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Editorial Open Access

MicroRNA and HIV

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Editorial

microRNAs (miRNAs) are non-coding RNAs (19-25 nucleotides) that regulate gene expression at transcriptional level [1-6]. They bind to messenger RNAs (mRNA), generally by imperfect base alignment in 3'-UTR region, and cause translational repression, mRNA destabilization and/or mRNA direct destruction [3-5]. It has been described that miRNAs can induce heterochromatin formation as well as it can induce protein translations sometimes [4]. There are over 2500 annotated and more than 60% of human genes are regulated by them [1,3,4]. A particular miRNA can regulate multiple mRNAs. miRNAs can be found into cells (cellular miRNAs) or in different fluids such as serum, plasma, urine, breast milk or saliva (circulating miRNAs). The latter are important to cell communication [2,6]. They may be encapsulated in microvesicles or bound to proteins; they can come from the immune system or other tissues and circulate in the bloodstream [2,5,6]. For instance, treatment with INF-alpha causes an exomal transfer of miRNAs to naive uninfected cells conferring resistance to HIV virus [7]. miRNAs have been used as biomarkers because they are stable, present in plasma, and their detection is easy [8]. It has been demonstrated that their analysis allows to know the immune status of patients with cancer or viral infections [2,3,9,10]. miRNAs are involved in different cellular processes (differentiation, development, death) and their deregulation is related to infectious diseases, cancer or altered immune response [4,10-12]. The impact of miRNAs on the regulation of inflammatory and antiviral immune response is widely characterized [5,6].

A large number of miRNAs interact with the immune system: development and differentiation of hematopoietic cells, differentiation and activation of immune cells (they can influence the signal cascades of the immune activation as well as modulate the proteins expression of the immune cells), inflammation, T-cell exhaustion, etc. [3-6,8,10,13-18] For instance, miR-155 regulates T cell differentiation as well as contributes to Treg development [15]. miR-223 has a role during infection, inflammation as well as hematopoietic cell differentiation [16]. miRNA let-7 actives TLR7 and the INF-alpha production and has been related to neurodegeneration [6] miRNA-181a-1 is associated with T-lymphopoiesis [14]. Changes in CD4 miRNAs profile have been observed according to the state of immune system activation and T-cell differentiation and function [8]. Changes of some miRNAs profiles have been associated with depletion of CD4 and CD8 during chronic infections (Let-7, miR-9, etc.) [8]. Recent studies have found that while apoptosis eliminates infected CD4, uninfected cells could be eliminated by pyroptosis (inflammatory cell death cascade). During this process microvesicles are released into the extracellular compartment transmitting pro-inflammatory signals to other cells [18]. Their mRNA and miRNA content is associated with the cells activation state as well as their origin [13]. miRNAs have been related to the production of interleukins (IL-10/Let-7; IL-6/miR-21, miR-122, miR-200a; IL-21/miRNA-29, miR-146a, miR-155) [4,5,12]. Factors such as cytokines, chemokines, Toll-like receptor ligands, IFN-alpha or IFN-beta have been associated with changes in the expression of miRNAs (miR-28, miR-125b, miR-150, miR-382) [6,10].

HIV/AIDS is one of the most serious health challenges over the world. More than 37 million people have been infected and more than 12 million have died because of the infection. Therefore, the relationship between miRNA and HIV infection is an area of growing interest. It has been observed that HIV infection causes changes in the profile of some miRNA such as miR-29a, miR-29b, miR-125b, miR-223, miR-382, miR-198, etc. This changes have been observed in infected $CD4^+$ T cell, PBMCs or serum [1-3,6,8-10,19-21]. However, it should be taken into account that miRNAs may be regulated in different ways providing different profiles depending on the different immune compartments. For example, miR-150 in HIV infected patients is much higher in plasma than in the cell compartments [1]. Cellular miRNA play a critical role in the pathogenesis of HIV intervening in viral infection, latency and mediating cell intrinsic resistance [6,10,19]. Here, we will focus on the role of miRNAs as innate antiretroviral defense. In plants, invertebrates and mammals it has been described that miRNAs play a crucial role in innate antiretroviral defense [10]. There are few described miRNAs having a direct effect on the virus but large numbers of them affect HIV indirectly throughout the regulation of factors that are necessary for viral cycle [1,2,6,8-10,19,21].

Some examples of those having a direct effect on the HIV are miR-28, miR-29, miR-125b, miR-149, miR-150, miR-223, miR-324-5, miR-378, miR-382, etc. miR-29 can bind directly to 3' UTR of viral mRNA, inhibiting virus protein translation and virus replication [4,9,10,19]. miR-149 joins to *vpr* gene, which is involved in the transport of proviral DNA to the nucleous [4]. Likewise, miR-378 can bind to *env* and *vpu* genes and miR-324-5 to *vif* gene, compromising virus infectivity [4]. The role as antiretroviral of miR-28, miR-125b, miR-150, miR-223 and miR-382 has been also described due to they also present the ability to bind to viral RNA [6,10]. They are able to inhibit the protein translation and the production of virus [1,4]. Considering the direct effect of some miRNAs on HIV, some authors have suggested that these miRNAs could be used as an anti-HIV therapy [2,8]. However, a couple of considerations should be taking into account. Firstly, some authors suggest that cellular miRNAs may bind to viral RNA more weakly than it has been observed in experimental analysis because of actual viral RNA secondary structures. Current and further studies would allow to elucidate this fact. Secondly, it should be considered that high mutation rates of viral RNA could allow virus to evade this defense mechanism unless miRNAs evolved at the same rate [21].

On the other hand, most miRNAs have an indirect effect on HIV virus cycle. After virus integration, different factors (site of integration,

cell activation status, host transcription factors, miRNAs, etc.) will determine its activation or latency [6,10]. The virus needs large numbers (>2000) of HIV Dependency Factors (HDF) that come from the host cell [6,20,21]. Most miRNAs related to HIV infection affect virus indirectly by the regulation of those factors. There are a large number of miRNA that have this indirect effect [1,2,4,6,8,10,20,21]. Briefly, let's see some examples to illustrate this fact. miR-17-5p and miR-20a inhibits HIV proviral transcription binding to histone acetyltransferase (PACF) and reducing its expression [1,4,20,21]. miR-17/92 cluster also targets PACF and inhibits HIV-1 infection [8,10]. miR-15a, miR-15b, miR-16, miR-20a, miR-93 and miR-106b reduces the expression of Pur-α protein (Purine-rich element binding protein alpha), which is a DNA- RNA-binding multifunctional protein that can join to viral elements and it is involved in viral transcription [4,20,21]. It has been described that the lower expression of this protein, because of this miRNAs, into monocytes could be associated to the lower HIV susceptibility of these cells [22]. miR-155 can join to at least three HDF: LEDGF/p75, which promotes the viral integration, ADAM10, which is necessary for HIV-1 replication, and the nucleoporin NUP153, which is involved in HIV nuclear import. Therefore, miR-155 inhibits preintegration complex (PIC) nuclear import and its main effect on HIV is the inhibition of viral integration [4,20,21]. Besides, TRIM32 can be a target of miR-155, inhibiting NF-kB and promoting viral latency [21]. miR-198 down-regulated Cyclin T1, which is involved in p-TEFb complex; as a consequence, there is an inhibition of Tat function and, thus, the viral transcription and replication [2,4,10,20,21]. Similar effect has been observed by miR-27b, miR-29b, miR-150, miR-223 [4,10,20,21]. In fact, it has been shown that when miR-27b, miR-29b, miR-150, and miR-223 were overexpressed, endogenous cyclin T1 protein levels decreased; on contrary, if cells were treated with their antagonmiRs, cyclin T1 protein levels increased [23]. In the same way, it has been described that miR-198 and miR-27b are highly expressed in monocytes and resting $CD4^+$ T cells as well as miR-198 is also over-expressed in macrophages [2,6,10]. Likewise, $CD4^+$ T cells activation seems to be associated with a down-regulation of this miRNAs and an up-regultion of Cyclin T1 [23]. SIRT1 can be targeted by miR-34a and miR-217, causing Tat function inhibition [20,21]. miR-1236 targets DCAF1 and inhibits Vpr function [21]. These are some examples of miRNA and their importance on HIV viral cycle; however, the number of miRNA involved indirectly in this cycle is progressively emerging.

The importance of miRNAs in HIV infection is demonstrated throughout the differences of miRNAs profiles observed in HIV elite controllers, who maintain HIV-1 viral loads below the limit of detection. It has been described different miRNAs profiles in HIV elite controllers (miR-9, miR-29, miR-31, miR-34a, miR-125b, miR-150, miR-155, etc), suggesting that miRNAs could contribute to a slower progression to AIDS [1-3,5,8,10,19]. For instance, a study analyzed 175 circulating miRNAs in plasma of three groups of individuals: elite controllers, chronic progressors and healthy donors. Sixteen miRNAs showed statistically different expression between chronic progressors and healthy donors but none of them were differentially expressed between elite controllers and healthy donors. These miRNAs were miR-33a-5p, miR-660-5p, miR-151a-5p, miR-29b-3p, miR-28-5p, miR-191-5p, miR-181a-5p, miR-18b-5p, miR-126-3p, miR-423-3p, miR-18a-5p, let-7i-5p, miR-19b-3p, miR-342-3p, miR-424-5p, miR-16-5p. Likewise, these miRNAs and miR-146a-5p were differentially expressed between elite controllers and chronic progressors [5]. Similar results were observed in another study in which miR-150, miR-146b-5p varied significantly among healthy individuals, asymptomatic HIV patients, and symptomatic patients receiving therapy [1]. miR-29 has been proposed as a marker that can distinguish healthy and non-progressing controls from those infected with HIV with viral replication [3]. It has also been observed that some miRNA profiles can correlate with viral load, CD4 counts, co-morbidities or co-infection with HBV [1-3,10,12,19]. For example, higher levels of miR-222 in serum has been proposed as a serum biomarker for early detection of diffuse large B-cell lymphoma and primary central nervous system lymphoma in HIV+ patients [24].

In conclusion, there is a wide range of processes in which miRNAs and HIV infection are connected, throughout the interaction direct/indirect with viral cycle or the regulation of immune system. The knowledge about miRNAs, and particularly their relation with HIV, is growing and may provide future new tools for HIV-infected patients manage. For instance, some studies point to the possible usefulness of some miRNAs as biomarkers of disease progression, inflammatory state, and response to therapy [1,4,13]. Moreover, the use of some of them as antiviral treatment is studied. For example, miR-122 is thought to be necessary for HCV replication. A drug, which consists of an oligonucleeotide that forms stable bonds with miR-122 and can inhibit it, has been designed and studied [25]. If further studies really demonstrated the utility of miRNAs either as biomarkers or therapy target, new powerful tools would be available for HIV patients manage and follow-up.

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