rom et al. 2010). Monocyte chemotactic protein-2 (MCP-2), a proinflammatory cytokine secreted by the acute HIV-infected microglia, is a ligand for C–C chemokine receptor type 5 (CCR5). There is a negative correlation between increased expression of miR-146a and MCP-2 inhibition, which suggests a possible role for miR-146a in modulating expression of MCP-2 during the course of HIV infection in cultured microglial cells (Rom et al. 2010). The activity of miR-146a does not interfere with viral replication in this cellular system.

miR-146a, together with miR-155, is thought to be involved in innate immunity by regulating the acute immune response after pathogen recognition by TLR. miR-155 participates in the maturation of human dendritic cells (DC). Since miR-155 decreases dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) expression, by downregulating transcription factor PU.1, miR-155 could be developed as a therapeutic target to prevent entrance of HIV through DC-SIGN binding (Martinez-Nunez et al. 2009).

HIV-associated neurocognitive disorders (HAND) develop in a subset of individuals infected with HIV-1. Since HIV does not infect neurons in the brain, but infects macrophages and microglia, it is suggested that HAND results from an indirect neurotoxicity. Significant upregulation of three miRNAs: miR-21, miR-142-3p, and miR-142-5p has been identified in brains of HIV/SIV-infected humans and monkeys (Yelamanchili et al. 2010). miR-21 expression has been found in a number of cell types, whereas miR-142 expression is largely confined to the hematopoietic system. Myocyte enhancer factor 2C (MEF2C), which is a CNS transcription factor and a target of miR-21 in neurons, expression in cells is repressed by miR-21. Repression of MEF2C could lead to deficits in neurocognitive functions seen in HIV and is a potential pathogenic factor in neurodegenerative disorders such as HAD and HAND (Yelamanchili et al. 2010).

Eletto and colleagues reported that a group of six miRNAs (374, 128a, 128b, 100, 25, and 99a) were upregulated and seven miRNAs (let-7e, 298, let-7f, let-7c, let-7b, 320, and 214) were downregulated by Tat in rat primary cortical neurons. Among these, miR-128a has been found to be enriched in the brain, preferentially in the mature neurons. Synaptosomal-associated protein 25 (SNAP25) is one of the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors which are key regulators of membrane fusion. HIV-Tat promotes miR-128a activity, leading to a reduction in SNAP25 expression in neurons (Berkhout 2008; Eletto et al. 2008). Tat-mediated the downregulation of SNAP25 through miR-128a, suggesting that increased upregulation of specific microRNAs could precede neuronal damage.

Both miR-125a and miR-22 were found to be upregulated in HIV or HIV/major depressive disorder (MDD, Tatro et al. 2010). Induction of these dysregulated miRNAs leads to decreased protein translation of interferon-induced transmembrane protein 3 (IFITM3), an intracellular membrane protein, and soluble tumor necrosis factor receptor (sTNFR1A), a secreted protein in primary human neuronal cultures. IFITM protein is shown to inhibit HIV

replication (Lu et al. 2011), and sTNFR1A is involved in neuroinflammation. miR219, which was shown to modulate NMDA receptor-mediated neurobehavioral dysfunction in schizophrenia (Kocerha et al. 2009), is also shown to be upregulated in HIV/MDD (Tatro et al. 2010).

HIVencephalitis (HIVE) brains show altered expression of multiple miRNAs (miR-129, miR-129-3, and miR-130). HIV-induced miRNA dysregulation in brain targets diverse biological processes, including neuroinflammation, metabolic processes, and cell death. Caspase-6, -7, -8, and -9 were associated with multiple miRNAs that were suppressed in HIVE brains (Noorbakhsh et al. 2010).

MicroRNA expression and drugs of abuse

The effect of different drugs of abuse and anti-HIV miRNA expression by different target cells is poorly understood. Among the five known anti-HIV miRNAs which are abundant in monocytes, expression of four (miRNA-28, miRNA-125b, miRNA-150, and miRNA-382) was found to be lower in monocytes treated with morphine compared with untreated cells, with little effect on the expression of miRNA-223. The reason for why anti-HIV miRNA-223 was not affected by opioid use is not clear (Wang et al. 2011). Combined effect of naltrexone (pan-opioid receptor antagonist) and CTAP (specific μ -opioid receptor antagonist) completely abrogated the suppressing effect of morphine on anti-HIV miRNA expression, whereas either of them alone had little effect on anti-HIV miRNA expression. Heroin-dependent subjects had significantly lower levels of anti-HIV miRNAs (miRNA-28, 125b, 150, and 382) in PBMCs than the healthy subjects. These findings paralleled the observation that morphine treatment of monocytes enhanced HIV replication.

Hollander et al. showed that rats had less addiction to cocaine with increase in microRNA-212 (miR-212) levels. This cocaine addiction behavior is modulated by miR-212 through its effect on a group of genes (Hollander et al. 2010). They showed that increase in miR-212 reduces cocaine intake through a stimulatory effect on striatal cAMP response element binding (CREB) signaling through Raf-1-mediated sensitization of adenylyl cyclase activity and increased transducer of regulated CREB (TORC) expression. They suggest that spree use of cocaine by human addicts activates CREB, which acts together with its cofactors to regulate the transcription of miR-212. This initiates a positive-feedback loop, further stimulating CREB–TORC activity and thereby limiting cocaine intake. Their group also showed the evidences for the regulation of cocaine intake by MeCP2 through interactions with miR-212 and striatal BDNF levels. These findings might help in reasoning the factor behind the vulnerability of some people to cocaine addiction compared to others (Im et al. 2010).

In our studies, we have shown that cocaine and methamphetamine significantly downregulated miR-155 and miR-20a in MDCC, thereby enhancing the HIV-1 infectivity. Transfection of MDCC with miR155 mimic specifically reversed the cocaine or methamphetamine-induced effects which in turn reduced HIV-1 infectivity (Unpublished data; presented at CPDD 2011).

Viral miRNA in HIV

To date, a total of 48 viral miRNAs have been described in herpes viruses (Pfeffer et al. 2004), polyomaviruses (SV40), and retroviruses (HIV-1, Omoto and Fujii 2005). Recent reports have demonstrated the existence of HIV-1-derived miRNAs, derived from coding and noncoding regions of the viral genome, which regulate both viral and host gene expression so that the repression can be relieved when no longer needed by the virus (Hariharan et al. 2005; Yelamanchili et al. 2010).

TAR miRNA

Functionally TAR-derived miRNA would target the complementary sequence of the TAR region itself, resulting in posttranscriptional or possibly even transcriptional inhibition of HIV-1 (Weinberg and Morris 2006). Downregulation of viral gene expression by TAR-derived miRNA has been demonstrated. HIV-1 miRNA derived from the TAR RNA sequence called TAR miRNA, expressed at all stages of viral life cycle and affects the host cell cycle (Klase et al. 2007). TAR miRNA have been shown to be anti-apoptotic independent of the source of the miRNA. TAR miRNA expression makes the infected cells resistant to apoptosis. Cellular genes, ERCCI and IER3, involved in apoptosis are downregulated by TAR miRNA, a mechanism by which a virus is able to extend the life span of the infected cell for increasing viral replication (Klase et al. 2009). It is suggested that the miRNAs produced by the TAR element contribute to the maintenance of the latent state.

TAR-derived miRNA can downregulate gene expression by recruiting the HDAC-1 to the HIV-1 long terminal repeat (LTR) promoter to silence transcription by chromatin remodeling. It was recently shown that CR8#13—third-generation cdk inhibitor—an effective inhibitor of HIV-1 LTR at the viral promoter, does so by increasing 3' and 5' TAR microRNA production in HIV-1-infected cells (Carpio et al. 2010).

Nef miRNA (miR-N367)

nef-derived miRNAs, a 70-nucleotide structure located in the nef/LTR overlap of the HIV genome, have been shown in HIV-1-infected cells (Yamamoto et al. 2002). nef miRNAs (miR-N367) which show perfect complementarity with nef have been shown to inhibit Nef expression and to downregulate the transcription and replication of HIV-1 (Omoto and Fujii 2005; Omoto et al. 2004). nef miRNAs have been detected in HIV-1-infected long-time nonprogressors that display low viremia.

HIV-miRH1

miR-H1, an 81-nucleotide stem-loop structure located immediately downstream of the two NF- κ B sites in the LTR, has been reported to downregulate the AATF gene product (Kaul et al. 2009), accompanied lowered Bcl-2, c-myc, Par-4, and Dicer levels. miR-H1 seems to be antagonistic to the anti-apoptotic effect afforded by TAR miRNA. It was also noted further that HIV miR-H1 downregulate expression of the cellular miRNA miR149, which is considered to target the Vpr gene encoded by HIV-1.

Conclusion

Many fundamental questions regarding the expression and function of miRNAs still remain unanswered, even though considerable advances have been made in this field. A better understanding on miRNAs associated with diseases, their mRNA targets, and associated changes in protein products will lead to a better perception of the miRNA's regulatory effects and its association to different diseases. miRNAs may be involved in fine-tuning the transition from latency to activation, the clearance of latent HIV-1 reservoirs, and the reduction of virion production. More studies on the role of miRNAs associated with HIV-1 latency mechanisms could help in developing new strategies that will intervene in the mechanism of viral persistence. Until and unless there is reversal of HIV-1 gene silencing in every latently infected cell, complete cure for HIV-1 will remain impossible. This is because of the fact that virus from a single cell could restart the infection. Polymorphisms in miRNA sequences targeting HIV-1 may also contribute to disease progression. Available literature does not report polymorphisms in the mature miRNAs. Detailed studies in future about the targets of miRNAs and their regulatory function in cell physiology may help us to develop more sophisticated technologies which in turn may be beneficial to treat infectious diseases in humans. Also, identifying impact of drugs of abuse on miRNA expression, knowledge about the role of miRNAs as regulators of complex actions of cocaine, and strategies to block their effect on miRNA expression will help in developing therapeutics for drug addiction by manipulating the actions of miRNAs.

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Abbreviations

AATF	Apoptosis-antagonizing transcription factor
BDNF	Brain-derived neurotrophic factor
CCR5	C–C chemokine receptor type 5
CNS	Central nervous system
CREB	cAMP response element binding
DC-SIGN	Dendritic cell-specific adhesion molecule-3-grabbing non-integrin
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorders
HDAC-1	Histone deacetylase-1

HIV	Human immune deficiency virus
HIVE	HIV encephalitis
IFITM3	Interferon-induced transmembrane protein 3
LTR	Long terminal repeats
MCP-2	Monocyte chemotactic protein-2
MDD	Major depressive disorder
MDDC	Monocyte-derived dendritic cells
MEF2C	Myocyte enhancer factor 2C
MeCP2	Methyl CpG-binding protein-2
miRNA	MicroRNA
mRNA	Messenger RNA
nt	Nucleotide
PBMC	Peripheral blood mononuclear cells
PCAF	P300/CBP-associated factor
PFV-1	Primate foamy virus type-1
RISC	RNA-induced silencing complex
SNAP25	Synaptosomal-associated protein 25
sTNFR1A	Soluble tumor necrosis factor receptor
TLR	Toll-like receptor
TORC	Transducer of regulated CREB
TRBP	TAR binding protein
UTR	Untranslated region

Table 1
Functions of cellular miRNAs identified in HIV

miRNA	Function	Reference
miR-28, miR-150, miR-223, miR-382	Contribute to latency	Huang et al. (2007)
miR-28, miR-150, miR-223, miR-382, miR-125b	Ability of macrophages/MDDCS to infect	Huang et al. (2007), Wang et al. (2009)
miR-125a, miR-22	Protein translation of IFITM3 and sTNFR1A	Tatro et al. (2010)
miR-146a	Modulate MCP-2, a CCR5 ligand, release	Rom et al. (2010)
miR155	Decreases DC-SIGN expression	Martinez-Nunez et al. (2009)
miR-21	Repress MEF2C expression in neurons	Yelamanchili et al. (2010)
miR-128a	Reduction in SNAP25 expression in neurons	Berkhout (2008), Eletto et al. (2008)
miR-219	Modulate NMDA receptor	Kocerha et al. (2009)
miR-17/92	Inhibit HIV-1 replication through PCAF	Triboulet et al. (2007)
miR-198	Repress HIV replication through cyclin T1	Sung and Rice (2009)
miR-29a, miR-29b	Inhibit nef expression and HIV replication	Ahluwalia et al. (2008), Hariharan et al. (2005)
miR-149	Targets vpr	Hariharan et al. (2005)
miR-324-5p	Targets vif	Hariharan et al. (2005)
miR-378	Targets vpu	Hariharan et al. (2005)